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 cortical 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 (MABP), 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.

In brief, the left MCA was exposed transorbitally and...
freed from its arachnoidal investiture so that a suture could be placed around it at its origin. A single knot was made in the suture and its ends were passed outside the incision through two small side holes of a tube which was apposed to the MCA and fixed to the wall of the orbit with epoxy cement. The opening in the dura and the enlarged optic foramen were sealed around the tube with Silastic sheeting, oxidized cellulose, and contact adhesive, and the empty orbit was filled with epoxy cement.

A shallow stainless steel cylinder covered with a thin Silastic membrane was implanted with contact adhesive and epoxy cement in a burr hole in the right parietal region, opposite the implanted occlusion device, in such a way that the Silastic membrane was as nearly coplanar with the underlying dura as possible. A stainless steel tube that passed from the cylinder outside the incision was closed with a sealed plastic tube after the cylinder was filled with bubble-free water.

Implantation of the Cranial Window

A portion of the scalp and the temporalis muscle of the left parieto-temporal region of the head were excised by electrocautery and the circumference of the exposed edge of the scalp was sutured to the underlying periosteal fibrous tissue. With a pneumatic drill and a small burr a cranioplast craniectomy about 2 cm by 2 cm was made in the exposed skull.

Transparent plexiglas, 1 mm thick and conforming in other dimensions to the craniectomy, was heated with a portable hot air dryer until flexible and malleable. The plexiglas then was pressed quickly against the inner surface of the bone that had been removed from the cranium. The excess plexiglas around the margins of the bone flap was trimmed, and the inner surface of the plexiglas window was treated with silicone fluid and sterilized with an antiseptic solution.

With an operation microscope the dura exposed by the craniectomy was incised and resected, leaving a margin approximately 1 to 2 mm wide around the edge of the bone. The plexiglas window then was placed in the opening of the skull and the correspondence of the contours of the window to the contours of the underlying cortical surface confirmed. Air was flushed from beneath the plexiglas with saline. Silastic adhesive was placed in the crevice between the edges of the window and the skull. Oxidized cellulose and contact adhesive (Eastman 910) were placed around the margins of the cranial window to fix it tightly to the skull. After observation to be certain there was no leakage of CSF, epoxy cement was used to reinforce the fixation of the cranial window and to provide an elevated margin or bank for filling with water for subsequent photography. The surface of the window then was covered with aluminum foil for protection. Figure 1 illustrates the cranial window in place.

The cats were allowed to recover from the anesthesia and the surgical procedures, and food and water were made available. Each cat was examined daily for evidence of neurologic deficit, leakage of CSF, or intracranial infection related to the implantation procedures.

Observations and Measurements after MCA Occlusion

Five to seven days after implantation of the occlusion device, the device for EDP measurement, and the skull window, each cat was sedated with phencyclidine hydrochloride, 1 mg/kg injected intramuscularly. Procaine hydrochloride, in a 2% solution, was injected into the skin over a femoral artery and a short incision made through the anesthetized area. A polyethylene catheter was passed through the femoral artery into the abdominal aorta for measurements of MABP and PR with a strain gauge and polygraph, and for collection of samples of arterial blood for analysis of arterial carbon dioxide tension (Paco2), arterial oxygen tension (Pao2), and arterial pH.

The cat then was placed loosely in a headholder with the body prone, and the EDP device was connected to a strain gauge by a nondistensible catheter and a continuous column of bubble-free water. The volume of water sufficient to produce a recorded value of 5 mm Hg for EDP on a polygraph was injected into the device from a microliter syringe attached to a side arm. The method for measurement of EDP has been described previously.

The aluminum foil was removed from the skull window and the plexiglas cleaned carefully with water. A pool of water was made inside the bank of epoxy cement to prevent irregular reflections of light from the uneven surface of the skull window. Photographs of the surface vessels of the cerebral cortex were taken through the operation microscope, with a magnification at the film plane of ×22 (or less commonly ×16).

Respiration was spontaneous; body temperature was measured rectally and maintained with a water blanket and heat lamp. Additional phencyclidine was injected as needed for sedation.

