Intracranial Pressure Gradients Associated With Experimental Cerebral Embolism

BY MARIO BROCK, M.D., JOACHIM BECK, M.D., EVANGELOS MARKAKIS, M.D., AND HERRMANN DIETZ, M.D.

Abstract: Intracranial Pressure Gradients Associated With Experimental Cerebral Embolism

In a series of 20 cats unilateral cerebral oil embolism was followed by the development of clinical signs of increased intracranial pressure. Simultaneous bilateral epidural pressure measurements revealed marked pressure gradients between both cerebral hemispheres. Such local (tissue) pressure gradients possibly influence local cerebral blood flow (mainly in the diseased areas) by means of alterations in local tissue perfusion pressure.

ADDITIONAL KEY WORDS cerebral blood flow tissue perfusion pressure intracranial pressure gradients

In patients suffering from cerebrovascular disease or brain tumor, hyperventilation may induce a redistribution of regional cerebral blood flow (rCBF) in favor of ischemic areas of the brain. In previous papers we suggested that this redistribution of rCBF, to a great extent, is secondary to the changes in intracranial pressure (ICP) associated with hyperventilation. We proposed that hyperventilation, by inducing constriction of reactive cerebral vessels in unaffected areas, leads to a decrease in intracranial blood volume and, consequently, to a reduction in ICP. This causes an increase in tissue perfusion pressure, the effects of which will become manifest mainly in the diseased areas of the brain, since there blood flow (through the unreactive, paralyzed vessels, compressed by local edema) is passively at the mercy of local tissue perfusion pressure. While on the one hand this mechanism clearly stresses the importance of what was called tissue perfusion pressure (as compared to the usually employed cerebral perfusion pressure), on the other hand it postulates the existence of different local pressures—and pressure gradients—within the brain tissue. Such pressure gradients have hitherto been measured in cases of brain tumor and of experimental cerebral compression by means of balloons. The experiments herein reported have demonstrated that marked intracranial pressure gradients can also develop in the presence of cerebrovascular lesions, and provide further evidence that such lesions can act as expanding processes from the pathophysiological point of view.

Methods

The present experiments were performed on 20 apparently healthy cats of both sexes (average weight: 2800 gm) under intraperitoneal Nembutal® anesthesia (40 mg/kg body weight). The femoral vessels were catheterized on one side to permit continuous recording of arterial blood pressure (electromanometer P-23Db, Statham) respectively, intravenous injections as necessary. All animals were tracheotomized, but breathed spontaneously to allow studying the changes in respiration throughout the experiment. We deliberately avoided influencing the time course of the experiments by therapeutic measures, since this will constitute the subject of future studies.

A thin polyethylene catheter (outer diameter: 1 mm) was centripetally introduced into the right lingual artery to its origin from the common carotid artery.

With a manual trephine (outer diameter: 10 mm) a parietal craniotomy over the median suprasylvian gyrus was performed on each side,
the dura mater remaining intact. A small rubber balloon filled with 0.2 ml of saline and connected to a pressure transducer (P-37, Statham) was gently laid on the dura mater on each side without compressing it, and the trephine holes were closed in a watertight way with dental cement, entirely encasing the balloons, with exception of those parts in contact with the dura mater (fig. 1).

The pressure in the system constituted by each small balloon and the corresponding pressure transducer was zeroed and calibrated before application of the balloon to the dura mater. Following the hardening of the cement the epidural pressures thus recorded were always within the normal range, and differences between both sides did not exceed 3 mm Hg. For the sake of comparison, these pressures (recorded after the hardening of the cement) were subsequently attributed the value zero.

After conclusion of the experiments the cement was carefully broken off and the balloons removed without disconnecting them from the transducers. Under such circumstances the indicated pressures always returned to zero or to near-zero values.

The arterial and epidural pressures, as well as the respiration curves (followed by means of a thermistor attached to the tracheotomy tube) were continuously recorded on a conventional polygraph (He-19, Hellige). Integrated cardiac and respiratory frequency were recorded intermittently. Changes in pupillary width were graphically noted at intervals of five minutes or less, and correlated with the other measured parameters.

