Cerebral Edema Associated With Craniectomy and Arterial Hypertension

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SUMMARY The present studies were performed to determine whether cerebral edema will develop as a consequence of arterial hypertension and/or craniectomy. Arterial hypertension was induced for 30 minutes by inflation of a balloon catheter situated in the descending aorta, and a parietal craniectomy was performed. The cerebral edema noticed was evaluated by macroscopic and microscopic observations, BBB permeability of HRP and Evans blue and water content. In addition, ICP was measured in the cisterna magna and ICPP by a catheter-tip transducer. In arterial hypertension or craniectomy alone, some small areas of Evans blue extravasation with increased water content were seen in the cortex, which corresponded to the occipito-parietal parts of the arterial boundary zones. In contrast, when arterial hypertension was combined with craniectomy, these lesions extended further into underlying white matter with increased water content. Forty-eight hours later, extensive brain edema with a shift of midline structures developed on the side of craniectomy which differed from that in arterial hypertension or craniectomy alone. It is suggested that some hydrostatic pressure gradients, particularly between blood vessel and surrounding extracellular space and among different areas within the brain parenchyma, may play an important role in the development of brain edema.

CEREBRAL EDEMA still remains a formidable clinical problem despite many years of study. Detailed information on basic mechanisms involved in edema development are needed to provide new approaches to more rational therapeutic modalities.

Experimentally, the investigation of brain edema has been based on a large number of experimental models of brain edema. It is generally considered that many factors known to modify the edema process include cerebrovascular permeability, cerebrovascular hydraulic conductivity, brain metabolism, tissue hydraulic conductivity and compliance, tissue and cerebrovascular osmotic and hydrostatic pressure, cerebral spinal fluid production (CSF) rate and pressure, and pathway for CSF excretion through arachnoid villi. Recently, some workers have demonstrated that bulk flow is a major mechanism for edema formation and extension. Hydrostatic pressure gradients may be crucial in the formation of cerebral edema.

The experiment reported here was designed to study pathophysiologically whether changes in hydrostatic pressure gradients lead to cerebral edema in normal brain. Cranioectomy and arterial hypertension were employed to control the changes in hydrostatic pressure.

Material and Methods

Surgical Protocol

The experiments were performed on adult cats weighing 2.1 to 4.0 kg. The animals were anesthetized with an intramuscular injection of Ketamine hydrochloride (10–15 mg/kg). A femoral vein was cannulated to infuse various drugs as necessary. Blood gases and body temperature were maintained within physiological limits. The heads of the cats were placed in a stereotactic frame. Arterial hypertension was induced by inflation of a double lumen balloon situated in the descending aorta immediately distal to the left subclavian artery, which caused a blood shift as a result of total aortic obstruction as previously described by Mangeau et al. The blood pressure was measured by the balloon catheter, and systolic blood pressure above 250 mmHg was maintained for 30 minutes. A craniectomy, approximately 2.5 × 2.0 cm, was made on the right parietal bone dorsal to the coronal suture. Great care was taken to avoid damaging the brain during the procedure. The scalp wound was then closed. All surgical maneuvers were performed with aseptic technique. Animals were divided into the following 4 groups: Group 1, sham-operated controls (n = 13); Group 2, arterial hypertension alone for 30 minutes (n = 21); Group 3, craniectomy alone (n = 27);
Group 4, craniectomy followed by arterial hypertension for 30 minutes (n = 31).

**Permeability to Evans Blue and Brain Water Determinations**

Forty-two cats were used to examine the morphology with permeability to Evans blue and tissue water content. Two percent Evans blue (2 ml/kg) was administered intravenously before the protocol. Animals were sacrificed at 1 and 48 hours after the procedures, and the brains were quickly removed. The location and magnitude of Evans blue extravasation and the degree of brain swelling were inspected grossly on the surface and coronal slices of each brain. Afterward, water content was determined by wet/dry weight measurement in each group. Water content was measured in cats with Evans blue extravasation and in the sham-operated cats. Tissue samples weighing 150 to 250 mg from right frontoparietal lobes with or without Evans blue extravasation were dissected in a humid chamber. The samples were dried in an oven at 95°C, and tissue water content was calculated according to Elliot and Jasper. The statistic test used to analyze the data was the Student’s t-test.