After initial observations, measurements, and photographs were made, the left MCA was occluded by tightening the suture in the implanted occlusion device. Observations and photographs were made at intervals subsequently. Twenty-four hours after occlusion the cats that survived were set free in the laboratory, and food and water made available. Observations and measurements were made at least one to two times daily up to five days after occlusion.

At the end of the five day period, surviving cats were killed by the intravenous injection of sodium pentobarbital. In all cats, including those that died before the end of the observation period, 0.5 ml of India ink was injected into the left common carotid artery as soon after death as possible for verification of MCA occlusion. The brain was removed, inspected closely, and fixed in 10% formalin. Coronal sections of the fixed brain were made and stained with hematoxylin and eosin for histopathologic examination.
Results

Cranial Window

In 19 of the 21 cats it was possible to observe and photograph the surface vessels of the cerebral cortex through the implanted cranial window after implantation. In one cat coagulated blood, presumably from the cut surface of the dura, obscured the surface vessels; in one other cat there was evidence of infection and inflammation beneath the window. In one cat the left MCA was inadvertently torn during the tightening of the suture for occlusion. In the 18 cats with MCA occlusion the cranial windows and underlying CSF and cortical surfaces remained unobscured, and observations and photography of surface cortical vessels were possible until termination of the study.

Changes of EDP and Histologic Findings

Slight decreases of EDP from 0.3 to 2.5 mm Hg were observed within one to three minutes of MCA occlusion in all cats except one, in which EDP increased 2.5 mm Hg. Ten of the 18 cats had EDP increases to greater than 30 mm Hg within 24 hours of MCA occlusion; all died within 48 hours with large ischemic infarcts, marked swelling of the brain, and herniation of cerebral structures. EDP increased gradually in these cats; 10 mm Hg was first exceeded from one and one-half to ten hours after occlusion, and 30 mm Hg was first exceeded at eight to 21 hours. In seven of the ten cats increases of EDP accelerated after EDP exceeded 30 mm Hg. The acceleration to 60 mm Hg or more occurred from 11 ½ to 22 hours after MCA occlusion. PR decreased in all seven cats during the accelerated increase of EDP. However, when EDP exceeded 60 mm Hg there was a sudden increase of BP accompanied by tachycardia or cardiac arrhythmia, followed by a sudden decrease of BP and death of the animal. In all these cats but one the maximal recorded EDP was greater than 100 mm Hg, but EDP never exceeded MABP.

Five cats had increases of EDP to between 10 and 30 mm Hg after MCA occlusion. One of these, in which EDP increased to 12 mm Hg, died nine hours after occlusion with a large infarct but no evidence of brain swelling. Of the others, one had a large infarct with little evidence of brain swelling; two had moderate infarcts, involving deeper structures of the brain, but not cortex, with evidence of swelling only in the region of the infarct; and the remaining cat had a small infarct, confined to the region of the basal ganglia.

Three cats did not have increases of EDP greater than 10 mm Hg after occlusion. In one of these a moderate sized infarct was hemorrhagic; this cat died less than seven hours after occlusion. The other two cats had small infarcts and survived the entire period of observation.

Changes in the Superficial Cortical Vasculature

Within seconds of MCA occlusion, pallor of the cortex, decreases of the velocity of the flow of blood, and aggregation of the formed elements of the blood were noted in venous vessels in all cats (fig. 2). The degree, extent, and duration of pallor and aggregation were variable. In general, the cats that had the greatest degree and greatest extent of pallor also had the greatest decreases of EDP immediately after MCA occlusion and the greatest increases of EDP subsequently. Six of the ten cats with increases of EDP to greater than 30 mm Hg developed immediate and severe pallor.

Aggregation of blood elements became visible in arterial vessels in eight of the ten cats with later increases of EDP to values greater than 30 mm Hg; this was indicative of a marked decrease of the velocity of the flow of blood in the arterial vessels. Aggregation was observed in arterial vessels in only three of the other eight cats.

In one cat focal constriction of cortical arteriolar vessels developed and spread within a few seconds to become generalized, involving much of the area under the window; the constriction was accompanied by other signs of ischemia.

