Ischemic Brain Edema Following Middle Cerebral Artery Occlusion in Baboons: Relationship Between Regional Cerebral Water Content and Blood Flow at 1 to 2 Hours

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SUMMARY The relationship between increase in water content in ischemic brain and levels of regional blood flow has been studied in 11 primates. Flows were recorded using the method of hydrogen (2-minute) clearance, from a total of 128 electrodes in cortex and white matter, and a gradation of ischemia was produced by middle cerebral occlusion transorbitally. The flows were reduced in the area of densest ischemia from control levels of 42.0 ± 12.0 ml/100g/min to 7.0 ± 5.4 ml/100g/min, with lesser decreases over the remainder of the ischemic hemisphere. Water content was measured in cortex and white matter, in regions topographically related to those of flow measurements, by densitometric assessment using precalibrated kerosene/bromobenzene columns. The average water content of cortex in regions remote from ischemia was 797.4 ± 5.8 mg/gm and in white matter 708.5 ± 8.2 mg/gm. Significant increases in water content (comparing corresponding regions of the two hemispheres) of up to 11.4 ± 7.5 mg/gm were demonstrated in the most ischemic cortical areas. A gradient of water increase was evident in the ischemic hemisphere, increases in water content being greatest in the opercular zone and least in the parasagittal area. Significant differences in white matter water content between the 2 hemispheres were demonstrated only in the most densely ischemic areas in the current experiments where ischemia was limited to 93 ± 20 mins in the 11 animals without reperfusion. The relationship between ischemic density and water content increase showed that significant increases in water content occurred in regions where terminal flows had been below 20 ml/100g/min, indicating that accumulation of water in ischemic brain begins at flow values comparable to those associated with the failure of synaptic transmission, higher than those associated with failure of the ionic pump of the cell. Possible pathophysiological mechanisms are discussed.

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uptake of water by ischemic brain, its relationship to the density and duration of ischemia, and its characteristics in terms of both progression and reversibility, are of clear importance in the clinical management of ischemic brain disease. The present study was designed to relate the regional cerebral water content to regional cerebral blood flow in the acute phase (1 to 2 hours) following middle cerebral occlusion.

Methods

Preparation and Measurements

Eleven baboons (Papio cynocephalus) in the weight range 9-25 kg were sedated with phencyclidine injected intramuscularly, intubated under light thiopentone anesthesia, and maintained normocapnic using pure O₂ delivered by a Starling pump at appropriate stroke volume following anesthesia with alphachloralose (60 mg/kg i.v.). The animals were immobilized with gallamine triethiodide (1 mg/kg i.v. as necessary) and systemic blood Po₂, pH and Pco₂ continually monitored.

A bipolar stimulating electrode was placed in the left trigeminal nerve (mandibular branch) for subsequent recording of the somatosensory cortical evoked potential (EP) on the right (ischemic) hemisphere. The temporal muscle on both sides was completely removed, the focus of the EP located extracranially, and a silver electrode placed extradurally at that site after a small hole had been made in the skull with an air drill and dental burr. Extrudural pressure transducers, capable of being zeroed in situ, were placed in the parietal region bilaterally and secured to the bone with acrylic cement. Six further small holes were drilled in the opercular, parietal and parasagittal regions in front of the Sylvian fissure bilaterally. These 6 regions, denoted here by RA, RB, RC, LA, LB and LC, corresponded topographically (fig. 1) to the regions designated A, B, and C in previous work. Four regions bilaterally were drilled in the opercular, parietal and parasagittal regions in front of the Sylvian fissure bilaterally. These 6 regions, denoted here by RA, RB, RC, LA, LB and LC, corresponded topographically (fig. 1) to the regions designated A, B, and C in previous work.11

Regional division of the baboon cerebral cortex. In the text, RA denotes region A of the right hemisphere, etc. The division is arbitrary and corresponds to that used in previous work.11

The contents of the right orbit were removed and a large Ag/AgCl electrode was placed subcutaneously in the thorax to act as a common reference electrode for all systems. The right orbit was removed and the right MCA exposed under the operating microscope for its subsequent occlusion with a Scoville clip. After a period of at least one hour during which control measurements of regional flow, electrical activity9 and extradural pressure were made, the artery was occluded proximally, the orbit filled with acrylic cement and additional measurements of the above variables made over the next 1-2 hours.