**Histological Examination**

Fourteen cats were used for histological examination by light microscope and electron microscope. The animals were perfused at 1 and 48 hours after the procedures with 1.2% glutaraldehyde in 0.075 M phosphate buffer (pH 7.45; 320 mOsm) by way of cannula inserted through the left ventricle into the ascending aorta with a balloon catheter used to induce arterial hypertension. ICP was measured from the descending aorta via the balloon catheter used to induce arterial hypertension. ICP was measured by a catheter-tip transducer (TCP2, 6F30, TOYODA), as has been previously demonstrated by Clark et al. The pressure sensor used was a silicon half-bridge strain gauge with 1.6 mm diameter. The catheters were stereotactically introduced through small burr holes into three different sites; i.e., two at the anterior ectosylvian gyri on both hemispheres and one at the posterior suprasylvian gyrus in the right hemisphere. The burr holes were sealed with bone wax.

The intracranial pressure (ICP) was measured before, during and 6 hours after the procedures only in 6 animals with craniectomy followed by arterial hypertension for 30 minutes. ICP was recorded as cerebrospinal fluid pressure in the cisterna magna with a 21 gauge needle connected to a pressure transducer. ABP was measured from the descending aorta via the balloon catheter used to induce arterial hypertension. ABP was measured as mean ± standard error (SE) and statistical comparisons were made with Student’s t-test.

**Results**

1. **Neuropathological Observations**

A. Gross morphological changes with the extravasation of Evans blue. In the four control brains, no abnormalities were seen. In 8 of the 10 cats sacrificed 1 and 48 hours after arterial hypertension alone, several small areas of Evans blue extravasation were usually located symmetrically in the posterior suprasylvian gyrus, and/or posterior lateral gyrus (fig. 1). Even in the 4 cats 48 hours after arterial hypertension, the blue staining rarely extended into the underlying white matter, and there was no gross swelling or shift of the midline structures. After craniectomy alone, on the other hand, 8 of the 16 cats sacrificed 1 and 48 hours later had some small areas of Evans blue extravasation, most commonly in the posterior suprasylvian gyrus on the side of the craniectomy (fig. 2). The exudation of Evans blue was rarely found in the brain underneath the bone defect. The extension of the dye was also limited to the cortical gray matter in 4 cats 48 hours after craniectomy alone. These findings were approximately similar to those with arterial hypertension. In contrast, in 5 of the 6 cats sacrificed 1 hour after combined arterial hypertension and craniectomy, some areas of Evans blue extravasation occurred predominantly in the posterior suprasylvian gyrus and/or poste-
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FIGURE 1. Gross view of the cat brain 1 hour after arterial hypertension. Note several small blue-stained areas in the bilateral posterior suprasylvian gyrus, left posterior ectosylvian gyrus and right middle suprasylvian gyrus.

The lesions extended into the underlying white matter. In 5 of the 6 cats 48 hours after the combined procedure, diffuse faintly blue-stained areas were observed in the cerebral hemisphere on the side of craniectomy in addition to the spotty Evans blue staining as seen 1 hour after procedures. Furthermore, all of the brains had gross cerebral hemisphere swelling with detectable shift of midline structures away from the side of craniectomy (fig. 3). These findings definitely differed from those with arterial hypertension alone or craniectomy alone.

B. Histological findings. In animals sacrificed 1 hour after arterial hypertension alone, section of tissue from the Evans blue permeable cortical areas showed narrow spaces around some arterioles and capillaries (fig. 4A). By electronmicroscopy, there was slight swelling of perivascular astrocytic foot processes. There was no evidence of vascular narrowing or obstruction. The neurons and astrocytes appeared normal. Similar changes were also seen 48 hours after hypertension alone. These same findings were similar to those seen after craniectomy alone.

