Experimental Regional Cerebral Ischemia in the Middle Cerebral Artery Territory in Primates

Part 3: Effects on Brain Water and Electrolytes in the Late Phase of Acute MCA Stroke

Alfonso M. Bremer, M.D., Kazuo Yamada, M.D., and Charles R. West, M.D.

SUMMARY Experimental regional cerebral ischemia was produced in the middle cerebral artery (MCA) territory in primates (M. mulatta) by macrosphere embolization. Determinations of percentage tissue dry weight and tissue sodium and potassium concentrations were obtained in samples from the ischemic and non-ischemic hemispheres at various times from 12 to 48 hours after the onset of cerebral ischemia.

Samples from the cortex normally supplied by the occluded MCA showed maximal accumulation of edema fluid with flux in sodium and potassium in reciprocal directions at 12 hours and similar edematous changes in putamen at 24 hours after embolization. By 48 hours after MCA occlusion and despite the presence of infarction, partial reversal was observed in the redistribution of water and electrolytes in these gray matter structures.

In contrast to cerebral cortex and putamen, the adjacent subcortical white matter showed progressive increases in water content from 12 to 48 hours and definite increases in tissue sodium with decreases in potassium were not observed until 48 hours after MCA occlusion.

This late severe white matter edema associated with cerebral infarction appears to be a major factor responsible for the hemispheric swelling observed at this stage.

CLINICAL and experimental studies have shown that cerebral edema following an acute stroke is at maximum within a few days and eventually subsides in about 3 weeks if the patient or the experimental animal survives the acute phase.1–4

Results obtained by Little et al.5–6 from morphological studies in brains of squirrel monkeys following surgical clipping of the middle cerebral artery (MCA) have demonstrated a primary and a secondary phase in the evolution of ischemic cerebral edema. The initial phase begins shortly after arterial occlusion, is characterized by mild swelling of the gray and white matter, increases gradually in severity and lasts from 3 to 6 hours. Thereafter, a secondary phase begins and is characterized by massive swelling, especially of the white matter. Rapid increases in severity of this edema reached its peak at 24 hours or longer.6

In a previous communication we demonstrated that hemispheric swelling became apparent in the experimental side as early as 4 to 5 hours after onset of regional cerebral ischemia in the MCA territory in primates.7 Obvious changes in gray matter water content and in tissue sodium and potassium concentrations were detected at this time. However, minimal increases in subcortical white matter water content was found without changes in electrolytes.7

The present study was designed to extend our observations of ischemic brain tissue water content and in tissue sodium and potassium concentrations after much longer periods of MCA occlusion in macaques.

Methods

The left MCA of 10 adult primates (M. mulatta) (3 to 4 kg body weight) was occluded by a method of...
TABLE 1 Animals, Number and Location of Emboli, Level of Consciousness and Postmortem Gross and Microscopical Ischemic Changes of the Experimental Hemispheres

<table>
<thead>
<tr>
<th>Animals</th>
<th>No. of emboli</th>
<th>Location of emboli</th>
<th>Duration of exp. (hrs)</th>
<th>Level of consciousness</th>
<th>Gross and microscopical ischemic changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>ICA-B</td>
<td>12</td>
<td>Stupor</td>
<td>++++ ++</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>ICA-B</td>
<td>12</td>
<td>Alert wakefulness</td>
<td>- - -</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>MCA-P</td>
<td>12</td>
<td>Stupor</td>
<td>++++ +++</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>ICA-B</td>
<td>24</td>
<td>Obtundation</td>
<td>++++ +++ +</td>
</tr>
<tr>
<td>V</td>
<td>1</td>
<td>ICA-B</td>
<td>24</td>
<td>Obtundation</td>
<td>++++ +++ +</td>
</tr>
<tr>
<td>VI</td>
<td>1</td>
<td>ICA-B</td>
<td>24</td>
<td>Stupor</td>
<td>++++ +++ +</td>
</tr>
<tr>
<td>VII</td>
<td>1</td>
<td>ICA-B</td>
<td>48</td>
<td>Lethargy</td>
<td>++++ +++ +</td>
</tr>
<tr>
<td>VIII</td>
<td>1</td>
<td>ICA-B</td>
<td>48</td>
<td>Lethargy</td>
<td>++++ +++ +</td>
</tr>
<tr>
<td>XI</td>
<td>1</td>
<td>ICA-B</td>
<td>48</td>
<td>Lethargy</td>
<td>++++ +++ +</td>
</tr>
<tr>
<td>X</td>
<td>2</td>
<td>ICA-B and terminal ICA occluding AChA</td>
<td>40</td>
<td>Coma - Died</td>
<td>++++ +++ ++</td>
</tr>
</tbody>
</table>