Following the preparation as described above, the animals were left undisturbed and all parameters were checked for 60 minutes in order to assure stable initial conditions. After this period of time 0.2 ml/kg body weight of an oil emulsion (Lipiodol®) was injected through the right lingual artery catheter, so as to cause unilateral oil embolism of the cerebral vessels. Oil embolism is more effective than embolism with air or microspheres.10

**Results**

**Survival Time**

All animals eventually died following the oil injection. According to the survival time there were three groups of animals: in the first group (group 1 = six animals) death occurred in an average of 16 minutes (10 to 22 min) following embolization. In this group there probably was primary involvement of the brain stem by the injected oil, as also observed in the rabbit,13 since almost immediately after the end of the injection, pronounced dilatation of the pupil homolateral to the injection occurred, and was soon followed by maximal dilatation also of the contralateral pupil and by severe respiratory anomalies. (In one animal there was an immediate onset of periodic breathing leading to a final respiratory arrest within a very short period of time, in three animals immediate respiratory arrest was followed by bradypnea with flattened respiration and eventual complete respiratory arrest, and in one animal immediate irreversible respiratory arrest took place at the end of the injection.)

The direct arrival of oil particles to the brain stem is possible on account of the rich vascular anastomoses at the base of the cat’s brain.1-18 Histological examination of the central nervous system of the animals of this group will probably further clarify the reason for their rapid death in the absence of correspondingly high and persistent intracranial pressures.

The second and third groups of animals (group 2 = eight animals, and group 3 = six animals) survived the oil embolization for longer periods of time. Following the oil injection a transient and moderate pupillary dilatation on the affected side and sometimes a brief bradypnea, accompanied by a small and shortlasting ICP rise, took place in most animals. However, the initial condition was regained within a short period of time. Thereafter, intracranial pressures progressively began to rise, eventually leading to the death of
EXPERIMENTAL CEREBRAL EMBOLISM

(Animal TP-63; group 3). The amplitude of intracranial pulsation and respiration waves increases as intracranial pressure rises.

(Animal TP-63; group 3). In the prefinal and final stages, after regular respiration has progressively subsided (A), rhythmic ICP waves disappear and intracranial pressures passively follow arterial pressure waves. When arterial and intracranial pressures decrease indicating impending death, irregular respiratory activity is transiently resumed (B). Toward the end of the experiment (234 to 241 min) the respiratory incursions seem to coincide with the periodic decreases in intracranial pressures. (The pressure values inscribed on top of the curves are systolic.)

(Animal TP-67; group 1). Abrupt respiratory arrest almost immediately after the end of the embolization, followed by periodic respiratory bursts associated with changes in arterial and intracranial pressures. (The pressure values inscribed on top of the curves are systolic.)
the animals. (In three animals of group 3 an additional oil injection—half of the initial dosage—had to be performed since no marked increase in intracranial pressures had developed within 60 minutes after the first embolization.)

In group 2 death occurred from 32 to 55 minutes following embolization (average: 45 minutes) with very high intracranial pressures (up to 175 mm Hg, animal 49) being attained.

In group 3 intracranial pressures rose less (maximal value attained: 112 mm Hg, animal 63) and more slowly; the animals survived from 103 to 238 minutes (average survival: 156 min).

CHANGES IN INTRACRANIAL PRESSURES
The rise in the intracranial pressures in all three groups was always accompanied by the well-known increase in amplitude of intracranial pulsation waves (fig. 2). 14, 16

In the preterminal stages, at relatively high intracranial pressure levels (which varied from animal to animal), large variations of intracranial pressure were observed following the correspondingly large changes in arterial blood pressure (figs. 3 and 4), indicating advanced impairment of autoregulation or "vasomotor paralysis." 10, 17

In no animal could rhythmic pathological ICP waves or plateau waves 18-21 be observed. Also, in no animal did intracranial pressures surpass mean arterial blood pressure except when final central failure supervened; then, blood pressure rapidly fell to zero following respiratory arrest, while intracranial pressure lagged somewhat behind (see Discussion),

Mean values of epidural pressures on the right ($P_{eR}$) and left ($P_{eL}$) sides in various groups of animals. Oil embolization was always performed on the right side. All pressures are positive. The animals in which epidural pressure increase was more pronounced on the right (embolized) side were inscribed above the x-axis. The animals in which epidural pressure increase was more pronounced on the left (nonembolized) side were inscribed below the x-axis. Interhemispheric pressure gradients were more pronounced when epidural pressure increased more on the nonembolized (left) side.