After combined craniectomy and arterial hypertension, on the other hand, in Evans blue stained areas of animals sacrificed after 1 hour, some neurons were swollen and many periarteriolar and pericapillar halos were seen in the cortex. By electronmicroscopy, numerous perivascular astrocytic processes were swollen and the lumen of capillaries were irregularly deformed and narrowed. In the underlying white matter, pallor of myelin staining and a pronounced degree of vacuolation were seen. In contrast, 48 hours after the combined procedure, tissue sections of occipital lobe with Evans blue extravasation showed extreme ischemic change. The majority of neurons were shrunken and there was prominent vacuolation of neuropil. By electronmicroscopy, shrunken and dark neurons surrounded by massive astrocytic swelling were seen. The perivascular glia processes were extremely swollen and the capillary lumens were reduced to slits. The cytoplasm of endothelial cells and pericytes were dam-

FIGURE 2. Surface (A) and coronal section (B) of the cat brain 1 hour after craniectomy. Note a few small blue-stained areas in the cortical gray matter of the posterior suprasylvian gyrus and middle ectosylvian gyrus on the side of craniectomy.
aged (fig. 5). Marked spongiform changes were seen in the subcortical white matter of the frontoparietal lobe in addition to that of the occipital lobe (fig. 4B).

C. Electronmicroscopic study of BBB permeability to HRP. In control animals, there was no electron opaque reaction product in the vascular walls or neuropil. The animals with arterial hypertension alone showed the reaction product also between the surrounding cellular processes in addition to the basement membranes of arterioles and capillaries. Some pinocytotic vesicles containing reaction product were present within some endothelial cells of arterioles and capillaries (fig. 6A). These findings were similar to those with craniectomy alone.

In animals with combined craniectomy and arterial hypertension, on the other hand, the reaction products were constantly observed in the endothelial basement membrane of vessels and also between the surrounding cellular processes. Furthermore, reaction products spread through the intercellular spaces in the neuropil (fig. 6B). A number of pinocytotic vesicles filled with electron opaque material were noted within the cytoplasm of the endothelial cells. Although reaction product was sometimes observed between endothelial cells, there was never a continuous column of reaction products extending from the vessel lumen to the subendothelial basement membrane.

2. Water Content in Brain Tissue

The water content in the brain tissue from frontal and occipital lobe in each group is summarized in table 1. The values of sham-operated cats were compared with those of animals with hypertension, craniectomy and both. In animals with arterial hypertension or craniectomy alone, there was a significant increase in water content in the Evans blue stained areas of occipital lobe 1 hour after the procedure. Forty-eight hours after, however, water content in the same areas were not different from those of control cats. There were no significant changes in the unstained brain tissues of frontal lobe.

In animals with combined arterial hypertension and craniectomy, however, the increase of tissue water was highly significant in the cortex and white matter of the cat brain 48 hours after arterial hypertension and craniectomy.
the occipital lobe with Evans blue extravasation 1 hour after procedures. Furthermore, water content from frontal and occipital lobes were also significantly high 48 hours after the procedures.

3. Neurophysiological Observations

The initial mean resting ABP was 142 ± 6 mmHg. The ABP was not significantly changed by craniectomy. Occlusion of the descending aorta by balloon inflation resulted in a significant increase of blood pressure of 55 mmHg ± 8 SE (p < 0.001) for 30 min. The systolic blood pressure remained constant at 293 ± 9 mmHg during this procedure. Afterward, mean ABP returned to the level of 132 ± 12 mmHg and did not change significantly throughout the experiment.

