Biomechanics of Brain Edema in Acute Cerebral Ischemia in Cats

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We studied whether the biomechanical properties of brain play an important role in the development of early ischemic brain edema in cats with middle cerebral artery occlusion. Brain tissue pressure, tissue compliance, and tissue resistance were measured from the gray matter in the core and the periphery of the middle cerebral artery territory for 6 hours after occlusion. Regional cerebral blood flow and water content were also measured from the same areas. Ventricular fluid pressure was recorded. Tissue pressure rose gradually in the core, where flow was 6 ml/100 g/min, over 4 hours and then stabilized. The pressure gradient measured between edematous tissue and ventricular fluid was 5.3 mm Hg. Tissue resistance increased 1 hour after occlusion when water content increased to 10 mg/g. Later, when water content increased by 40 mg/g, tissue resistance decreased and tissue compliance increased significantly. In the periphery, where flow was 17.6 ml/100 g/min, tissue pressure rose slightly while tissue compliance and tissue resistance did not change within 6 hours. Our data indicate that as ischemic injury progresses, edema fluid accumulates in highly compliant brain parenchyma, then migrates through highly conductive tissue into the cerebrospinal fluid spaces, driven by the hydrostatic pressure gradient between the edematous tissue and the cerebrospinal fluid. (Stroke 1988;19:91-97)

Water movement across a functional blood-brain barrier into the brain parenchyma follows the Starling equation. Many factors can modify the edema process, but their contributions to the formation and resolution of edema are poorly understood. These factors include cerebrovascular permeability and capillary hydraulic conductivity, hydrostatic and osmotic pressure gradients, tissue compliance and conductivity, and brain metabolism.

The mechanism for movement and resolution of vasogenic edema is thought to depend mainly on biomechanical and hydrodynamic properties of brain tissue. In addition, elastic and plastic mechanical properties of brain are known to change in the pre-edematous state.

We recently demonstrated that a cortical tissue pressure gradient develops within ischemic cortex and that the gradient is associated with ischemic brain edema. Moreover, the magnitude of the gradient is related to the severity of ischemic edema in that tissue, but the biomechanical properties of ischemic brain tissue, in particular tissue elastic compliance and tissue hydraulic resistance, still remain unclear.

The present experiment was designed to study whether the biomechanical properties of brain parenchyma play an important role in the development of early ischemic brain edema. We sought to clarify the relation between brain tissue pressure (TP), tissue compliance (TC), tissue resistance (TR), ischemic edema, and blood flow in adjacent cortical gray matter made variably ischemic.

Materials and Methods

Surgical Preparation

Adult cats (2.0–4.5 kg) were anesthetized with 30 mg/kg i.p. sodium pentobarbital. Cannulas were placed in the femoral artery and vein to measure systemic arterial pressure; to sample arterial blood gases, hematocrit, and serum osmolality; and to administer drugs as necessary. All cats underwent tracheostomy, were paralyzed with 1.5 mg/kg i.v. gallamine triethiodide, and were mechanically ventilated with a Harvard respirator (South Natick, Massachusetts). Each cat was held in the sphinx position by a stereotactic apparatus. Body temperature and blood gases were maintained within physiologic limits by a heating pad and ventilator adjustment, respectively. End-tidal carbon dioxide was continuously monitored and maintained within the physiologic range.

Two small burr holes were made in the left temporo-parietal area to accommodate apparatus for the measurement of TP, TC, TR, and regional cerebral blood flow (rCBF). The first burr hole was posterior to the coronal suture exposing the anterior lateral gyrus, anatomically a “peripheral area” of the middle cerebral artery (MCA) territory in cats. The second burr hole was posterior to the zygomatic bone to expose the sylvian gyrus, anatomically a “central core area” of the MCA territory. A burr hole was also made in the right parietal bone at coordinates A12, L4.5, H8 to accommodate a needle system for the measurement of ventricular fluid pressure (VFP). All exposed regions were sealed with moistened oxidized cellulose and dental cement.