The brain was then quickly removed, placed in a kerosene/bromobenzene mixture, and at least 3 samples of cortex and white matter taken from each of the 6 regions specified above, as well as from regions on the left side remote from the others. The samples (10-15 mg) were immediately dropped into precalibrated columns of a kerosene/bromobenzene mixture prepared with graded density from top to bottom and their specific gravity thus measured.13 The average water content, in units of mg/g of tissue, was calculated for each of the 6 designated regions in both cortex and white matter, using an assumed constant value for the specific gravity of tissue solids.12

As in previous experimental series involving MCA occlusion,9 the somatosensory cortical EP was not invariably abolished and to obtain uniformity in this respect the systemic blood pressure was reduced (by partial exsanguination) to abolish the EP, in 4 of the 11 animals.

Techniques of Analysis

A simple physiological model to describe the formation of edema in ischemic tissue is one in which a threshold of flow is assumed, analogous to those described in our earlier work.2,9 the water content increasing when local tissue flow falls below this threshold. Three modifications of this concept were investigated in this study with the intention of finding the model that best accounted for our data.

The first model employs the hypothesis that the water increase depends on the depth of ischemia and is proportional to the amount by which the flow falls below the threshold (FBT = flow below threshold), irrespective of the time for which this condition occurs. In the second model, the water increase occurs at a constant rate, but only during those periods when flow is below the threshold value. In this case, the increase measured at termination of the experiment should be proportional to a quantity which we term the time below threshold (TBT) and which is defined as the sum of all such sub-threshold periods, expressed in minutes. In the third, the water increase is proportional to both time and the depth of ischemia below

FIGURE 1. Regional division of the baboon cerebral cortex. In the text, RA denotes region A of the right hemisphere, etc. The division is arbitrary and corresponds to that used in previous work.11
threshold and so should be proportional to the time-integral of the amount by which flow is less than the threshold; this integral, termed the time-integrated flow below threshold (IBT), has units of ml/100g since flow is expressed in ml/100g/min. These concepts are explained in figure 2. In this study, regional flows were calculated as averages over all available flow electrodes in a given region at a given time. The flow in each of the 6 designated regions was plotted against time and, for each of 3 trial flow thresholds, the FBT, TBT, and IBT were then found by graphical calculation for each region.

Results

Analysis of Hydrogen Clearances

Flows were recorded from a total of 128 electrodes in 11 animals. Over one-third (47) of the clearances in the control phase of the experiments displayed biexponential characteristics and were subjected to 2-compartmental analysis. Initial (2-min) flow overall was 40.1 ± 11.8 ml/100g/min (mean ± SD) and the fast component averaged 67.3 ± 16.7 ml/100g/min. These electrodes, therefore, were considered to lie in cortex.

The remaining 81 control clearances displayed essentially monoexponential characteristics with an initial flow of 18.6 ± 6.7 ml/100g/min and the electrodes were considered to lie in white matter. In contrast with earlier work using the open-skull preparation, no monoexponential flow greater than 40 ml/100g/min was observed.

Throughout this paper, flow values are expressed as 2-minute values, averaged over all available electrodes in each of the 6 designated regions (A, B, and C on each side). Initial flow was taken for the sake of consistency since it can be measured no matter what the degree of ischemia, whereas compartmental analysis of clearances in ischemic tissue is frequently impossible.

![Figure 2: Explanation of the terms FBT, TBT and IBT used in the text. The curved line represents a plot of flow versus time in a particular cortical region. A trial threshold of flow (Thr) is specified and the FBT (flow below threshold) read off from the graph as indicated; the TBT is the total time for which the flow goes below the threshold. The IBT is found graphically as the (shaded) area between the flow plot and the threshold during the TBT.](image)

<table>
<thead>
<tr>
<th>Region</th>
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<th>P</th>
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<tr>
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<tr>
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<td>7</td>
<td>→</td>
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<tr>
<td>C</td>
<td>27.8</td>
<td>9.4</td>
<td>4</td>
<td>→</td>
</tr>
</tbody>
</table>

Cortex: Flow Changes During Clip Phase

The flows in control and clip phases are summarized in table 1 for each of the 6 regions. Duration of the clip phase (from clip to termination of the experiment) was 93 ± 20 min (N = 11 animals). A gradation of ischemia produced by MCA occlusion in the right hemisphere is evident and similar to that previously reported. Terminal flow averaged over R_A was 7.0 ± 5.4 ml/100g/min and over R_B was 8.4 ± 6.7 ml/100g/min, both significant decreases from control values (p < 0.001, N = 11). There were small decreases in flow in R_C and also in all regions of the contralateral or control hemisphere, but these were not statistically significant.