In normal animals (n = 5), there was no significant change in the ICPP among the different areas tested over 1 hour. The control value of ICPP was 6.1 ± 1.1 mmHg. Animals with arterial hypertension alone (n = 5) showed no differences in ICPP between the two hemispheres or the two areas of the same hemisphere for 1 hour after the procedure, despite a significant increase in the pressure of 2.6 ± 0.4 mmHg (p < 0.05) during arterial hypertension. On the other hand, animals with craniectomy alone (n = 5) had significant reductions in ICPP of 2.1 ± 0.2 mmHg (p < 0.01) in the craniectomized hemisphere for 1 hour after the procedure. However, no pressure difference was observed between the two different areas within the same craniectomized hemisphere.

In contrast, when craniectomy was followed by arterial hypertension (n = 7) pressure gradients developed between the two areas within the craniectomized hemisphere as well as the two hemispheres. The maximal mean value of the pressure gradient was 2.3 ± 0.5 mm Hg (p < 0.01) between the anterior ectosylvian gyrus of two hemispheres and 1.1 ± 0.3 mmHg between the anterior ectosylvian and posterior suprasylvian gyrus of the craniectomized hemisphere (fig. 7). The lowest ICPP value was observed at the posterior suprasylvian gyrus of the craniectomized hemisphere. These parenchymal pressure gradients decreased gradually and showed a tendency to disappear within 1 hour after the procedure.

In animals with combined craniectomy and arterial hypertension (n = 6), ICP was decreased significantly from 5.6 ± 0.4 mmHg before to 3.8 ± 0.3 mmHg after craniectomy. During induced hypertension, however, ICP was elevated to 6.3 ± 0.6 mmHg. Afterward, ICP gradually declined to 3.9 ± 0.3 mmHg and was constantly maintained at a significantly low level for 3 to 6 hours after the procedures. Then, the value was approximately equal to that after craniectomy but before hypertension (fig. 8).
Table 1: Regional Percentage Water Content of Brain Tissue

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>n</th>
<th>Right frontal lobe</th>
<th>Right occipital lobe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cortex</td>
<td>White water</td>
</tr>
<tr>
<td>Control</td>
<td>1 hr</td>
<td>4</td>
<td>79.7 ± 1.8</td>
<td>69.3 ± 1.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 hr</td>
<td>4</td>
<td>80.0 ± 1.5</td>
<td>70.3 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>48 hr</td>
<td>4</td>
<td>79.9 ± 1.4</td>
<td>69.5 ± 1.8</td>
</tr>
<tr>
<td>Craniectomy</td>
<td>1 hr</td>
<td>4</td>
<td>80.4 ± 1.5</td>
<td>69.8 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>48 hr</td>
<td>4</td>
<td>80.5 ± 0.9</td>
<td>70.3 ± 1.6</td>
</tr>
<tr>
<td>Craniectomy and</td>
<td>1 hr</td>
<td>4</td>
<td>79.9 ± 2.0</td>
<td>69.1 ± 2.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>48 hr</td>
<td>5</td>
<td>83.0 ± 1.2*</td>
<td>74.0 ± 1.3*</td>
</tr>
</tbody>
</table>

Data presented is mean ± standard deviation; n = number of animals. % gm H2O/gm tissue.
Time = hours after insults. *Value is significant from controls (p < 0.01).

Discussion

Several authors have described brain edema associated with arterial hypertension, craniectomy and/or trauma.11,12,16 Concerning brain edema produced by arterial hypertension, extravasation of Evans blue-bound albumin or HRP has been observed in various experimental models of acute arterial hypertension.10 The pathogenetic mechanism of BBB lesions in acute hypertension has been assumed to be vascular distension caused by the high intraluminal pressure. Our study of arterial hypertension showed that the extravasation of macromolecules with increased water content was induced by an increase of blood hydrostatic pressure. These blue-stained areas seem to correspond mostly to the occipito-parietal parts of arterial boundary zones. This is in line with the “dead points” explanation of Gannushkina et al9 that the greatest vulnerability of the arteries is a result of a maximal increase of intraluminal pressure during arterial hypertension. We also assume that BBB lesions can be induced by the increase in the transmural hydrostatic pressure gradient due to arterial hypertension. In addition, the lower hydraulic resistance in the arteries of arterial boundary zones may be in part connected with those lesions.