FIGURE 2. Superficial cortical vasculature before and after MCA occlusion. A. Before occlusion. EDP = 5 mm Hg; MABP = 150 mm Hg. B. 2 minutes after occlusion. EDP = 3.8, MABP = 115. C. 1 hour after occlusion. Note pallor of cortex and aggregation of the formed elements of the blood. D. 8 hours after occlusion. Note increased vascularity, and slight compression of vessels at EDP = 12 (evident in upper left).
and the cat died within ten hours of massive infarction with herniation. Transient focal arteriolar constriction, or spasm, was noted in four other cats.

Red venous blood, indicating greater than usual oxygen saturation, was seen at one time or another in all but two cats, one with moderate and one with minimal increases of EDP. The time of appearance of hyperoxygenation of venous blood was variable, from five minutes to ten hours after occlusion. In eight cats venous blood of different colors was observed within the same vessel flowing in a streamlined or laminar fashion. Once hyperoxygenation of venous blood developed it could be observed for prolonged periods of time in the individual cats, often for several days or until the end of the period of observation.

In seven of the ten cats with increases of EDP to greater than 30 mm Hg cortical pallor decreased within a few hours of MCA occlusion, except in the temporal region. In these cats congestion of vessels and hyperemia were observed around focal areas of cortical pallor (figs. 2, 3). In two of the other three cats of this group the cortex that could be seen through the cranial window remained severely pale, and in the other cat marked hyperemia and tortuosity of venous vessels developed on the cortical surface, beginning one hour after occlusion (fig. 4).

As EDP increased to about 10 mm Hg there was evidence of brain swelling (figs. 2, 3) indicated by compression of venous vessels by arterial vessels, and flattening of gyri and venous vessels against the cranial window.

During the period of acceleration of EDP from 30 mm Hg to approximately 60 mm Hg in seven of the cats, cortical pallor became more severe and focal regions extended and coalesced (fig. 3). When EDP exceeded about 50 mm Hg, small venous vessels collapsed on the surface of the pale cortex. Aggregation of formed elements and decreases of the velocity of the flow of blood became more obvious in larger veins and also in arterial vessels. In several cats changes of velocity became synchronous with respiratory movements.

Finally, the color of the arterial blood became dark; the entire cortical surface observable through the cranial window became severely pale and then dark; there was collapse of most venous vessels; and a progressive decrease of the velocity of flow in all vessels was evident. Very slow flow of blood elements was observable in large arterial and venous vessels for several minutes after cessation of cardiac function.

In those cats with small or moderate infarcts that survived until the end of the period of observation, cortical pallor was variable shortly after MCA occlusion and lessened within two hours, and decreases of the velocity of the flow of blood and aggregation of the formed elements of the blood were not as apparent as in the cats that later died. In the cats that survived, the changes in the superficial vasculature gradually lessened, such that within twelve to twenty-four hours the cortex appeared to be nearly normal. However, red blood and lamination of different colors of blood was observed in the venous vessels of most.

Both cats that died shortly after MCA occlusion without a major increase of EDP had considerable cortical pallor, decreases of the velocity of the flow of blood, and aggregation of formed elements in both venous and arterial vessels. In one cat progressive hypotension was associated with severe changes in the cortical vasculature and, eventually, cessation of cardiac function. In the other cat MABP increased progressively but cortical pallor and changes in the surface vessels worsened; this cat had a hemorrhagic infarct.

Miscellaneous Results

In the cats that died before the end of the period of observation PaO₂ remained normal until the terminal stages, during which it decreased. PacO₂ increased slightly shortly after MCA occlusion, but increased in the terminal stages. In four of six cats with adequate numbers of measurements, pH decreased slightly with increases of EDP. There were no meaningful changes of MABP, PR, or blood gases in the cats that survived.

**FIGURE 3.** Continuation of Fig. 2. E. Swelling continues. F. EDP = 79, MABP has increased to 194. Pallor has extended and aggregation is more apparent. G. 3 minutes after F. EDP is decreasing. H. EDP and MABP decreasing further. Cardiac function stopped several minutes later.
Discussion

Cranial Window

Studies of the surface vessels of the cerebral cortex in animals have provided a great deal of information about cerebrovascular physiology and pathophysiology. In many studies, the brain has been exposed, although protected, and observed through a craniotomy; however, an open skull and removal of CSF act to influence intracranial pressure and regional tissue pressure, and may affect the integrity of the surface vessels. In other studies, flat cranial windows have been used, they have been surrounded by metal flanges, or have required flushing of fluid underneath. With such windows the brain and the surface vessels may be compressed against a flat surface or a metal flange, and flushing with artificial fluid under pressure may affect the regulatory responses of the surface vessels and their responses to various stimuli.