![Table 2: Cortex - Regional Flow Decreases. (ml/100g/min) During Clip Phase](image)

**Table 2** Cortex - Regional Flow Decreases. (ml/100g/min) During Clip Phase

<table>
<thead>
<tr>
<th>Right side</th>
<th>Left side</th>
</tr>
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<tbody>
<tr>
<td>A</td>
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</tr>
<tr>
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<td>P</td>
<td>NS</td>
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All available areas

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<td>2.5</td>
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<tr>
<td>sd</td>
<td>4.7</td>
<td>3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>12</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.01</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2 summarizes the changes in flow, by areas, measured from the beginning to the end of the clip phase. In the right hemisphere, the decrease in flow was 4.6 ± 4.7 ml/100g/min (N = 12 regions), significant at the p < 0.01 level, although there was a significant decrease only in R_c when areas were considered separately (mean = 5.0 ml/100g/min, p < 0.03, N = 5 animals). The left hemisphere displayed a similar trend (mean flow decrease = 2.5 ml/100g/min), but this was not significant. These data were obtained from the 7 animals not subjected to exsanguination, in which there was no significant decrease in the mean systemic blood pressure (108 ± 14 to 105 ± 18 torr).

White Matter: Flow Changes

Table 3 shows the flow data relating to white matter. In R_A, mean flow fell from 20.9 ± 5.7 to 3.9 ± 1.7 ml/100g/min (control phase to termination), and in R_B from 19.4 ± 4.6 to 5.8 ± 5.2 ml/100g/min (both significant, p < 0.001). In the other 4 regions the flows also decreased, but not significantly. During the clip phase itself, white matter flows did not change significantly.

Cortex: Regional Water Increases

The average water content of cortex in the regions remote from areas A, B, and C in the left hemisphere was 797.4 ± 5.8 mg/g in the 11 animals. Significant water differences were present between corresponding regions of the 2 hemispheres in areas A, and B, but not in C (table 4). The difference (R - L) in A was 11.4 ± 7.5 mg/g (p < 0.002, N = 9 animals), in B was 6.2 ± 6.1 mg/g (p < 0.01, N = 11), and in C was 1.4 ± 8.3 mg/g (NS, N = 11).

A gradient of water increase was also evident (table 4) in the ischemic hemisphere. The difference (R - L) in A was 11.4 ± 7.5 mg/g (p < 0.002, N = 9 animals), in B was 6.2 ± 6.1 mg/g (p < 0.01, N = 11), and in C was 1.4 ± 8.3 mg/g (NS, N = 11).

Between R_A and R_B was 5.0 ± 4.1 mg/g (p < 0.002, N = 11) and that between R_B and R_C was 4.2 ± 4.8 mg/g (p < 0.02, N = 11). There were no significant regional differences in the control hemisphere.

White Matter: Regional Water Increases

Table 5 shows that a significant difference in white matter water content was present between the hemispheres only in area A. No intrahemispheric gradients were observed. The average water content of the regions remote from A, B, and C in the left hemisphere was 708.5 ± 8.2 mg/g.

Cortex: Relationship Between Water Increase and Flow

Figure 3 illustrates the relationship between increase in water content, measured relative to the remote region in that animal, and the terminal blood flow in the same region; the data from all 6 cortical regions are shown. The trend of increasing edema with decreasing flow is clear. In figure 4 the same data are expressed in histogram form with means and SD of terminal water increase calculated for each interval of
flow of width 5 ml/100g/min. Significant differences exist between each of the means below 20 ml/100g/min, on the one hand, and the mean of all points above 20 ml/100g/min, on the other.

The points plotted in figure 3 to the right of 20 ml/100g/min are, with one exception, all above the flow axis, a distribution unlikely to be attributable to purely random errors in the tissue density measurements. In fact, our data indicate that there was a systematic, although small, elevation of water content in tissue samples taken from non-ischemic regions (flow > 26 ml/100g/min) regions A, B, or C in the left hemisphere, relative to samples taken from the remote regions (also on the left side) in the same animal. This water increase, averaging 2.7 ± 1.7 mg/g, was statistically significant (p < 0.02, paired t-test); regions in the right hemisphere were excluded from this calculation to eliminate the possibility that water might have spread into them from edematous ischemic areas. The increase, which from considerations of our methodology most likely arose from the initial exposure of the regions A, B and C (the remote regions were only exposed at termination), must be regarded as an unavoidable background in experiments of this type.