On the other hand, Schutta et al16 demonstrated that no swelling was seen in the cat brain if the craniectomy was performed with great care. However, in our study, despite the fact that craniectomy was performed with meticulous care to the brain, some small areas of Evans blue extravasation with increase in water content were found in the cortex on the side of craniectomy. The histological alterations found in these lesions were essentially the same, though somewhat less obvious, as those in arterial hypertension alone. The pathogenetic mechanism of these BBB lesions is not known. The change of the tissue pressure and intracranial pressure brought about when the cranium is an open box may be related to these lesions. Cooper et al demonstrated that craniectomy enhanced cold induced edema formation in experimental animals. They suggested that it may be caused by a decrease in the interstitial fluid pressure, based on measurements of ICP. In our measurements of the regional pressure within the brain parenchyma, the parenchymal pressure was found to differ between the two hemispheres by induced craniectomy. Although the decrease in parenchymal pressure by craniectomy was much smaller as compared to the increase in the intraluminal pressure produced by arterial hypertension, the transmural hydrostatic pressure gradient, i.e., the difference between the intravascular and extracellular pressure, was found to increase even in craniectomy alone. We assume that these BBB lesions may also be primarily produced by the increase in the transmural hydrostatic pressure gradient, similar to arterial hypertension.

In contrast, the present study with combined arterial hypertension and craniectomy demonstrated focal brain edema at an early stage. The lesions with increased permeability of BBB to Evans blue and HRP were produced in some areas of the cortex which corresponded to the occipito-parietal arterial boundary.
zones. These lesions are markedly intensified as compared to those induced by arterial hypertension or craniectomy alone, and extend further into the underlying white matter with increased water content. Histologically, the lumen of capillaries and arterioles were narrowed by the swollen perivascular astrocytic processes in the cortex and spongiosis were seen in the underlying white matter. There was no area of necrosis.

The mechanism of this focal edema produced by arterial hypertension and craniectomy seems to be different from vasogenic edema in the cold-induced model. Trauma to brain and arterial hypertension has been shown to cause brain edema in experimental studies. Marshall et al\(^1\) reported that arterial hypertension followed by trauma (jets of nitrogen gas) to the exposed brain of cats produced brain swelling. Schutta et al\(^1\) demonstrated that edema occurred in the cerebral cortex and underlying white matter within less than one hour when the brain was deliberately injured with craniectomy and blood pressure was acutely raised. The brain edema associated with arterial hypertension following trauma has been assumed to be caused by bulk or regional vasoparalysis followed by increasing intraluminal pressure. However, the present study indicates clearly that arterial hypertension following craniectomy differs from trauma to the brain in producing focal brain edema. The possible mechanism causing focal edema is not known.

According to our parenchymal pressure measurements, the parenchymal pressure gradients were noticed even between an arterial boundary zone and a nonboundary zone within the cranietomized hemisphere, in addition to between the two hemispheres. The gradient seems to be possibly due to the transient increase in the volume of cerebral vascular bed, i.e. vascular engagement, as has been thought to be caused by craniectomy or acute arterial hypertension.\(^3\) The lowest level of parenchymal pressure was at the occipital parts of the cranietomized hemisphere. Therefore, it is supposed that the greater degree of leakage of edema fluid originates from blood vessels into surrounding extracellular spaces by the increased transmural hydrostatic pressure gradient, as compared to arterial hypertension or craniectomy alone. Furthermore, the edema fluid may migrate from the areas supplied by the abundant arteries to relatively avascular areas according to parenchymal pressure gradients, preferentially through the extracellular space of the white matter rather than the gray matter.