The left MCA was exposed by the transorbital approach. After the dura was opened and the arachnoid...
membrane incised, the MCA was occluded with bipolar coagulation proximal to the lateral lenticulostriate artery. The dural opening was then sealed with oxidized cellulose and rapid-drying tissue glue.

**Tissue Pressure and Ventricular Fluid Pressure**

TP was measured with our modified needle system previously described elsewhere. Briefly, a Statham P23dB pressure transducer (Cleveland, Ohio) was connected to a 1-ml syringe, held in a Harvard constant infusion pump, and attached to a needle (o.d. = 0.635 mm, i.d. = 0.343 mm). Connections were made via PE-50 tubing through a three-way stopcock attached to a transducer; the system was filled with saline free of air bubbles. Needles were introduced with the aid of a surgical microscope from an oblique angle into the cortex. The data were discarded if bleeding around the tip of a needle was detected at that time or if Evans blue staining in the area was observed later.

VFP was recorded from the right lateral ventricle. A 23-gauge needle was inserted stereotactically into the right lateral ventricle and connected to a Statham P23ID transducer by polyethylene tubing. All pressure systems were zeroed at the level of the interaural line.

**Brain Tissue Compliance and Tissue Resistance**

TC and TR were measured by Marmarou’s method of a bolus injection of saline into brain tissue, using the same TP needles. The infusion rate was 0.63–0.73 \( \mu l/min \). TC was defined as the volume increase per change in pressure and was calculated as ml/mm Hg by dividing the change in infusion volume by the observed increase in pressure and then correcting for gauge compliance. TR was defined as change in pressure per change in flow and was calculated as mm Hg/ml/min by the increase in steady-state pressure by the change in infusion rate.

**Regional Cerebral Blood Flow**

rCBF was measured by the hydrogen clearance method. A 250-\mu m diameter Teflon-coated platinum electrode, with the tip exposed 0.5 mm, was placed 2 mm posterior to each TP needle; a silver chloride reference electrode was placed in the temporal muscle.

Hydrogen gas (4–7%) was administered for about 2 minutes through the inspired air. The desaturation curves were analyzed by the initial-slope method.

**Brain Water Content**

After the cats were killed the brains were removed. Coronal sections 3.0 mm thick were cut immediately at the level of the TP needles and immersed in kerosene. Two tissue samples 1.5 mm\(^2\) each were taken from the gray matter surrounding each TP needle. Samples were suspended in a kerosene-bromobenzene column for specific gravity determination. Brain water content was calculated and expressed as percent water.

**Experimental Protocol**

Systemic arterial pressure, end-tidal CO\(_2\), VFP, and TP were measured continuously with a Gould electrostatic recorder (Cleveland, Ohio). When steady state had been maintained for 1 hour, the MCA was occluded in 22 cats. rCBF was measured before and hourly after occlusion. TC and TR were measured before death. Eight cats were killed after 1 hour of occlusion, 7 after 3 hours of occlusion, and 7 after 6 hours of occlusion. Fifteen control cats were killed at intervals of 1, 3, and 6 hours after a sham operation. Water content was measured in all cats after death.

**Data Analysis**

Statistical significance of results was determined by Student’s \( t \) test; \( p<0.05 \) was considered significant. All values were expressed as mean±SEM.

