Acute Effect of Angiographic Contrast Medium on Cortical Specific Gravity After Middle Cerebral Artery Occlusion in Rats

Jeffrey J. Olson, MD, David W. Beck, MD, and David S. Warner, MD

Early angiography after cerebral arterial occlusion has been cited as potentially detrimental. This investigation evaluates the effect of acute angiographic contrast medium administration on the cortical edema induced by middle cerebral artery (MCA) occlusion. Sixteen rats underwent MCA occlusion, and after 1 hour half the rats underwent ipsilateral internal carotid injection of meglumine diatrizoate, whereas the remainder underwent cervical internal carotid exposure only. Six rats had only sham operations on the MCA and internal carotid, and 4 other rats served as normal controls. Cortical specific gravity was measured to reflect cerebral edema 4 hours after occlusion or sham operation. Specific gravity of the lateral frontal cortex in the hemisphere ipsilateral to occlusion was 1.0396 ± 0.0011 (mean ± SEM) when no angiographic contrast medium was administered, significantly less (p<0.01) than in rats exposed to contrast medium (specific gravity 1.0442 ± 0.0005). The latter value was not significantly different from normal. Other cortical areas on the side of the contrast medium injection were also relatively dehydrated compared with normal controls. Early meglumine diatrizoate administration after MCA occlusion results in a decrease in cerebral cortical edema, possibly by inducing an osmotic gradient that draws water from the extravascular space. (Stroke 1987;18:924–926)

The initial diagnostic study in a patient with an acute stroke syndrome is usually computed tomographic (CT) scanning or nuclear magnetic resonance imaging (NMR) of the brain. Sometimes therapy depends on knowledge of the site and nature of the vascular abnormality. Angiography is often the procedure of choice to define the requisite information. A potential risk of neurologic deficit is attached to this choice.1-7 Besides catheter-induced complications, such as embolization and dissection, it has been suggested that enhancement of edema in the region of the stroke, with further compromise of the already ischemic parenchyma, may play a role.4-8

The purpose of this investigation was to evaluate the effect of angiographic contrast medium on the cortical edema induced by cerebral arterial occlusion.

Materials and Methods

The right proximal middle cerebral artery (MCA) occlusion (MCAo) as described by Tamura et al8 was used to induce cortical edema in 26 300–400 g male Wistar rats. Angiographic contrast medium (undiluted meglumine diatrizoate, 1768 mosm/l, 29% iodine content) was injected at 0.04 ml/sec for 1.5 seconds via retrograde cannulation of the external carotid artery ipsilateral to the MCAo. These parameters were chosen to parallel an internal carotid angiogram in a 70-kg human using a total contrast volume of 12 ml delivered at 8 ml/sec, calculated as [representative contrast volume in humans]/[representative human weight]) x (average rat weight) = (12 ml/70 kg) x 0.35 kg = 0.059 ml of contrast medium. This volume was rounded to 0.06 ml and injected at a rate such that ½ of the volume was delivered in the first second, ½ in the next ½ second; i.e., 0.04 ml/sec for 1.5 seconds. During infusion, the ipsilateral pterygopalatine branch of the internal carotid artery was occluded.10 Anesthesia for the MCAo and the carotid dissection was 350 mg/kg chloral hydrate administered intraperitoneally.

Cortical specific gravity (SG) was measured as an index of edema.9 The rats were anesthetized in an ether chamber until immobile and then decapitated. The brain was removed in ≤2 minutes, placed on a dry surface, and transferred to an enclosed chamber with >90% relative humidity at 25°C. A bicoronal section of the brain at the level of the main cortical branch of the MCA was made. The cortical ribbon from the hemispheric convexity was dissected free in each hemisphere and trisected into lateral, mediolateral, and medial samples weighing approximately 20 mg each. This pattern of cortical segmentation was chosen to obtain progressively less MCA perfusion in each fragment, lateral to medial. The right lateral sample contained no macroscopic evidence of surgical manipulation in any rat. Cortical fragments were then introduced into a Percoll (Pharmacia AB, Uppsala, Sweden) linear density gradient with a sucrose concentration of 0.125 M, generated according to the method of Tengvar et al11,12 and calibrated using spherical glass floats with known densities of 1.0300, 1.0350, 1.0400, 1.0450, and 1.0500 g/cm3 (Scientific Glass, Bloomfield, N.J.). Plotting the height in the column occupied by the floats vs. their SG assured...
linearity of the column and allowed determination of the density of the brain samples from their height in the column 3 minutes after introduction.