**FIGURE 5**
EXPERIMENTAL CEREBRAL EMBOLISM

thus transitorily remaining above arterial blood pressure levels.

The increases in intracranial pressures in group 1 were not as pronounced as in the other two groups and appeared to be an immediate consequence of the respiratory arrest and CO₂ accumulation rather than the result of edema or swelling of brain tissue.

INTRACRANIAL PRESSURE GRADIENTS

Pressure differences between the affected and the unaffected hemisphere developed in all studied animals. Even in group 1, despite the very brief survival, such gradients were observed. In this group, however, they never surpassed 35 mm Hg. The differences in epidural pressures were more pronounced and developed faster in group 2 (largest gradient attained: 120 mm Hg, animal 49) than in group 3 (largest gradient attained: 48 mm Hg, animal 40) as shown in figure 5. The details on the development of such gradients will be presented elsewhere (in preparation).

The epidural pressure was higher on the nonembolized side in 12 animals (without group predilection). When this was the case, the interhemispheric pressure gradients appeared to be more marked than when the epidural pressure increased more on the affected side (fig. 5). This might be explained by the obstruction of a large part of the vascular bed on the side of the oil injection.

BLOOD PRESSURE AND HEART RATE

At the beginning of the experiments all studied animals had mean arterial blood pressures within the normal range for the cat (lowest value: 70 mm Hg; highest value: 140 mm Hg). The same applies to the heart rate (lowest value 80/min; highest value 140/min). The oil embolization usually caused no or only very slight and transient blood pressure changes in the animals of groups 2 and 3. In group 1 a clearcut increase in mean arterial blood pressure was the rule immediately following embolization and was reverted after a short period of time by the impending death of the animal. This primary rise in blood pressure was interpreted as a further sign of direct brain stem involvement by embolism in this group.

When intracranial pressures began to increase in groups 2 and 3, arterial blood pressure also started rising as classically described. In this phase usually a tachycardia could be observed; only in the final stages, when signs of central failure had become evident and blood pressure alternated in a rapid and disordinate way from very high to very low values without definite rhythmicity, did we observe the bradycardia often described as a part of the Cushing response. In some animals the final bradycardia was associated with extrasystoles. In this stage blood pressure oscillations persisted even after complete respiratory arrest had taken place.

RESPIRATORY ALTERATIONS

Two main types of respiratory changes were observed in the prefinal and final periods: (1) progressive decrease in respiratory amplitude (fig. 3) and frequency leading to complete respiratory arrest, followed or not by periodic respiration, and (2) abrupt respiratory arrest without previous decrease in respiratory frequency or amplitude, also followed (fig. 4), or not by periodic respiratory bursts. All animals of group 1 presented abrupt respiratory arrest.

In a few animals the prefinal periodic respiratory excursions seemed to take place during the episodes of decreased blood and intracranial pressures (fig. 5). Whether this is coincidental or whether a “decompression” of the respiratory center takes place, allowing transient resumption of function whenever ICP has fallen sufficiently, remains speculative at present.

Discussion

THE EMPLOYED MODEL

Unilateral carotid embolization has been chosen since it is known that the hemodynamic conditions in the cat are such that this route causes a damage fairly restricted to the homolateral hemisphere. However, as evidenced by the animals of group 1, under certain circumstances the rich anastomotic network at the base of the skull may allow the injected material to also reach the brain stem.

Although extrapolations from animal experiments to the human are not free from criticism, and intracranial compartmentation in the cat (bony tentorium) differs from that in man, our model aimed at producing a situation similar to that caused by complete and abrupt hemispheric infarction (as would be the case, for example, in the presence of an
occlusion of the internal carotid artery in man).