**Results**

**General Physiologic Effects**

Mean systemic arterial pressure, arterial blood gases, hematocrit, and serum osmolality are summarized in Table 1. Systemic arterial pressure remained in the normotensive range throughout each experiment. Serum osmolality and hematocrit did not change significantly after MCA occlusion. Arterial blood pH, Paco\(_2\), and Pa\(_2\) were maintained within normal limits in all cats. Data from cats with MCA occlusion did not differ from that recorded from sham-operated controls.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Before</th>
<th>1 hour</th>
<th>2 hours</th>
<th>3 hours</th>
<th>4 hours</th>
<th>5 hours</th>
<th>6 hours</th>
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<td>Systemic arterial pressure</td>
<td>(mm Hg)</td>
<td></td>
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<tr>
<td>118 ± 1.3</td>
<td>119 ± 1.1</td>
<td>120 ± 1.4</td>
<td>120 ± 1.4</td>
<td>119 ± 1.4</td>
<td>118 ± 1.4</td>
<td>119 ± 1.4</td>
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<tr>
<td>Gas analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>pH</td>
<td>7.36 ± 0.01</td>
<td>7.36 ± 0.01</td>
<td>7.36 ± 0.01</td>
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<td>7.34 ± 0.01</td>
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<tr>
<td>Paco(_2) (mm Hg)</td>
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<td>29.9 ± 0.3</td>
<td>29.7 ± 0.2</td>
<td>29.4 ± 0.4</td>
<td>30.4 ± 0.4</td>
<td>30.4 ± 0.5</td>
<td>29.8 ± 0.4</td>
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<tr>
<td>Pa(_2) (mm Hg)</td>
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<td>157.3 ± 2.4</td>
<td>158.1 ± 2.5</td>
<td>155.2 ± 2.4</td>
<td>157 ± 3.5</td>
<td>156 ± 1.1</td>
<td>153.9 ± 1.8</td>
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<td>Hematocrit</td>
<td>36.8 ± 0.7</td>
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<td>35.2 ± 1.1</td>
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<tr>
<td>Serum osmolality (mosm)</td>
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<td>300.2 ± 2.1</td>
<td>298.7 ± 3.6</td>
<td>300.8 ± 3.4</td>
<td>300.8 ± 2.5</td>
</tr>
</tbody>
</table>

Values are mean±SEM; \( n \), number of cats.
Regional Cerebral Blood Flow

rCBF was measured in 22 cats with 1, 3, and 6 hours of MCA occlusion and in 15 cats with sham occlusion. The mean preocclusion rCBF in the core and periphery of the MCA territory was 44.15 ± 1.05 and 43.91 ± 1.03 ml/100 g/min, respectively, similar to those of sham-operated control cats. rCBF did not change significantly during 6 hours after sham operation in control cats.

Significant focal ischemia was seen after MCA occlusion (Figure 1). The reduction of rCBF in the core was greater than that in the periphery after occlusion. rCBF fell to 6.27 ± 0.30 ml/100 g/min in the core and 17.65 ± 0.73 ml/100 g/min in the periphery 1 hour after occlusion; rCBF in both areas did not fall further over the next 5 hours.

Brain Tissue Water Content

The change of water content in the core and periphery at 1, 3, and 6 hours after MCA occlusion and sham operation is shown in Figure 2. Water content increased significantly in the core 1 hour after occlusion compared with sham-operated controls. The increase of water content in the same area progressed at 3 and 6 hours after occlusion, reaching 82.83 ± 0.18% at its maximum. There was a significant increase in water content 6 hours after occlusion in the periphery of the MCA territory, but not before. Water content was 79.90 ± 0.09% 6 hours after occlusion. The increase of water content in the periphery was significantly less than that observed in the core.

Tissue Pressure and Ventricular Fluid Pressure

TP and VFP were measured in 22 cats killed 1, 3, and 6 hours after MCA occlusion and in 15 cats with sham operation. There were no significant differences between TP at the two sites and between VFP over 6 hours in sham-operated controls. The control values of TP in the lateral and Sylvian gyri were 6.6 ± 0.7 and 6.9 ± 0.8 mm Hg, respectively, whereas control VFP was 6.5 ± 0.1 mm Hg.

TP and VFP in cats with MCA occlusion are shown in Figure 3. The values of TP and VFP before occlusion were similar to those found in sham-operated controls. After MCA occlusion, TP in the core increased
progressively after 2 hours of occlusion, then the rate of increase slowed; TP in the core was 14.3 ± 0.4 mm Hg 6 hours after occlusion. In contrast, TP in the periphery rose to 9.7 ± 0.5 mm Hg and VFP to 8.7 ± 0.3 mm Hg 6 hours after occlusion. Both TP in the periphery and VFP were significantly greater 6 hours after occlusion than before.

