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occur. If a bruit is heard over the common carotid artery low in the neck, compression is deferred until angiography establishes that the bruit is the result of a proximal orifice stenosis, which is usually the case. Release of compression should not be abrupt, but gradual. This precludes the sudden return of maximum blood flow with its concomitant turbulence. Compression is released immediately if any signs of neurological impairment is observed. Compression is not advised in any patient who is within a four-week time period since having a stroke, even if full recovery has occurred. One of the authors (W.G.) has performed more than 1,400 carotid compressions in accordance with these criteria, and no patient has suffered any neurological deficit or serious cardiac dysrhythmia.

Comments

Ocular pneumoplethysmography is proposed as a simple, safe, accurate method for screening patients for unilateral carotid occlusion or preocclusive stenosis. In combination with carotid compression, it has proved quite valuable in assessing the tolerance of a cerebral hemisphere to carotid occlusion, whether this be the result of resection, ligation, progression of atherothrombosis, or temporary operative clamping. The instrument is self-contained and portable, and its operation and application are well within the province of paramedical personnel.

References


ALTERATIONS IN BEHAVIOR, BRAIN ELECTRICAL ACTIVITY, CEREBRAL BLOOD FLOW, AND INTRACRANIAL PRESSURE PRODUCED BY TRIETHYL TIN SULFATE INDUCED CEREBRAL EDEMA

LAWRENCE F. MARSHALL, M.D., DEREK A. BRUCE, M.D., DAVID I. GRAHAM, M.B., PH.D., MRC PATH., AND THOMAS W. LANGFITT, M.D.

SUMMARY The interrelationships between cerebral edema, intracranial pressure (ICP), and cerebral blood flow (CBF) were studied in acute and chronic triethyl tin sulfate treated rats. Prior to pentobarbital anesthesia behavioral observations were made. ICP and regional CBF were measured under steady state conditions and brain water content was determined by vacuum drying of the right cerebral hemisphere. Control and chronic animals were neurologically normal. There were two distinct acute groups: (1) acute low pressure (ALP) animals — alert but tetraparetic, and (2) acute high pressure (AHP) animals — deeply stuporous, with minimal pain response and gross EEG slowing. ICP was significantly elevated only in AHP animals.

Introduction

RECENT investigations of cerebral edema have drawn attention to the adverse effects of edema on regional cerebral blood flow (rCBF) and brain metabolism.1,2 Meinig et al.3 found that rCBF was inversely related to tissue water content in global brain edema produced by water intoxication, and Frei et al.,4 from the same laboratory, presented evidence that a reduction in high energy phosphate metabolism occurred in regions adjacent to an acute experimental cold lesion. This impairment of metabolism has been attributed to compression or squeezing of the microcirculation by edematous brain, thus producing local tissue ischemia hypoxia. Because this reduction in high energy metabolism occurred in the absence of a significant increase in intracranial pressure (ICP) or a reduction in the general cerebral perfusion pressure, P5il et al.6 suggested that local increases in tissue pressure, resulting in tissue pressure...
gradients, might be responsible for the impairment of brain function found when brain edema occurred in the absence of large changes in cerebral perfusion pressure. Another explanation for the deleterious effects of edema is a change in the cellular milieu unrelated to changes in local blood flow.

None of the studies reported previously have examined the effects of cerebral edema on neurological function correlated with changes in rCBF in the same model. Moreover, experimental edema has usually been produced in acute models, thus making it impossible to study longitudinally the pathophysiological and functional consequences of edema formation. Since clinical observations have suggested that the time course in the development of edema might be more critical in terms of function than the actual volume change, one purpose of these studies was to compare acute and chronic cerebral edema.

Triethyl tin sulfate induced intramyelinic edema was selected as the model for these studies because previous experiments have shown that the rate of edema formation is dose dependent. The study was designed to correlate the time course of edema formation and its severity, measured by changes in water content, with brain function assessed by rCBF, the EEG, and neurological behavior. We hoped to produce a chronic group of animals with marked edema and little or no increased ICP to be compared with a more acute group with less edema but some intracranial hypertension. We postulated that then we might be able to determine whether: (1) edema per se disturbs brain function; (2) edema reduces CBF without increased ICP, supporting the concept of increased tissue pressure and compression of the microcirculation; or (3) increased ICP produced by edema has a more profound effect on CBF than edema or intracranial hypertension alone.