Our cranial window (see Methods) was molded to the contours of the removed bone, and presumably also to the contours of the underlying cortical surface. There were no ridges or flat surfaces to compress the brain or surface vessels. Moreover, with care during implantation, the underlying cortex and CSF remained clear, and flushing was unnecessary. A rim of dura left around the edge of the bone protected the brain from the implantation adhesives.

An advantage for photography was provided by the built-up rim of epoxy cement, which permitted the use of a small pool of water with its flat surface to minimize reflections from the photographic flash. Other advantages included ease of preparation and implantation, without the danger of accidental dislodgement or separation from the bone after implantation.

Although there have been a number of studies of the superficial cortical vasculature after MCA occlusion, the present study is the first to relate changes in the surface vessels to changes of ICP and to relate early changes to the eventual outcome. However, marked increases of EDP caused by swelling of the brain in and around large ischemic and infarcted areas occurred with a frequency that was much greater than in previous studies. The additional operative procedures of implantation of the cranial window and resection of a portion of dura may have modified the effects of MCA occlusion.

Focal arteriolar constriction, observed during ischemia in earlier studies of squirrel monkeys with craniectomies, also occurred in these cats with closed skulls. Focal constriction, or spasm, may be caused by the release of vasoactive agents from ischemic brain tissue. These observations again indicate that vasomotor paralysis during and after cerebral ischemia is not due solely to maximal vasodilatation.

No platelet thrombi, previously reported, were observed. Previous studies were in squirrel monkeys; a species difference may be responsible for the earlier observations. However, in previous studies craniectomies were done, and it is now apparent that most of the monkeys were slightly hypotensive; the earlier findings may have been artifactual or related to a systemic process such as disseminated intravascular coagulation.

Correlation of vascular changes with electroencephalographic or electrocorticographic changes would have been of interest, but were not done because of the difficulty in implanting electrodes in the plexiglas. Perhaps in the future windows with integral electrodes will allow such correlations.

Predictive Value of Changes in the Superficial Vasculature

Cortical pallor was not of predictive value: both prolonged pallor and early revascularization with reactive hyperemia could be associated with large lesions and considerable edema. This finding is similar to that of a previous study in which it was observed that the severity of the initial neurologic deficit caused by MCA occlusion was not of
value in predicting the severity of a later neurologic deficit or the final outcome.\textsuperscript{16}
Visible aggregation of the formed elements of blood, or "particulate flow," which is indicative of a decreased velocity of the flow of blood, was of predictive value when observed in arterial vessels. Ten of the 12 cats that died before the end of the period of observation (but only one of the six cats that survived) had particulate flow in arterial vessels.

The Superficial Vasculature and EDP

Immediate Decreases of EDP

The small decreases of EDP that were noted immediately after MCA occlusion in association with cortical pallor presumably were caused by decreases of intracranial blood volume resulting from the occlusion in the inflow pathway. Rapid compensatory mechanisms, such as vasodilatation of collateral channels, may have accounted for the brief duration of the decreases of EDP.

Infarction Without Swelling

In two cats, death occurred early after MCA occlusion without an increase of EDP or evidence of herniation of cerebral structures. Similar findings have been reported earlier.\textsuperscript{14, 26} In both cats severe and extensive cortical pallor appeared immediately after MCA occlusion and spread rapidly. On pathologic examination of the brain there were large infarcts, but without gross swelling. There may have been a direct influence of ischemia on a cerebral or brain stem vasomotor center, with a disturbance of systemic circulation.