Figure 4 shows the hydrostatic pressure gradient between TP in the core and VFP over 6 hours after MCA occlusion. The pressure gradient increased gradually during the first 3 hours, then reached a plateau during the next 3; the gradient was 5.3 mm Hg 6 hours after occlusion. The pressure gradient in control cats did not change.

**Tissue Compliance**

TC in the 37 cats is shown in Figure 5. In sham-operated controls, TC in the core and periphery of the MCA territory did not change significantly over 6 hours. TC in both areas was similar during that period. Mean control values of TC in the core and periphery were 9.06 ± 0.93 × 10⁻⁵ and 8.90 ± 0.86 × 10⁻⁵ ml/mm Hg, respectively.

After MCA occlusion, TC in the core decreased slightly to 7.41 ± 0.53 × 10⁻⁵ ml/mm Hg during the first hour. TC rose gradually to control values 3 hours after occlusion and then increased significantly to 15.75 ± 1.84 × 10⁻⁵ ml/mm Hg by 6 hours. There was no significant change in TC over 6 hours after occlusion in the periphery of the MCA territory. The mean TC of 9.36 ± 0.60 × 10⁻⁵ ml/mm Hg was equal to that in sham-operated controls.

**Tissue Resistance**

TR is shown in Figure 6. There was no significant change of TR in the core and periphery of the MCA territory over 6 hours in sham-operated controls. The mean control values of TR in the core and periphery were 10.49 ± 1.03 × 10³ and 10.71 ± 0.93 × 10³ mm Hg/ml/min, respectively.

TR increased significantly to 12.84 ± 0.82 × 10³ mm Hg/ml/min in the core within the first hour after MCA occlusion when compared with that observed in sham-operated controls. TR in the core then gradually decreased over the next 5 hours and was reduced significantly to 6.68 ± 0.93 × 10³ mm Hg/ml/min 6 hours after occlusion. In contrast, TR did not change significantly in the periphery over 6 hours after MCA occlusion, remaining similar (9.8 ± 0.52 × 10³ mm Hg/ml/min) to that in sham-operated controls.

**Tissue Pressure, Tissue Compliance, Tissue Resistance, and Water Content**

The correlation between changes in TP and water content during 6 hours of MCA occlusion is illustrated in Figure 7. An increase in TP after MCA occlusion was directly related to the water content until edema
FIGURE 6. Brain tissue resistance in core (top) and periphery (bottom) 1, 3, and 6 hours after middle cerebral artery occlusion (MCAO) and sham operation. Tissue resistance increased at 1 hour after MCAO and then decreased at 6 hours. *Difference between MCAO and sham-operated control cats significant.

FIGURE 7. Correlation between change in brain tissue pressure and corresponding brain water content before and 6 hours after middle cerebral artery occlusion. Increase in tissue pressure is related to water content but only until increase in water content reaches a moderate degree.

Discussion

Water movement across capillaries of brain tissue contributes to hydraulic conductivity and to hydrostatic and osmotic pressure gradients between blood and brain.1,2 The driving force for fluid accumulation in vasogenic brain edema is the transmural pressure gradient in the capillary bed.3 We have observed that when intraluminal arterial pressure is increased with the inflation of an aortic balloon in the early stages of focal cerebral ischemia in cats, edema fluid accumulation is exaggerated.12 Thus, it seems that a hydrostatic pressure gradient across the capillary wall has an important effect on the formation of brain edema.

In the current study we demonstrated that cortical tissue pressure increases significantly in the ischemic core 2 hours after occlusion, continues to rise as water accumulates, and then stabilizes. This finding confirmed our previous results.6

The hydrostatic pressure gradient between arterial blood and surrounding cortical tissue in the core was predicted to be maximal soon after occlusion, when TP is minimal; that the transmural gradient probably falls as tissue pressure rises was also predicted. In fact, we detected slight but significant edema 1 hour after occlusion in the same area where TP was initially low. This observation suggests that the mechanism for water passage across the endothelium during the initial stage of ischemia, when the blood–brain barrier is still relatively intact, is primarily related to a hydrostatic pressure gradient between arterial blood and brain tissue in addition to the alteration of capillary hydraulic conductivity. This suggestion is supported by the observation that the osmotic pressure gradient, which is the other driving force for the extravasation of edema fluid, does not develop between arterial blood and ischemic cortical tissue immediately after the onset of ischemia.13