Methods

Twenty adult Lewis rats (250 to 350 gm) were divided into three groups. Group 1 (six animals) served as a control. Group 2 (nine animals), acute edema, was given water containing triethyl tin sulfate, 40 mg per liter. The animals were allowed to drink ad libitum for nine days. Group 3 (five animals), chronic edema, was given triethyl tin sulfate added to their water at a concentration of 5 mg per liter, and allowed to drink ad libitum for four to five weeks. During the period of triethyl tin ingestion, observations were made on the level of consciousness and running behavior.

At the conclusion of triethyl tin administration each animal was anesthetized with pentobarbital, and the quantity was recorded as another criterion of neurological status. They required about three-fourths of the dose of pentobarbital for induction compared to the control animals. The EEG was normal in all animals. Mean CBF (33.9 ± 4.4 ml/100 gm per minute) was not significantly different from controls (43.6 ± 6.1 ml/100 gm per minute, fig. 1) despite a significant increase in water content compared to control animals (79.2 ± 0.3 versus 76.4 ± 0.5, P < 0.01, fig. 1). These animals were alert but had some weakness of the hindlimbs. They required about three-fourths of the dose of pentobarbital for induction compared to the control animals. The EEG was normal in all animals. Mean CBF (33.9 ± 4.4 ml/100 gm per minute) was not significantly different from controls (43.6 ± 6.1 ml/100 gm per minute, fig. 1) despite an apparent reduction. There also was no significant reduction in gray rCBF for any of the regions sampled. Deep white matter rCBF was reduced, but to a lesser extent than in the other experimental groups (table 1).

The AHP animals were quite different from the ALP group. Although hemispheric water content (79.4 ± 0.3) was almost identical to that of the ALP group (79.2 ± 0.3), ICP was significantly elevated above controls (25.0 ± 10.9 versus 2.17 ± 1.1 cm H2O, P < 0.05, fig. 1). Autoregulation was also noted to be impaired in three of five
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The combination of cerebral edema and elevated ICP produced the greatest reduction in flow. 

The ALP animals had a significant increase in water content. There was an apparent reduction in CBF that did not reach statistical significance. ICP was the same in the ALP and chronic animals, but the volume of edema fluid was larger, and CBF was lower in the chronic compared to the ALP animals. Therefore, it appears that triethyl tin edema per se reduces CBF independent of changes in ICP.

The largest reduction in CBF occurred in the AHP group. The volume of edema fluid in the AHP and ALP animals was nearly equal, but ICP was some 20 cm H2O higher in the former group. Therefore, the decrease in CBF was due to intracranial hypertension superimposed on edema. In normal animals this level of increased ICP would have no effect on CBF because of intact cerebral autoregulation. In the AHP animals, however, there was indirect evidence that autoregulation was defective (ICP varied with changes in SAP). Therefore, we can conclude that the reduction in CBF in this group is due to a combination of edema and defective autoregulation to increased ICP.

Despite the largest increase in water content in the chronic animals, the EEG was normal, and neurologically they were indistinguishable from controls. Therefore, triethyl tin edema does not disturb brain function as long as the CBF is adequate. In the AHP animals, in contrast, the volume of edema was less than in the chronic animals, but these rats were lethargic, and the EEG was abnormal. One can infer from these observations that not only was CBF reduced in the AHP group, it was reduced below the critical level required to maintain normal brain function.

Therefore, a marked increase in brain water content produced by triethyl tin intoxication (chronic animals) reduces CBF independent of ICP, but CBF is not reduced below the critical level of O2 required by the brain, since the animals were functionally normal. Also, the intramyelinic white matter edema produced by triethyl tin does not alter the water and electrolyte milieu of the axon sufficiently to produce dysfunction as long as CBF is adequate to meet the metabolic needs of these axons and their somata of origin.

Discussion

There are many experimental models of cerebral edema that simulate clinical edema to varying degrees. A disadvantage of triethyl tin edema is that there is no known clinical counterpart. The advantages of the model are that acute and chronic edema can be produced with the same agent, edema is confined to white matter so that rCBF and other variables are indistinguishable from controls. Therefore, triethyl tin edema does not disturb brain function as long as CBF is adequate. In the AHP animals, in contrast, the volume of edema was less than in the chronic animals, but these rats were lethargic, and the EEG was abnormal. One can infer from these observations that not only was CBF reduced in the AHP group, it was reduced below the critical level required to maintain normal brain function.

