Experimental Brain Infarcts in Cats

II. Ischemic Brain Edema

F. J. Schuier, M.D. AND K.-A. Hossmann, M.D.

SUMMARY In cats, the early development of ischemic brain edema was studied 1 to 4 hours after transorbital occlusion of the left middle cerebral artery (MCA). Two groups of animals were compared: those in which blood flow in the territory of the MCA decreased below the threshold of 10-15 ml/100 g/min (critical ischemia) and those in which it remained above this level (non-critical ischemia).

In animals with critical ischemia, water content in the cortex of the MCA territory increased from 80.7 ± 0.4 to 83.0 ± 0.3 vol. % (means ± SE) within 4 h. Edema was associated with an increase in tissue osmolality by 16–22 mosm/kg w.w., and a rise of sodium from 262 ± 9 to 454 ± 13 meq/kg d.w. and a decrease of potassium from 442 ± 20 to 305 ± 32 meq/kg d.w. The sodium/potassium ratio rose from 0.60 ± 0.03 to 1.55 ± 0.17. The water and electrolyte disturbances were accompanied by a major shift of extracellular fluid into the intracellular compartment, as evidenced by the increase in cortical impedance from 282 to 660 ohm/cm within 2 h. According to the Maxwell equation, this reflects a narrowing of the extracellular space from 19.8 to 11.4%. Brain volume was continuously monitored using an induction transducer; swelling began within a few minutes of vascular occlusion, and it continued throughout the 4 h observation period. During this time the blood-brain barrier remained intact as evidenced by the absence of Evans blue staining. Edema was associated with disturbances of the energy producing metabolism, but there was no strict correlation with either lactate or the concentration of high energy phosphates.

In animals without critical ischemia, i.e. in which blood flow remained above 10-15 ml/100 g/min, edema was absent despite a distinct deterioration of the energy state of the brain. Edema was also absent in the border zone, in the territory of the posterior cerebral artery and in the contralateral hemisphere of animals with both critical and non-critical ischemia.

It is concluded that the early ischemic brain edema following middle cerebral artery occlusion is of the cytotoxic type, that it develops at a flow rate below 10–15 ml/100 g/min, and that it is not strictly correlated with the energy state of the brain.

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REGIONAL CEREBRAL ISCHEMIA following middle cerebral artery occlusion was studied in cats, using the intracardiac microsphere injection technique. Changes in blood flow were correlated with changes of EEG activity, tissue water and electrolyte content, and with the energy state of the brain in order to determine flow thresholds for functional and biochemical disturbances. There was a well-defined threshold of 10–15 ml/100 g/min which was of critical importance for the development of stroke because it determined whether ischemia was progressive or not. When blood flow was reduced below this threshold, brain edema developed which caused microcirculatory compression and gradual further decrease in blood flow (critical ischemia). On the other hand, ischemic brain edema was absent when blood flow remained above this threshold, and blood flow generally improved (non-critical ischemia). From the point of view of prevention of stroke after a critical reduction in blood flow, it might be possible to either treat ischemic brain edema or to lower the threshold for its development. Both approaches require a better knowledge of the pathophysiology of focal ischemic brain edema. The time course and the main cause of initiation and promotion of ischemic edema, will be described.

Material and Methods

Animal Preparation

Adult cats were anesthetized with 30 mg/kg pentobarbital, and artificially ventilated with room air. Physiological variables such as body temperature, blood gases and blood pressure were continuously monitored and kept close to normal. The middle cerebral artery (MCA) was occluded permanently by a transorbital approach, and the animals were kept alive for 1 to 4 h after occlusion. Blood flow was measured before MCA occlusion, 15 min after occlusion, and at the end of the experiments, using the intracardiac microsphere injection technique.