It has been well documented in literature that the brain swelling associated with the acute occlusion of a major cerebral artery may act as an expanding process. Signs of increased intracranial pressure and distortion of cerebral structures are the rule in such instances and probably constitute one of the major factors leading to death within the first week following a "stroke." Bilateral experimental cerebral embolization in the dog is always associated with marked increases in CSF pressure.

The occurrence of different pressures within the cranium was first proved experimentally by Ziegler and later also suggested by Cairns, based on clinical observations. Gerlach measured the tension of the dura mater through burr holes in patients undergoing bilateral ventriculography and found that dural tension was constantly higher on the side of the tumor.

Huber et al. and Weinstein et al. observed local intracranial pressure differences in animals with implanted epidural and intracerebral balloons. Such differences were also noted in man between the epidural space and tumor cavities, and between the epidural and the intraventricular compartments. The experiments herein reported demonstrate that intracranial pressure gradients also occur in the presence of extensive cerebrovascular occlusion.

The reason why in some of the animals studied epidural pressure increased more on the embolized hemisphere and in others on the nonembolized side remains unclear and may be related to the degree of vascular occlusion achieved or to the distribution pattern of oil emboli. Interhemispheric pressure differences were constantly smaller when the pressure increased more on the embolized side (fig. 5).

The recorded asymmetric increases in intracranial pressure are not artifactual (e.g., due to smallest differences in balloon size) since they were never observed when ICP was globally increased in the intact animal, for example by means of tracheal occlusion or water infusion.

The volume of the cerebral hemispheres (determined postmortem) correlated well with the observed pressure increase; macroscopically the brain swelling was always more pronounced on the side from which higher pressures had been recorded. Cerebellar herniation and more or less pronounced caudal dislocation of the brain stem were present in all animals of the present series.

PATHOPHYSIOLOGICAL MEANING OF INTRACRANIAL PRESSURE GRADIENTS

The present findings substantiate the concept that occlusive cerebral vascular lesions—mainly if extensive and of acute development—behave as true expanding processes. Due to the more or less evident encasement of the various structures of the CNS within the different compartments of the craniocerebral system a localized increase in volume within one hemisphere will give rise to physical forces producing: (1) transversal shifting of midline structures, and (2) caudal displacement of the brain stem. The transversal shifting are responsible for the interhemispheric pressure gradients as observed in the present series. The axial (caudal) shifting originates pressure differences between the cerebral and the cerebellar fossae, and between the cranial and the spinal compartments.

Pressure gradients can also be expected to occur between various points of the tissue contained in one single larger cranial compartment. The angiographical picture of vascular shiftings within one hemisphere is a typical example of such pressure differences. From the circulatory point of view it has been suggested that such gradients in tissue pressure will affect tissue perfusion pressure mainly in the diseased areas, where the unreactive paralyzed vessels show a pressure passive reaction. Additionally to the effect on rCBF, it is conceivable that differential local pressures generate shearing forces which alter the membrane properties of the cells, as suggested by Weinstein et al.

Tissue pressure gradients could also be one of the factors responsible for the propagation of the extracellular "edema fluid" to areas quite distant from a brain lesion itself. However, this point remains speculative at the moment.

The clinical and therapeutic importance of local tissue pressure gradients for cerebral blood flow and metabolism is not fully understood at the moment, and further studies on the influence of local intracranial pressures...
on regional cerebral blood flow and metabolism are needed to clarify some of the still controversial aspects of this problem.

**Acknowledgments**

The authors are indebted to Miss M. Dietz and to Miss C. Kruse for their valuable technical aid, to Mrs. I. Harkins for her help in preparing the manuscript and to Mrs. U. Hausen for the bibliographical research work.

**References**


32. Farmer TW, Wood EH: Unilateral cerebral edema with thrombosis of the internal carotid or middle cerebral artery. Trans Amer Neurol Assoc 81: 105-108, 1952


Intracranial Pressure Gradients Associated With Experimental Cerebral Embolism
MARIO BROCK, JOACHIM BECK, EVANGELOS MARKAKIS and HERRMANN DIETZ

Stroke. 1972;3:123-130
doi: 10.1161/01.STR.3.2.123
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1972 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/3/2/123

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/