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Table 1  rCBF in Control and Acute Triethyl Tin Fed Animals

<table>
<thead>
<tr>
<th>Region</th>
<th>Control (n=5)</th>
<th>ALP (n=5)</th>
<th>ACH (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior frontal gray</td>
<td>49.8 ± 7.5</td>
<td>34.6 ± 3.7 (NS)</td>
<td></td>
</tr>
<tr>
<td>Posterior frontal gray</td>
<td>47.6 ± 7.6</td>
<td>29.3 ± 3.2 (P &lt; 0.05)</td>
<td></td>
</tr>
<tr>
<td>Caudate</td>
<td>51.8 ± 8.1</td>
<td>25.0 ± 3.2 (P &lt; 0.01)</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>54.0 ± 10.0</td>
<td>35.8 ± 7.4 (NS)</td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td>38.5 ± 5.9</td>
<td>20.6 ± 3.3 (P &lt; 0.05)</td>
<td></td>
</tr>
<tr>
<td>Internal capsule</td>
<td>29.6 ± 5.6</td>
<td>8.9 ± 2.0 (P &lt; 0.01)</td>
<td></td>
</tr>
<tr>
<td>Deep white</td>
<td>28.1 ± 7.1</td>
<td>7.0 ± 1.1 (P &lt; 0.01)</td>
<td></td>
</tr>
</tbody>
</table>

The largest reduction in CBF occurred in the AHP group. The volume of edema fluid in the AHP and ALP animals was nearly equal, but ICP was some 20 cm H2O higher in the former group. Therefore, the decrease in CBF was due to intracranial hypertension superimposed on edema. In normal animals this level of increased ICP would have no effect on CBF because of intact cerebral autoregulation. In the AHP animals, however, there was indirect evidence that autoregulation was defective (ICP varied with changes in SAP). Therefore, we can conclude that the reduction in CBF in this group is due to a combination of edema and defective autoregulation to increased ICP.

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Table 3  rCBF in ALP Animals Compared With Chronic Triethyl Tin Fed Animals

<table>
<thead>
<tr>
<th>Region</th>
<th>ALP (n=5)</th>
<th>Chronic (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior frontal gray</td>
<td>48.8 ± 7.5</td>
<td>34.6 ± 3.7 (NS)</td>
</tr>
<tr>
<td>Posterior frontal gray</td>
<td>37.2 ± 7.3</td>
<td>29.3 ± 3.2 (NS)</td>
</tr>
<tr>
<td>Caudate</td>
<td>39.2 ± 5.3</td>
<td>23.0 ± 3.2 (P &lt; 0.05)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>48.3 ± 9.9</td>
<td>35.8 ± 7.4 (NS)</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>36.9 ± 5.1</td>
<td>20.6 ± 3.3 (P &lt; 0.05)</td>
</tr>
<tr>
<td>Internal capsule</td>
<td>18.4 ± 3.9</td>
<td>8.9 ± 2.0 (P &lt; 0.05)</td>
</tr>
<tr>
<td>Deep white</td>
<td>12.6 ± 2.8</td>
<td>7.0 ± 1.1 (P &lt; 0.05)</td>
</tr>
</tbody>
</table>

In four of seven regions rCBF was significantly lower in the chronic animals despite no difference in ICP between the groups.
What is the mechanism for reduction of CBF in edematous brain when ICP is normal? In a previous report, we presented evidence that cerebral edema, without increased ICP, reduced CBF in patients with a variety of acute brain insults. Following the administration of hypertonic mannitol in these patients, CBF increased by as much as 100%, whether ICP was reduced or remained the same after mannitol administration. We postulated that the reduction in CBF was due to pericapillary edema that compressed the microcirculation and reduced CBF, even though the volume of edema was not sufficient to increase ICP as measured from a lateral ventricle. These clinical observations were a major reason for undertaking the present animal experiments, and the reduction in CBF in the rats could be on this basis. However, rCBF was reduced in gray matter, particularly the caudate, in chronic animals without increased ICP (table 2) despite the fact that triethyl tin edema is confined largely to the white matter. If the caudate is not edematous and ICP is normal, why is rCBF in the caudate reduced? The data do not provide a firm answer. Figure 2 shows gross expansion of the white matter that does not require a measurement of water content to prove the presence of white matter edema. Perhaps the microcirculation of the nonedematous deep gray structures is reduced in volume by expansion of the white matter that compresses the circulation within the caudate even though ICP is not elevated. To this point in the discussion we have concluded that either edema or increased ICP can reduce CBF. This compression phenomenon may be a third mechanism to explain a focal reduction in CBF.