Furthermore, the present study indicates that at later stages craniectomy followed by arterial hypertension resulted in extensive edema of the whole hemisphere with the shift of midline structures away from the side of craniectomy, as was not seen with arterial hypertension or craniectomy alone. The histological findings demonstrated that the nerve cells were shrunken and the lumens of capillaries were reduced to slits by the extreme swelling of perivascular glia. The obvious ischemic change of neural elements was observed in the blue-staining cortical lesions. It is not clear why these focal lesions result in the development of delayed diffuse hemispheric edema. According to the histological finding at the early and late stages of the cortical lesions in this study, intense accumulation of fluid in brain tissue may compress the blood vessels, thus leading to the subsequent decrease in cerebral blood flow. This may cause a secondary metabolic disturbance of tissue, resulting in the further development of extensive cerebral edema. In addition, in our observation of ICP, the CSF pressure continued to be below the control for a long time after the procedures. As bulk flow has been considered to be a main mechanism for vasogenic edema spreading through the white matter by some authors,\(^15\) the spreading of this edema may follow the pressure gradient between the tissue in the edematous areas and CSF pressure for a long time even though the pressure gradients in the brain parenchyma produced at the early stage dissipate within a few hours.

The present experiments suggest that some hydrostatic pressure gradients which were produced between blood vessel and surrounding extracellular space, among neighboring parenchymas within the same hemisphere, between the two hemispheres and between the edematous areas and CSF, may play an important role in the development of brain edema. The developmental mechanism of this cerebral edema may be appropriately described as hydrostatic cerebral edema, to be distinguished from vasogenic or cytotoxic types as classified by Klatzo.\(^9\)

Acknowledgment

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References

Simultaneous Therapy with Antiplatelet and Anticoagulant Drugs in Symptomatic Cardiovascular Disease

ARNOLD MILLER, M.B., CH.B., FRCS, AND ROBERT S. LEES, M.D.

SUMMARY  Twenty of approximately 1000 patients attending the arteriosclerosis clinic at MIT during a 13 year period were treated simultaneously with aspirin and warfarin for symptomatic atherosclerotic (19) or rheumatic (1) heart or vascular disease. The average duration of therapy was 5.8 years. Thirteen patients suffered from familial hyperlipoproteinemia; only one patient had none of the major risk factors for arteriosclerosis. Refractory symptoms were related to the central nervous system in 13, peripheral vascular system in 5 and the heart in 2. All twenty patients became asymptomatic or showed marked clinical improvement on aspirin plus warfarin therapy. While on this therapy, complications, both thrombotic and hemorrhagic, occurred in 7 of the 20 patients (graft embolus in 1, and bleeding in 6; with one death as a result of intracranial bleeding) and sudden death, probably from acute myocardial ischemia, in a further 2 patients. We conclude that when alternative therapies are impossible or have proven to be of no avail in patients suffering from the complications of advanced arteriosclerosis, the simultaneous administration of aspirin and warfarin may be a therapeutic alternative, although very close and careful followup of the patients' prothrombin times and clinical status is essential.

PATIENTS WITH ADVANCED ATHEROSCLEROSIS which affects multiple organ systems present a major therapeutic challenge. In these patients, commonly accepted modalities of treatment are often either ineffective or, in the case of surgery, impracticable. For instance, vasodilator and anticoagulant drugs may not alleviate symptoms of end organ ischemia, nor prevent thromboembolism to distal vessels. Surgical relief of atherosclerotic occlusive disease may be impossible or contraindicated by the extent or severity of accompanying disease. In transient cerebral ischemia, antiplatelet or antithrombotic drugs are given, and often provide symptomatic relief. Such drugs are also frequently used in coronary and peripheral arterial disease, even when symptomatic improvement does not accompany their use. In many patients with cerebral arterial disease as well, neither anticoagulants nor antiplatelet drugs produce relief of symptoms. The simultaneous use of both antiplatelet and anticoagulant therapy has generally been considered too dangerous, as reflected by the paucity of reports in the literature.

We present here a retrospective study of a group of patients with vascular disease treated with a combina-
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