ICA-B = internal carotid artery bifurcation; ICA = internal carotid artery; MCA-P = middle cerebral artery - proximal segment; AChA = anterior choroidal artery.

Determinations of vital signs and vital functions at the end of each experiment were obtained with similar instrumentation as in earlier reports.8 9

Results

After the embolization procedure anatomical location of the radiopaque silicone spheres (Heyer-Schulte Corp., Santa Barbara, CA) was demonstrated by plain skull radiographs and confirmed at postmortem examination (table 1).

All 10 animals tolerated the embolization procedure without apparent difficulties or significant change in vital signs and vital functions (table 2). However, 3 developed Horner's pupil on the side of the carotid surgery.

TABLE 2 Vital Signs, Arterial Blood Gases, Plasma Electrolytes, Plasma Osmolarity and Hematocrit at the End of the Experiments

<table>
<thead>
<tr>
<th>Vital signs</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MABP (mm Hg)</td>
<td>138 ± 10</td>
</tr>
<tr>
<td>Pulse rate (per minute)</td>
<td>135 ± 24</td>
</tr>
<tr>
<td>Respiration (per minute)</td>
<td>36 ± 12</td>
</tr>
</tbody>
</table>

Arterial blood gases

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.384 ± 0.029</td>
</tr>
<tr>
<td>PO2 (mm Hg)</td>
<td>83.9 ± 7.7</td>
</tr>
<tr>
<td>PCO2 (mm Hg)</td>
<td>36.9 ± 2.9</td>
</tr>
</tbody>
</table>

Plasma electrolytes

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>139.0 ± 1.9</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>3.2 ± 0.3</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>123.3 ± 6.0</td>
</tr>
</tbody>
</table>

Plasma Osmolarity

<table>
<thead>
<tr>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>300.3 ± 4.5</td>
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Hematocrit (%)

<table>
<thead>
<tr>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>39 ± 1.4</td>
</tr>
</tbody>
</table>

The values correspond to 9 monkeys. (Monkey X is not included).

FIGURE 1. Posterior view of a coronal section of a monkey brain 24 hours after MCA occlusion. Note on the left side of the figure the swollen hemisphere with midline shift from left to right. There is ischemic pallor and widening of the Sylvian and insular cortices. The affected putamen is also pale with increased surface area.
Clinical and Morphological Observations

Contralateral motor weakness and ipsilateral conjugate eye deviation, developing shortly after macrosphere embolization, persisted in 9 of 10 monkeys throughout the entire 12, 24 and 48 hour observation periods. These animals also manifested alterations in the level of consciousness of variable degree (table 1).

Grossly, these brains showed flattening of gyri with increased distances between sulci of the affected Sylvian cortex. Hemispheric swelling with marked midline shift was unmistakable on coronal sections (fig. 1). Variable degrees of advanced ischemic necrosis were recognized in histological sections of both gray and white matter within the territory of the occluded MCA (table 1). Hemorrhagic infarct was found in only one animal (Monkey VI) of the entire series.

Water and Electrolyte Content

Results presented in figures 2 and 3 show that 12 hours after MCA occlusion, swollen Sylvian cortex and putamen (9.3% to 37.7% tissue swelling) also exhibited increases in tissue sodium (up to 96% of control value) and decreases in potassium (down to 61% of control value). In the 24 hour experiments, changes in percentage of dry weight and electrolytes of ischemic Sylvian cortex were variable, but putamen edema was massive (38.7% to 58.9% tissue swelling) with large increases in tissue sodium (up to 133% of control value) while potassium was markedly decreased (down to 77% of control value). By 48 hours after MCA occlusion and despite evidence for the presence of infarction, partial reversal in the redistribution of water and electrolytes in both Sylvian cortex and putamen was observed.