Tissue elastic compliance and tissue hydraulic conductivity, in addition to tissue pressure, are major biomechanical factors that characterize water movement between the intracranial compartments. We have recently observed that TC is higher and TR lower in
normal white matter than in cortical gray matter; this is probably due to the inherent structure of intact brain tissue. Walstra et al. have reported that TC of white matter increases and TR decreases rapidly when fluid is infused into the tissue. These changes in compliance and resistance presumably are due to the distension of extracellular spaces.

We have demonstrated that cortical TR increases in the core of the MCA territory 1 hour after occlusion, whereas TC falls. These findings imply that accumulation of water is primarily intracellular and that the extracellular space is reduced. This notion is supported by other studies that show that cortical tissue impedance increases rapidly in the ischemic cortex soon after arterial occlusion. In our study, cortical TP did not rise significantly within 1 hour after occlusion. At the same time, only a slight increase in water content was found in the ischemic core, even though a hydrostatic pressure gradient developed soon after the ischemic insult. It follows, therefore, that low hydraulic conductivity of ischemic cortical tissue, in addition to low compliance, limits the amount of edema fluid that can accumulate and prevents rapid movement of that same fluid.

Our study has shown that as fluid accumulates in the ischemic core, cortical TP continues to rise, then reaches a plateau. Cortical TR decreases gradually in the ischemic core, while TC increases. These findings indicate that rising TP overcomes the opposing structural resistance of brain tissue and thereby opens extracellular channels.

Following an initial rise, cortical TR decreased markedly in the core 6 hours after occlusion; TC increased significantly in the same area. This alteration of TC and TR is probably due to enlargement of extracellular compartments caused by disruption of cell membranes and fluid accumulation. At that time, ischemic edema reached a moderate degree (82.8%) and cortical TP rose to 14.3 mm Hg. It seems that fluid extravasated across the capillary accumulates easily in surrounding cortical tissue, which becomes more compliant depending on the duration of ischemia. Then the increase in cortical tissue conductance facilitates the spread of edema fluid in ischemic edema.

Our study further shows that a pressure gradient between edematous tissue and cerebrospinal fluid (CSF) develops as TP rises in the ischemic cortex and is maintained at about 5.0 mm Hg from 3 to 6 hours after occlusion. The pressure gradient does not continue to increase since cortical TP equilibrates with TC and TR; however, the magnitude of the pressure gradient is maintained for some time. Rapoport has noted, in a mathematical model for vasogenic brain edema, that volume flow from the brain compartment to CSF contributes to overall brain conductivity and to the pressure difference between brain and CSF. Even in the early stages of cerebral ischemia, we suggest that the pressure gradient between edematous tissue and CSF allows edema fluid to migrate through highly conductive brain tissue into subarachnoidal or ventricular CSF. The clearance of edema fluid into CSF probably commences even as edema begins to form.

In the periphery of the MCA territory, rCBF did not continue to fall after the initial hour even though cortical TP rose slightly. During that 6 hours both TC and TR failed to change. These findings imply that a small increase in water content is not enough to open extracellular channels in the areas where ischemic blood flow is above the threshold for membrane failure.

We conclude that a hydrostatic pressure gradient across the capillary develops soon after the onset of ischemia and that it is the driving force for early edema fluid formation. However, the compliance of surrounding cortical tissue limits the amount of edema fluid that can accumulate. Low hydraulic conductivity
of ischemic tissue probably prevents rapid movement of edema fluid initially. Later, as the ischemic injury progresses, edema fluid accumulates in highly compliant brain parenchyma and then migrates through highly conductive tissue into CSF spaces, driven by the pressure gradient that develops between the edematous tissue and the CSF.

References


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