Brain Volume and Cortical Impedance

Brain volume was monitored in 13 animals by recording the displacement of the brain surface in respect to the bony calvarium. For this purpose a piston was placed on the surface of the left middle ectosylvian gyrus, and its movement measured with an induction coil implanted in the skull. Cortical impedance was assessed in 8 cats at the middle ectosylvian gyrus of both hemispheres, using a modification of the 4-needles method described by Fenstermacher et al. A rectangular constant current pulse of 1 ms duration and 1 mA intensity was passed at a frequency of 3/min through the outer electrodes, and the voltage drop was recorded across the inner electrodes. The signal was amplified with AC amplifiers (time constant 1 sec), stored on a digital os-
Sampling of Brain Tissue

In one group (16 experiments) 8 ml of India ink (Pelikan Werke, Hannover, FRG) were injected into the left ventricle of the heart, and 4 seconds later a 5 ml-barbital bolus was given for inducing cardiac arrest (single dye-passage). The brain was subsequently dissected in a humild chamber, and samples taken from grey and white matter of the territories of the middle cerebral artery, the posterior cerebral artery, and the marginal zone between both. The samples were processed for regional cerebral blood flow, as previously described and for water and electrolyte content, as described below.

In a second group (31 experiments) the heads were frozen in situ by pouring liquid nitrogen on the exposed calvarium. The low-perfused areas of frozen brain were visualized by injecting 8 ml of 2% Evans blue (EB) in physiological saline intravenously immediately before the start of freezing. This resulted in a clear demarcation of the unstained MCA territory from the blue color of the rest of the brain. The frozen head was sawed into 1 cm-thick slices under intermittent liquid nitrogen irrigation, and subsequently dissected at −20°C in a cryostat. Samples containing both grey and white matter were taken from the middle cerebral and posterior cerebral artery territories and from the marginal zone. Aliquots of these samples were processed for blood flow, tissue metabolites, tissue osmolality, water, and electrolyte content.

Tissue Water and Electrolytes

Brain samples from both groups were dried in an oven at +95°C to constant weight, and tissue water content was calculated according to Elliott and Jasper. The dry tissue was drowned, reweighed and suspended in 5 ml of 0.75 mol H2NO₃. After determination of radioactivity for the calculation of blood flow, the tissue was digested for one week in nitric acid, and sodium and potassium were determined in the supernatant by flame photometry (Eppendorf Photometer, Hamburg, FRG).

Tissue Osmolality

Frozen tissue samples from the second group of animals were weighed in precooled vials. Two ml of boiling distilled water were added, and the vials were placed in boiling water for 1 h. The vials were reweighed after reaching room temperature, and osmolality of the supernatant was measured by cryoscopy. Tissue osmolality was calculated by

\[ O_t = O_s - \frac{W_s + W_t}{W_t} \]

Where \( O_t \) is sample osmolality in mosm/kg wet weight, \( O_s \) is supernatant osmolality, \( W_s \) is distilled water added in g, and \( W_t \) is sample water in g. After measurement, the sample was dried to constant weight and processed for tissue water and electrolyte content, as described above.

Tissue Metabolites

Frozen tissue samples — aliquots of those processed for CBF, osmolality and electrolyte content — were drowned in liquid nitrogen, and homogenized in perchloric acid, using standard extraction methods. ATP, ADP, AMP, lactate and glucose were measured by specific enzymatic techniques. All determinations were done with kits provided by Boehringer Mannheim, FRG.

Results

Animals were grouped according to the initial reduction in blood flow in the brain in the territory of the middle cerebral artery following MCA occlusion. Animals in which blood flow initially decreased below 10–15 ml/100 g/min developed significant brain edema and were referred to as those with critical reduction of blood flow. Animals in which MCA occlusion led to flow values of more than 15 ml/100 g/min did not develop brain edema and were referred to as those without critical reduction in blood flow. In the following, the 2 groups will be described separately.

Animals with Critical Reduction in Blood Flow

Brain Swelling and Intracerebral Fluid Shifts

The development of ischemic brain swelling was monitored by continuous recording of the displacement of the cortical surface. Cortical displacement over a wide range is linear with the increase in brain volume, and, therefore, is a reliable indicator of brain swelling. One minute after MCA occlusion, the brain began to swell, and swelling gradually increased during the duration of the experiment (fig. 1, 3). Brain swelling was accompanied by a shift of water from the extracellular space into the intracellular compartment. This could be demonstrated by measuring cortical impedance which is a function of the size of the extracellular space, and which initially increased rapidly and then more slowly from 282 to 660 ohm/cm within 2 h (fig. 2). Calculation of the volume of the extracellular space by the Maxwell approach revealed an initial rapid shrinkage from 19.8 to 14.6% within 5 min of ischemia. Subsequently it decreased more slowly to 11.4% within 2 h (fig. 3). In the opposite hemisphere extracellular space did not change, which is an advantage of the Maxwell approach.