In contrast to cerebral cortex and putamen, the percentage of tissue swelling in adjacent subcortical white matter showed a rapid upward trend 12 hours after MCA occlusion. Definite increases in tissue sodium (up to 45% of control value) with decreases in potassium (down to 32% of control value) were only seen by the end of 48 hours after MCA occlusion (figures 2 and 3).

Discussion

We have previously demonstrated that cerebral ischemia in primates following acute MCA occlusion...
produced by macrosphere embolization is sufficient to induce brain edema within the territory of the occluded MCA.\(^7\) We also emphasized the importance of the gray matter edema as a major contributory factor for the development of hemispheric swelling during the early phase of MCA stroke.\(^7\)

This study provides evidence that cerebral cortical edema with large increases in sodium and decreases in potassium concentrations is maximal at 12 hours and similar edematous changes in putamen are at their peak 24 hours after MCA occlusion. These extensive chemical changes have been considered as indicative of cell death by several investigators.\(^{18,20}\) Indeed, advanced ischemic necrosis was found on histological sections of both Sylvian cortex and putamen from the experimental hemispheres of these monkeys.

Despite the presence of large infarction in all the monkey brains 48 hours after MCA occlusion, partial clearing of gray matter edema, in both deep subcortical structures and cortex, is clearly demonstrated by the end of this period. It is not clear what mechanism is involved in the resolution of ischemic edema, but it is possible that improvement in residual blood flow through collateral channels may contribute to some clearing of cortical edema fluid. However, it is more difficult to explain on this basis the reversible edematous changes in the putamen in which the collateral vascular supply is less extensive.\(^{6,20}\)

It is worthy of mention that our percentage dry weight values of cortical samples from non-ischemic hemispheres (opposite side) of one 12 hour and of all the 48 hour monkeys after MCA occlusion were significantly lower (\(P < 0.05\)) when compared against the percentage dry weight control value (19.73 ± 0.65) obtained from cortical samples of non-ischemic hemispheres of 14 monkeys that sustained from 2 to 5 hours of regional cerebral ischemia previously reported.\(^7\) We failed to recognize definite significant histological or morphological change in these cortical samples with abnormal increases in water content, however, contralateral structural abnormalities have been recognized in another morphological study on squirrel monkey brains sacrificed 12 hours or longer after MCA clipping.\(^{21}\)

In contrast to findings on cerebral cortex and putamen, the delayed extensive chemical changes in subcortical white matter are similar to those seen in vasogenic edema.\(^{22,23}\) This severe white matter edema associated with tissue necrosis of adjacent gray matter structures appears to be the main factor responsible for the hemispheric swelling recognized in all the monkeys surviving 48 hours after MCA occlusion.

The question remains as to whether ischemic cerebral edema, more pronounced than that induced by macrosphere embolic occlusion of the MCA alone in the primate, can be a major cause of death in the acute phase. In this respect, we call attention to Monkey X which died at 40 hours after embolization. In this animal, simultaneous occlusion of the anterior choroidal artery and MCA with resultant massive cerebral infarction extending beyond the territory of the MCA and ipsilateral uncal herniation was found on post mortem examination (table 1 and fig. 4). According to Symon et al.,\(^{24}\) when severe brain swelling was desired in their primate MCA clipping model, simultaneous occlusion of the anterior choroidal artery and MCA or terminal ICA and MCA was necessary. Therefore, it seems that we cannot overemphasize the importance of the involvement of the anterior choroidal artery in our primate MCA stroke model. In fact, occlusion of both of these arteries resulted in massive brain swelling associated...
with extensive cerebral infarction and was also a relatively early lethal combination. Further studies are proceeding on this point.

Acknowledgment

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References

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