Reactive Hyperemia and Increases of EDP

Congestion of surface vessels and hyperemia, manifested by redness of the brain, reddening of the venous blood, and vasodilatation, were noted to be surrounding areas of focal cortical pallor in association with increases of EDP and compression of the brain beneath the cranial window. In one cat, severe hyperemia with markedly tortuous venous vessels appeared shortly after MCA occlusion that led to a fatal outcome. These results suggest that hyperemia developing early after MCA occlusion, through collateral channels or by disaggregation of blood elements, may not be favorable because of worsening of ischemic edema. Similar findings were observed in an earlier study in which CBF was measured by clearance of hydrogen,\textsuperscript{21} and by others.\textsuperscript{22-24}

Hyperemia developing later may have a different mechanism, and a different effect. Later hyperemia may be related to the proliferation of small vessels in and around the ischemic zone, or to the establishment of permanent collateral channels.\textsuperscript{29} Later hyperemia, developing six to thirteen days after the onset of ischemia, can be associated with a more favorable outcome.\textsuperscript{30, 37}

Terminal Events

In those cats with marked increases of EDP after MCA occlusion, severe and extensive cortical pallor and marked decreases of the velocity of the flow of blood appeared suddenly in all vessels of the cortical surface in the terminal stages, when EDP was still less than both MABP and diastolic blood pressure. However, intravascular blood pressure in the cerebral ischemic zone may have been much less than that in nonischemic brain tissue; local intravascular pressure may have been lower than EDP, preventing perfusion.

Alternatively, the sudden development of severe impairment of flow might have been related to occlusion of the posterior cerebral artery by transventricular cerebral herniation, interfering with flow through collateral channels to the territory of the MCA. Certainly, those cats that did not have sudden increases of EDP to greater than 60 mm Hg also did not show the sudden intravascular changes, suggesting that gradual increases of ICP are more easily compensated for than sudden ones.

Acknowledgment

Technical assistance and advice were provided by Margaret M. Jordan.

References

Comparative Effects of Chloralose Anesthesia and Sernylan Analgesia on Cerebral Blood Flow, CO₂ Responsiveness, and Brain Metabolism in the Baboon

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SUMMARY A comparison was made between the effects of two different anesthetics, alpha-D-glucocloralose and 1-phenylcyclohexyl piperidine hydrochloride (Sernylan®), on cerebral blood flow (CBF), brain metabolism and cerebrovascular CO₂ responsiveness in primates.

The experiments were carried out on immobilized and artificially ventilated baboons. Anesthesia was induced either with 100 mg/kg chloralose (i.p.) or with 1 mg/kg Sernylan (i.m.). CBF in 8 different brain regions was measured by the intra-arterial Xe clearance technique. The CO₂ responsiveness of the cerebrovascular bed was tested by a gas mixture containing 5% CO₂.

Chloralose depressed total as well as regional CBF compared to the effect of Sernylan. A significant shift occurred toward lower CBF values in the grey matter while white matter flow was identical in the two groups. Brain O₂ consumption was significantly higher during Sernylan analgesia (3.35 ± 0.34 ml/100 g/min) than during chloralose anesthesia (2.42 ± 0.22 ml/100 g/min). There were no differences in glucose uptake, lactate and pyruvate production, or in arterial and cerebral venous blood gases in the two types of anesthesia. The cerebrovascular CO₂ sensitivity of the Sernylan-treated baboons was higher than that of the chloralose-anesthetized animals, in both the grey and white matter.

SINCE THE EARLY works of Alexander and Cserna, Schmidt and Hendrix, Jowett and others, it is well known that anesthetic agents have common basic features in their cerebrovascular hemodynamic effects. These agents affect the tone of the smooth muscle of the cerebral vessels, as well as alveolar ventilation, blood gas tensions and arterial blood pressure.

In spite of their common features anesthetics with different chemical structures can induce a wide variety of cerebrovascular and metabolic reactions. This must be borne in mind when interpreting the results of clinical and experimental studies of cerebral hemodynamics and metabolism.

It is often difficult to compare studies of anesthetics and brain blood flow and metabolism because of differences in methodology and species. Only those results obtained under standardized experimental conditions in the same species can be compared.

One of the long used experimental anesthetics is chloralose, which is one of the general anesthetic agents that contains Cl in its structure. Though there are several excellent papers and reviews which discuss its hemodynamic effects no detailed study has so far been published concerning the effect of chloralose on regional cerebral blood flow (CBF).

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