Brain Water and Electrolytes

Cortical water in the MCA territory increased from 80.7 to 83.0% wet weight within 4 h of ischemia (table...
The water gain of the tissue was accompanied by a shift of sodium and potassium: net sodium concentration increased from 262 to 454 meq/kg dry weight within 4 h, while net potassium decreased from 442 to 305 meq/kg dry weight at this interval (table 1, fig. 4). The inverse ion change was best revealed by the ratio of sodium/potassium content which, in the ischemic cortex, rose from 0.60 to 1.55 within 4 h after the insult (fig. 4).

It was surprising to see that the relationship between electrolyte and water changes in an individual specimen was not as close as it might appear from the mean values. As shown in fig. 5 a considerable scatter was present although measurements were performed in the same tissue sample. It is, therefore, not unlikely that the derangements of water and electrolyte homeostasis are indirectly, not directly, linked to each other.

The consequences of MCA occlusion were not restricted to the ischemic area alone. As has been described, local cerebral blood flow decreased tran-
TABLE 1  Cerebral Water and Electrolyte Content Before and After Transorbital Occlusion of the Middle Cerebral Artery

<table>
<thead>
<tr>
<th></th>
<th>H2O</th>
<th>Na</th>
<th>K</th>
<th>Na/K</th>
<th>Border zone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCA territory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical ischemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>80.7 ± 0.4</td>
<td>262 ± 9</td>
<td>442 ± 20</td>
<td>0.60 ± 0.03</td>
<td>79.9 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>(6)</td>
<td>(6)</td>
<td>(6)</td>
<td>(6)</td>
<td>(6)</td>
</tr>
<tr>
<td>1 hour</td>
<td>81.4 ± 0.5</td>
<td>303 ± 20</td>
<td>382 ± 20*</td>
<td>0.80 ± 0.05*</td>
<td>79.2 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>(5)</td>
<td>(5)</td>
<td>(5)</td>
<td>(5)</td>
<td>(4)</td>
</tr>
<tr>
<td>2 hours</td>
<td>82.4 ± 0.7*</td>
<td>368 ± 36</td>
<td>352 ± 14**</td>
<td>1.10 ± 0.07**</td>
<td>80.1 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>(6)</td>
<td>(6)</td>
<td>(6)</td>
<td>(6)</td>
<td>(3)</td>
</tr>
<tr>
<td>4 hours</td>
<td>83.0 ± 0.3**</td>
<td>454 ± 13**</td>
<td>305 ± 32**</td>
<td>1.55 ± 0.17**</td>
<td>79.6 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>(5)</td>
<td>(5)</td>
<td>(5)</td>
<td>(5)</td>
<td>(3)</td>
</tr>
<tr>
<td>Non-critical ischemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4 hrs</td>
<td>80.8 ± 0.3</td>
<td>251 ± 12</td>
<td>412 ± 15</td>
<td>0.60 ± 0.03</td>
<td>79.9 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>(11)</td>
<td>(11)</td>
<td>(11)</td>
<td>(11)</td>
<td>(7)</td>
</tr>
</tbody>
</table>

Values are means ± se (number of animals in parenthesis). Water is expressed as vol. % and electrolytes as meq/kg d.w. Statistical difference from control: *p < 0.05, **p < 0.001.

experimental situation, therefore, confirms the absence of vasogenic edema during the initial 4 h after MCA occlusion.

**Tissue Metabolites and Tissue Osmolality**

Control values were obtained in 2 sham-operated animals with dissection and manipulation of the left MCA but without clamping the vessel, and in 3 animals without exposure of the MCA. The sham-operated animals exhibited a distinct decrease of high energy phosphate, but not of adenylate energy charge, in the territory of the manipulated MCA. The initial values given in table 2 are lumped data of all 5 experiments.