In white matter, however, we found no trend for water content to increase with depth of ischemia. Three trial thresholds, 10, 15 and 20 ml/100g/min, were considered and the FBT (derived from the data on terminal flow) calculated for each region in each animal. A linear regression of regional water increase at termination on FBT was then performed, for each of the 3 thresholds. The correlations obtained in each case were all greater than 0.73 and highly significant (table 6).

Cortex: Relationship Between Water Increase and Time

The correlation of water increase with TBT, calculated in the same manner as for FBT indicated above, was not significant for the threshold of 10 ml/100g/min and only just significant for the other two thresholds (table 6). The time-integrated flow below threshold (IBT), however, was highly correlated with water increase for

### Table 6 Correlations of Flow/Flow + Time Variables with Terminal Water Increase

<table>
<thead>
<tr>
<th>Threshold (ml/100g/min)</th>
<th>Flow below threshold (FBT)</th>
<th>Time below threshold (TBT)</th>
<th>Time-integrated flow below threshold (IBT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.92 9 &lt;0.001</td>
<td>0.49 13 NS</td>
<td>0.77 12 &lt;0.01</td>
</tr>
<tr>
<td>15</td>
<td>0.73 14 &lt;0.005</td>
<td>0.55 19 &lt;0.03</td>
<td>0.78 18 &lt;0.001</td>
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<tr>
<td>20</td>
<td>0.74 19 &lt;0.001</td>
<td>0.49 19 &lt;0.05</td>
<td>0.73 19 &lt;0.001</td>
</tr>
</tbody>
</table>

For definitions see text.
Changes in Intracranial Pressure and Systemic Blood Pressure

Extradural pressure in the right hemisphere during the control phase (157 ± 58 mm H$_2$O) was not significantly different from that in the left (188 ± 58 mm H$_2$O). A small but significant increase in pressure was observed on both sides from the start of the clip phase to termination (25 ± 22 mm H$_2$O, p < 0.03, on the right side, and 22 ± 17 mm H$_2$O, p < 0.03, on the left), in the 7 animals not subjected to exsanguination in the clip phase.

Mean systemic blood pressure just prior to the clip was 104 ± 15 mm Hg (all animals). In the 7 animals not bled, this was 108 ± 14 mm Hg, falling to 105 ± 18 mm Hg at termination; this difference was not significant (paired t-test). The terminal pressure for the 4 exsanguinated animals ranged from 20 to 75 mm Hg.

Cortical Evoked Potential

The chosen monitor of ischemic depth in this group of experiments was abolition of the cortical evoked response which never recovered before termination.

Discussion

The data from the present study confirm previous results, namely, that following MCA occlusion a marked and immediate decrease in regional flow occurs in the field of the artery, most pronounced in region A (opercular), the area of potential infarction, intermediate in B (fronto-parietal) and least (and not statistically significant) in the parasagittal region C of anterior cerebral collateral perfusion. Corresponding changes in white matter were less pronounced.

In this study for the first time, however, we have related regional blood flow in primate cortex to regional tissue water content following ischemia.

It is of interest that the value of the fast flow component of clearance curves found here under basal conditions was, on average, nearly twice that quoted by Sandor et al. for flow in gray matter obtained using a $^{133}$Xe technique and the same anesthetic (chloralose). The average slow component flow, however, was similar to ours. The difference in the fast component may be accounted for by the larger dose of chloralose, 100 mg/kg used by Sandor et al., as compared to our 60 mg/kg. Initial (2-min) flows recorded by us here tended to be slightly lower, on average, than those recorded in earlier work in which a large craniectomy was performed, but the much greater proportion of biexponential clearances found in the present study could well have accounted for this reduction, since the 2-min flow value always lies between the associated fast and slow values.

Decrease in Flow During Clip Phase

The initial drop in flow due to MCA occlusion was followed in 7 animals by a further decrease in flow, averaging about 5 ml/100g/min (14%) in the right hemisphere during a period when the mean systemic blood pressure decreased by an average of only 3 mm H$_2$O (3%). The remaining 4 animals were partially exsanguinated to demonstrate abolition of the EP and, since in these cases the fall in blood pressure might have produced a flow decrease, they were excluded from the calculation.) From other data describing the autoregulatory characteristics of partially ischemic brain, it seems unlikely that the insignificant decrease in blood pressure could have accounted for the decrease in flow. Such a decrease was not seen, however, in earlier experiments employing a similar protocol but with the surface of the brain at atmospheric pressure. Since a small but significant increase in intracranial pressure was recorded in both hemispheres in the present study during the clip phase, one explanation for the observed slight reduction in tissue perfusion during the clip phase might be that raised tissue pressure secondary to the ischemia reduced the collateral perfusion, as has been speculated previously. Alternatively, vasoactive substances may have been released during ischemia to reduce flow. There was no evidence for diaschisis occurring within the time-scale of the present study.