Finally, the large reduction in CBF in edematous white matter might be a function of the increase in white matter volume without any interference with blood flow through the microcirculation. White matter is grossly expanded by the increase in fluid content (fig. 2), and the intercapillary distance is increased. Since CBF is measured as volume of flow per weight of tissue per unit time, an increase in tissue volume (weight) uncompensated by an increase in capillary density and blood flow through each capillary will be recorded as a decrease in flow per weight per time. This is not an artifact of the methodology but a reflection of the true anatomical situation; the volume of the brain is increased with edema fluid, but the number of capillaries and the flow through them is the same as in the pre-edematous state. This explanation of our findings requires further investigation; if it is correct, the actual flow through a vascular bed in edematous brain, using any diffusible material, cannot be determined unless the increase in the volume of tissue supplied by that vascular bed can be calculated.

Acknowledgment

Ms. Wendy Rieder, Mr. Frank Harper, and Mrs. Helen Hyder provided invaluable assistance.

Figure 2 C14-antipyrine autoradiographs in (a) control animal, (b) ALP triethyl tin sulfate treated animal, (c) AHP triethyl tin sulfate treated animal and (d) chronic triethyl tin sulfate treated animal. There is significant edema of the white matter in all the experimental animals, but the combination of edema and a significant elevation in ICP present in (c) yields the greatest decrease in flow.
MICROCIRCULATORY OBSTRUCTION IN FOCAL CEREBRAL ISCHEMIA/Little et al.

References


Microcirculatory Obstruction in Focal Cerebral Ischemia: An Electron Microscopic Investigation in Monkeys

JOHN R. LITTLE, M.D., FREDERICK W. L. KERR, M.D., AND THORALF M. SUNDT, JR., M.D.

SUMMARY The fine structure of the microvasculature in areas of focal cerebral ischemia was studied in squirrel monkeys and the changes in areas of impaired and unimpaired microvascular filling, as defined by carbon perfusion, were compared. Microcirculatory obstruction became evident three hours following middle cerebral artery (MCA) occlusion and appeared to be partly the result of compression of capillaries by perivascular glial swelling and developing cerebral edema. Slight endothelial swelling was a common finding. Intraluminal membrane-bound bodies were occasionally identified but they did not appear to be producing significant obstruction. The tight endothelial junctions remained intact and there was no evidence of accelerated microcytosis. Severe neuronal injury frequently preceded the development of the microvascular obstruction and was more widespread than the zones of impaired perfusion.

The main steps in the procedure were as follows. (1) The right middle cerebral artery (MCA) in eight squirrel monkeys was occluded with a miniature aneurysm clip through a transorbital exposure. (2) Arterial blood samples (0.3 ml) were taken hourly for the determination of pH, Pao2, and Paco2. Rectal temperature and arterial blood pressure were constantly monitored. (3) Animals in groups of two were perfused after ischemic periods of 90 minutes, three hours, six hours, and 12 hours. They were initially perfused with 100 ml normal saline followed immediately by a mixture of colloidal carbon (250 ml) and phosphate-buffered 4% paraformaldehyde (250 ml). The clip was removed immediately prior to perfusion. (4) The brains were left undisturbed for two hours following perfusion. Then they were carefully removed from the skulls and placed in jars containing 50 ml phosphate-buffered 4% paraformaldehyde at 4°C for 24 hours. (5) The brains were cut coronally into 5 mm slices and the tissue was examined macroscopically. Thin (5 μ and 25 μ) coronal sections were prepared from paraffin-embedded slices of both hemispheres and stained with hematoxylin and eosin and with thionine. (6) Multiple specimens were taken from the gray and white matter of both hemispheres of each brain. Tissue was taken from the poorly stained, intermediate, and surrounding well-stained areas of those brains which had macroscopic evidence of impaired perfusion. It was postfixed in phosphate-buffered 1% osmium tetroxide for two hours and embedded in epon. The ultrathin sections were stained with uranyl acetate (2%) and lead citrate (0.1%).

METHODS

The techniques used for the production of the ischemic lesions and carbon perfusion have been described in detail.

From the Cerebrovascular Clinical Research Center and the Department of Neurologic Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901.

This investigation was supported in part by Grant NS 6663 from the National Institutes of Health, Public Health Service.

PROGRESSIVE microcirculatory obstruction in areas of focal cerebral ischemia has been demonstrated with the carbon perfusion technique by Crowell and Olsson and by Little and associates. Light microscopic examination has shown that the obstruction lies primarily at the capillary level and appears to be related to compression of the capillary channels by the developing cerebral edema. Severe neuronal alterations were invariably identified before the development of the parenchymal vessels does not play a primary role in the production of a cerebral infarct.

The object of this investigation was to study the fine structure of the microvasculature in areas of focal cerebral ischemia and to define the nature of the microcirculatory obstruction. The relationship between the parenchymal changes and the developing obstruction was also studied in order to elucidate further the significance of the obstruction.

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L F Marshall, D A Bruce, D I Graham and T W Langfitt

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