Acute and persistent ischemia in the MCA territory produced an initial drop of creatine phosphate, ATP, and glucose tissue concentrations to only 50–70% of control, although blood flow was decreased to as low as 5 ml/100 g/min. Lactate, on the other hand, increased more than 10-fold, indicating a stimulation of anaerobic glycolysis (Table 2). Lactacidosis was accompanied by a rise in tissue osmolality, which in the territory of the MCA increased by 16–22 mosm/kg. Although this value corresponds numerically to the increase in lactate, it cannot be solely related to this substrate because other osmotically active particles such as electrolytes, glucose and phosphate, also changed. Brain water and lactate were not significantly correlated (fig. 5), indicating that edema formation did not depend on lactacidosis alone.

The measurement of metabolites and osmolality in brain regions which were supplied by the MCA revealed changes with decreasing severity in the border zone of the ischemic territory, in the territory of the ipsilateral posterior cerebral artery, and the opposite hemisphere, in that order. The most pronounced change was of lactate, which even in the opposite hemisphere increased more than 4-fold (table 2).

**Animals Without Critical Reduction of Blood Flow**

In 8 animals, MCA occlusion caused only a minor decrease of brain blood flow in the MCA territory although occlusion was done under visual control, and postmortem inspection confirmed the correct position of the vessel clip. In these animals collateral circulation apparently was efficient enough to maintain an adequate blood supply to the ischemic territory. There was, however, a decrease in EEG intensity, indicating that the clamping had a functional impact on the brain tissue.1
TABLE 1 (Continued)

<table>
<thead>
<tr>
<th>EC</th>
<th>Border zone</th>
<th>Lactate</th>
<th>CrP</th>
<th>ATP</th>
<th>EC</th>
<th>Lactate</th>
</tr>
</thead>
<tbody>
<tr>
<td>405 ± 10</td>
<td>0.61 ± 0.01</td>
<td>80.2 ± 0.4</td>
<td>240 ± 11</td>
<td>401 ± 16</td>
<td>0.60 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>(5)</td>
<td>(5)</td>
<td>(6)</td>
<td>(6)</td>
<td>(6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>391 ± 10</td>
<td>0.64 ± 0.05</td>
<td>79.6 ± 0.6</td>
<td>272 ± 38</td>
<td>425 ± 16</td>
<td>0.63 ± 0.07</td>
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</tr>
<tr>
<td>(4)</td>
<td>(4)</td>
<td>(4)</td>
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<td>(4)</td>
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<td></td>
</tr>
<tr>
<td>403 ± 18</td>
<td>0.62 ± 0.07</td>
<td>79.4 ± 0.6</td>
<td>242 ± 17</td>
<td>409 ± 1</td>
<td>0.59 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>466 ± 92</td>
<td>0.60 ± 0.17</td>
<td>79.6 ± 0.9</td>
<td>241 ± 4</td>
<td>392 ± 8</td>
<td>0.61 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
<td></td>
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</tr>
<tr>
<td>434 ± 16</td>
<td>0.58 ± 0.02</td>
<td>80.2 ± 0.2</td>
<td>245 ± 7</td>
<td>423 ± 10</td>
<td>0.58 ± 0.01</td>
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</tr>
<tr>
<td>(7)</td>
<td>(7)</td>
<td>(7)</td>
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</tr>
</tbody>
</table>

In this group of animals brain water and electrolyte content did not change significantly in the territory of the MCA nor in the rest of the brain (table 1). This is not surprising because in none of the areas investigated did brain blood flow decrease below the critical threshold for induction of ischemic brain edema.