Time Factor in Development of Regional Water Increases in Cortex

This study clearly demonstrates that the water increase in a given cortical region is directly related to the degree of ischemia in that region. Specifically, there were significant differences in water content between corresponding regions of the 2 hemispheres and a gradation of water increase along the hemisphere on the side of the occlusion, with corresponding differences in flow, while there was a clear trend (figures 3, 4) for cortex to accumulate additional water the greater the depth of ischemia. Further, the
superior correlation of terminal water increase with the initial level of ischemia (FBT), as compared to that with the time below threshold (TBT) calculated for a range of trial flow thresholds (table 6), suggests that the depth of ischemia is a more reliable predictor of final water content than the duration of the ischemic period in the first 1 to 2 hours following occlusion. This suggestion is reinforced by the fact that introducing a time-integral into the FBT (to form the IBT) does not improve the correlations obtained with the FBT alone.

Thus, there is a clear suggestion of a trigger mechanism for edema formation in the early stages of ischemia, the trigger being the initial reduction in flow. While this idea has some support in the results of Fujimoto et al, who demonstrated a significant increase in water content in the gerbil cortex within 5 min of the onset of ischemia, it would require further investigation in experiments using shorter periods of occlusion to confirm this.

Flow Threshold for Edema Formation

There appeared to be a significant elevation of regional water content in cortex where the flow had been reduced to the range 15 to 20 ml/100g/min, as compared to tissue where flow had been relatively well preserved (fig. 4). We have shown previously that the integrity of the cortical cell membrane, in terms of the ionic pump, is impaired at flows below a threshold of 9 to 11 ml/100g/min, as manifested by a substantial increase below this threshold of extracellular potassium activity and electrical impedance. These changes involve an uptake of water into the cells from the extracellular space. Such a re-distribution of water within cortex, by itself, should not change the specific gravity of the tissue. However, from the results of Hospmann and his colleagues, it may be deduced that under conditions of partial (as distinct from total) ischemia, water could be expected to enter the extracellular space from the vascular compartment in response to an associated osmotic and ionic imbalance across the blood-brain barrier. This additional effect would reduce the tissue density. One might therefore expect that edema should begin only at tissue flows below the threshold of 9 to 11 ml/100g/min. The results of the present study suggest, however, that it commences at significantly higher flows, above 15 ml/100g/min, at flow levels associated with electrical failure and, presumably, failure of synaptic transmission. This suggestion is directly strengthened by additional (unpublished) results of ours, obtained by methods essentially the same as those of the present study, in which significant water increases were measured in regions where the extracellular potassium activity, recorded throughout the experiment, remained at normal values.

Although at the higher flow levels (above 15 ml/100g/min) the ionic homeostasis as a whole is still preserved, impairment of synaptic activity and, in particular, of neurotransmitter re-uptake mechanisms might permit the release of active neurotransmitter substances, normally localized at the terminals, into synaptic clefts and the vicinity of blood vessels. Such changes in local neurotransmitter concentration, as well as possibly decreasing the blood flow as discussed above, might then cause an increase in vascular permeability to water (as has been demonstrated in other organs), either by direct action at the vessel wall, indirectly via astrocytes, or by mimicking changes in sympathetic tone normally produced by the sympathetic or central noradrenergic systems. A further possible effect of the failure of neurotransmitter synthesis might be the accumulation, within functionally disturbed cells, of small molecules which normally comprise the larger transmitter molecules, resulting in a net increase in osmolality and, therefore, in tissue water content. Other sources of idiogenic osmoles in ischemia have been discussed elsewhere, and include the known increase in tissue lactate concentration which has been demonstrated by Siesjö and his colleagues to occur during hypoxemia or hypotension at levels higher than required to produce major disturbances in tissue content of the other major metabolites and at levels, for example, appreciably higher than the failure of autoregulation in tissue.

Acknowledgments

We thank Robert Pullen for expert technical assistance in the tissue density measurements. This study was supported by the Medical Research Council and the Wellcome Trust.

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ISCHEMIC BRAIN EDEMA AND rCBF/Symon et al.
Ischemic brain edema following middle cerebral artery occlusion in baboons: relationship between regional cerebral water content and blood flow at 1 to 2 hours.

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*Stroke*. 1979;10:184-191
doi: 10.1161/01.STR.10.2.184

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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