In 6 animals metabolites were determined after 2 to 4 h of non-critical reduction of blood flow following MCA occlusion. High energy phosphates were significantly decreased and lactate increased, although less pronounced than in the first group (table 2). These observations are in contrast to the stable situation of water and ion homeostasis, and may explain the changes in the EEG activity in this group of animals.1

Discussion

There is increasing evidence that brain edema plays a major role in the pathophysiology of stroke.16,14 Clinico-pathological studies indicate that hemispheric edema and brain swelling with subsequent tentorial herniation are the direct reason for fatal outcome of supratentorial ischemic stroke in at least 10% of the patients.18 Our own observation of a gradual decrease of blood flow in the presence of local ischemic brain edema indicates that brain edema causes progressive microcirculatory compression, and thereby aggravates the primary ischemic impact.1

Experimental data from stroke models in animals, although obtained from different species under different experimental conditions, consistently show
TABLE 2. Substrates of the Energy Producing Metabolism Before and After Transorbital Occlusion of the Middle Cerebral Artery

<table>
<thead>
<tr>
<th>Time</th>
<th>CrP ± SE (nmol/g wet weight)</th>
<th>ATP ± SE (nmol/g wet weight)</th>
<th>EC ± SE</th>
<th>Lactate ± SE (meq/kg w.w)</th>
<th>Border zone CrP ± SE (nmol/g wet weight)</th>
<th>Border zone ATP ± SE (nmol/g wet weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical ischemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2.96 ± 0.32 (5)</td>
<td>2.00 ± 0.19 (5)</td>
<td>0.84 ± 0.01 (5)</td>
<td>1.6 ± 0.1 (5)</td>
<td>2.89 ± 0.10 (5)</td>
<td>1.92 ± 0.05 (5)</td>
</tr>
<tr>
<td>1 hour</td>
<td>1.73 ± 0.35** (5)</td>
<td>1.28 ± 0.20* (5)</td>
<td>0.83 ± 0.04 (5)</td>
<td>13.8 ± 4.1*</td>
<td>1.70 ± 0.25** (6)</td>
<td>1.28 ± 0.23* (6)</td>
</tr>
<tr>
<td>2 hours</td>
<td>1.64 ± 0.07** (7)</td>
<td>1.46 ± 0.08* (7)</td>
<td>0.78 ± 0.01** (7)</td>
<td>24.1 ± 3.3**</td>
<td>1.96 ± 0.19** (6)</td>
<td>1.39 ± 0.11** (6)</td>
</tr>
<tr>
<td>4 hours</td>
<td>1.44 ± 0.11** (6)</td>
<td>1.10 ± 0.09** (6)</td>
<td>0.80 ± 0.01* (6)</td>
<td>17.7 ± 4.6*</td>
<td>1.81 ± 0.08** (7)</td>
<td>1.38 ± 0.07** (7)</td>
</tr>
<tr>
<td>Non-critical ischemia</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2-4 hrs</td>
<td>1.70 ± 0.14** (6)</td>
<td>1.38 ± 0.08* (6)</td>
<td>0.82 ± 0.01 (6)</td>
<td>14.9 ± 4.2*</td>
<td>1.75 ± 0.23** (6)</td>
<td>1.43 ± 0.10** (6)</td>
</tr>
</tbody>
</table>

Values are means ± SE (number of animals in parenthesis). CrP = creatine phosphate; ATP = adenosine triphosphate; EC = adenylate energy charge. Values are expressed as nmol/g wet weight. Statistical difference from control. *p < 0.06, **p < 0.01.

an increase in water content or decrease in specific gravity.11, 14-22 Edema commences within the first hours after the onset of ischemia and reaches a peak after about 2 days.11 Water content seems to recover to normal during the end of the first and during the second week, a time course which matches well with that of general, most probably edema-related neurological symptomatology.14 It also correlates with the time course of decreased tissue-radiodensity in computerized axial tomography, supposed to represent edema.14, 26

The most significant amount and rate of edema accumulation occurs days after the vascular occlusion.11 It is accompanied by a significant breakdown of the blood-brain barrier to macromolecules, first observed at 4–6 h and having a maximum at 2–4 days. It is, therefore, referred to as "vasogenic."12, 19, 23 The numerically smaller, early water uptake without significant permeability changes of the blood-brain barrier is thought to be a "cytotoxic" type of brain edema.14, 29 In the present series of experiments, animals were allowed to survive up to 4 h, and edema, in consequence, was mainly of the cytotoxic type. This was confirmed by the absence of Evans blue staining and the absence of serum protein accumulation in the brain tissue, as evidenced by specific immunohistochemical techniques.

The pathophysiology of the cytotoxic type of ischemic brain edema has been investigated in detail in an experimental model of global ischemia in which total blood flow was temporarily completely interrupted.20-32 It could be demonstrated in this model that osmotic and ionic concentration gradients between blood and brain built up during ischemia, and

Fig. 5. Correlation between tissue water and the sodium/potassium ratio (above) and lactate content (below) 1 to 4 hours after occlusion of the left middle cerebral artery. Measurements were performed in the territory of the occluded vessel.
are equilibrated upon recirculation. In focal incomplete ischemia, as in the present experiment, the situation is different because water, ions and substrates are available from any remaining flow and the peri-ischemic, normally perfused brain tissue. Ionic and osmotic gradients which build up during ischemia are therefore equilibrated with a time constant which depends on the individual constellation of flow, size and geometry of the infarct. This presumably is the reason that osmolality of the ischemic brain tissue increased only by about 20 mosm/kg in comparison to the 30–50 mosm/kg increase during complete ischemia, and that brain swelling began immediately after vascular occlusion.

The reasons for the build up of ionic and osmotic gradients are only partially understood. One factor is a change in transmembrane ion homeostasis. Disturbances of the ion exchange pumps and/or changes in cell membrane permeability cause an influx of sodium and water from the extracellular into the intracellular compartment, resulting in cell hydrops at the expense of the size of the extracellular space. In the present experimental situation, beginning shrinkage of the extracellular space could be demonstrated as early as 1 min after vascular occlusion, leading to a steep increase in cortical impedance. This change in impedance corroborates earlier findings by Branst who observed a similar phenomenon following middle cerebral artery occlusion in monkeys.

Intracellular uptake of sodium was associated with a release of potassium into the extracellular fluid. An increase in extracellular potassium has been reported by several authors both in global and focal ischemia. It is accompanied by severe functional disturbances because it is associated with a breakdown of cell membrane potentials. The change in extracellular ion concentrations leads to concentration gradients between extracellular fluid on one hand, and blood and cerebral spinal fluid on the other. This causes a loss of potassium and an uptake of sodium into the brain tissue, which in turn is accompanied by an increase in net water content. The resulting changes in electrolyte content of the brain are well known, and have been described by several authors before.

Another reason for increased water uptake in the ischemic tissue is an increase of catabolic products. In fact, it could be shown that the osmotic activity of the ischemic tissue increased by about 20 mosm/l. An important factor is accumulation of lactate but other catabolic products are probably also involved.

Evidence has been found that the threshold of blood flow for edema formation and biochemical changes is not the same. Our present data further demonstrate that substantial amounts of energy-rich phosphates were present despite severe electrolyte shifts, indicating that the disturbance of ion homeostasis was not solely related to the amount of energy-rich phosphates. There are also previous reports that energy metabolites are not completely depleted following middle cerebral artery occlusion. Held et al. found a reduction of tissue energy phosphates to only about 50% of control at 24 h, and Michenfelder and Sundt observed a depression of ATP to 30% of control after 3 to 4 h. These values are very close to our own measurements in the brain supplied by the middle cerebral artery. One factor which may lead to electrolyte disturbances in the presence of energy-rich compounds could be a selective change in membrane permeability for sodium, such as during spreading depression or in the presence of high glutamate levels. Another factor might be a shutdown of cortical activity, leading to a saving of the energy demands of the tissue. A decrease in EEG amplitude has been observed at substantially higher flow values than those causing a breakdown of energy metabolism. A discrepancy between energy state and metabolic activity of the brain has also been observed following complete ischemia, and this may be the reason for the fact that measurements of regional glucose utilization revealed an almost complete cessation of metabolism in the ischemic territory.

In a situation in which the local vascular occlusion is permanent, the development of ischemic brain edema is the major risk factor for the eventual sequel of ischemia. Therapy to improve ischemic brain damage, therefore, should focus on the prevention of brain edema. As has been demonstrated, edema cannot be explained by energy failure but rather seems to
be an accompaniment of transmembrane ion shifts and tissue hyperosmolality. An improvement of collateral blood supply, on the other hand, will be less efficient because any increase in perfusion pressure in the presence of developing edema is annihilated by the associated increase in vascular resistance. Future research, therefore, should be directed toward the prevention or treatment of the accumulation of osmotically active products and the changes in membrane permeability to ions.

Acknowledgment

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References

35. Astrap J, Symon L, Branston NM, Lassen NA: Cerebral evoked potential and extracellular K+ and H+ at critical levels of brain ischemia. Stroke 8: 51–57, 1977
Intra-Arterial Nitroprusside Treatment of Acute Experimental Vasospasm

LEONARD F. HIRSH, M.D.

SUMMARY The effect of intra-arterial sodium nitroprusside infusions on acute experimental basilar artery spasm was studied in dogs. Vasospasm produced by subarachnoid hemorrhage at normal intracranial pressure was partially relieved by nitroprusside. When given by the intra-arterial route, 15 times the recommended maximum intravenous dose can be infused without significant hypotension or elevation in intracranial pressure.

Intra-Arterial Nitroprusside Treatment of Acute Experimental Vasospasm

ALTHOUGH MANY TREATMENTS for cerebral vasospasm have been proposed, none has achieved general acceptance. Treatment with sodium nitroprusside has seemed promising but its use has been limited by the severe hypotension produced by intravenous infusion, necessitating simultaneous administration of another vaso-active drug.1-7 During treatment of a patient with ergot poisoning,8 the author made the serendipitous discovery that the intra-arterial use of nitroprusside appeared to have less effect on systemic blood pressure than intravenous administration, and yet the arterial vasodilatory response was maintained. Because of this, the effect of nitroprusside delivered directly into the vertebral artery on acute experimental basilar artery spasm following subarachnoid hemorrhage was studied in dogs.

Materials and Methods

Ten mongrel dogs, weighing 22 to 27 kg, were initially anesthetized with Innovar-Vet, 2 cc subcutaneously followed by 2 cc intramuscularly. An intravenous line for D2/2 normal saline was established in one forepaw, and further anesthesia was achieved with 60 mg increments of intravenous sodium pentobarbital. Sodium pentobarbital was needed during the nitroprusside trials in only one animal (dog #10). A cuffed endotracheal tube was inserted. Systemic mean arterial blood pressure (MAP) was recorded with a heparinized transducer connected to a polyethylene line placed in the inferior aorta through the left femoral artery. The right temporals muscle was elevated from the cranium with the Bovie coagulator. A ¼ inch burr hole was placed with a dental drill in the right parietal region, the hole tapped, the dura incised in a cruciate fashion, and a subarachnoid bolt with a Luer-lock connector threaded into the hole. Intraocular pressure (ICP) was recorded with a transducer. The suboccipital region and the posterior arch of Cl were exposed with the Bovie coagulator.

MAP and ICP were displayed on a strip chart recorder running at 0.25 mm per second. For angiography retrograde catheterization of the left vertebral artery was performed through the right femoral artery under fluoroscopic control. The dog was continuously ventilated with a mechanical volume respirator. The dog was then placed prone and a control angiogram was done demonstrating the basilar artery. The cisterna magna was tapped with a 20 gauge spinal needle, 2 cc of spinal fluid were removed, and 2 cc of fresh arterial blood were injected slowly while monitoring the ICP to produce no elevation. After 26.1 ± 1.3 minutes, during which the dog’s feet were elevated 30°, angiography was repeated to demonstrate the presence or absence of basilar artery spasm (D1: diameter basilar artery after hemorrhage, percentage of control).

An infusion of 5% dextrose in water was begun at 3.82 cc per minute (dogs 1 through 8) or at 7.64 cc per minute (dogs 9 and 10) through the vertebral artery catheter for 7.69 ± 0.35 minutes followed by angiography to evaluate the basilar artery diameter (D0, percentage of control). Three picture angiograms were performed in each animal with 10 cc of lothalamate meglumine (Conray).

An infusion of 50 mg of sodium nitroprusside in 500 cc of 5% dextrose in water was then given for 7.69 ± 0.35 minutes at 382 μgm per minute in 8 dogs.

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