Twenty-six rats were divided into 4 groups: MCAo/contrast medium (n = 8), MCAo only (n = 8), sham-operated (n = 4), and normal (n = 6). MCAo/contrast medium rats underwent MCA occlusion at time zero, angiographic contrast medium infusion at 1 hour, and sacrifice and cortical SG measurement at 4 hours. MCAo-only rats underwent MCA occlusion at time zero and dissection of the ipsilateral carotid complex at 1 hour, but no cannulation or contrast medium injection. The rats were killed and underwent cortical SG measurement at 4 hours, as in the first group. Sham-operated rats underwent the surgical approach to the MCA, without occlusion, at time zero and ipsilateral carotid complex exposure without cannulation at 1 hour. As with the previous 2 groups, the rats were killed at 4 hours after MCA approach, and cortical SG was measured. Normal rats underwent no surgical manipulation and were killed at random times for cortical SG measurement.

The data were analyzed using Student’s t test for unpaired data with the criterion for significance being \( p < 0.05 \). Data are reported as mean ± SEM.

Results

SG for the 4 groups is shown in Table 1. SG of the lateral segment of the right hemispheric cortical ribbon of the MCAo-only group was 1.0396 ± 0.0011. This is the segment proposed to receive the greatest proportion of its blood flow from the MCA. This SG was significantly less than that of analogous segments from the MCAo/contrast medium (1.0442 ± 0.0005, \( p < 0.01 \)), sham-operated (1.0447 ± 0.0005, \( p < 0.02 \)), and normal (1.0443 ± 0.0002, \( p < 0.01 \)) groups, suggesting greater water content in the MCAo-only group.

SG of the lateral segment of the right hemisphere of the MCAo/contrast medium rats was not different from sham-operated or normal rats. SG of the mediodlateral (1.045 ± 0.0001) and medial (1.0451 ± 0.0002) segments of the MCAo/contrast medium rats was significantly greater (\( p < 0.01 \)) than of normal rats, indicating a lower water content. These segments are relatively less dependent on MCA perfusion. There was no difference between sham-operated and normal rats, indicating relative stability of major physiologic variables with these procedures. None of the various manipulations resulted in any significant change from normal in left hemispheric cortical SG.

Discussion

Angiographic investigation is useful in defining the anatomic abnormality responsible for various stroke syndromes. Proper early diagnosis may speed the institution of appropriate therapy. Instances of posttraumatic cerebral carotid dissection or aneurysm, early or delayed postoperative deficits following carotid endarterectomy or intracranial aneurysm clipping, and stroke in young patients are some examples. In addition to the known risks of angiography, such as catheter manipulation, we have been concerned that angiography can induce endothelial injury and exacerbate cerebral edema.\(^4,8\) This investigation was designed to address these concerns.

We found that MCAo resulted in a decrease in SG (i.e., an increase in water content) of the region primarily perfused by the occluded vessel when compared with analogous regions in rats undergoing occlusion followed by contrast medium injection \( (p < 0.01) \). MCAo-only rats had clearly increased water content compared with normal rats \( (p < 0.01) \). MCAo-only rats also had significantly increased water content compared with sham-operated rats \( (p < 0.02) \). There was no significant difference between the SG of cortex in the territory of the vascular occlusion in rats receiving contrast medium injection and normal rats, indicating that contrast medium injection results in dehydration of the cortex in rats with MCAo. Dehydration was also noted in the mediodlateral and medial segments of the contrast medium-injected rats; SG of these segments was significantly greater than in normal rats, again implying local tissue dehydration, even in areas unlikely to be so clearly perfused by the occluded MCA.

The data must be interpreted in light of the limitations of this model. A permanent occlusion of the MCA with no reflow was induced. Thus, no extrapolation can be made to situations in which transient occlusion occurs with reflow initiated shortly thereafter, as in embolic phenomena. Angiographic contrast medium was injected very soon after arterial occlusion, a circumstance that occurs only in selected clinical settings, mainly early postoperative complications. The effects of angiographic contrast medium were measured only in the acute state, 3 hours after injection and 4 hours after the initial insult. Recognizing this, no

### Table 1. Cortical Specific Gravity

<table>
<thead>
<tr>
<th>Group</th>
<th>Right hemisphere</th>
<th>Left hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lateral</td>
<td>Mediodlateral</td>
</tr>
<tr>
<td>MCAo/contrast medium</td>
<td>1.0442 ± 0.0005</td>
<td>1.0452 ± 0.0001</td>
</tr>
<tr>
<td>MCAo-only</td>
<td>1.0396 ± 0.0011</td>
<td>1.0443 ± 0.0001</td>
</tr>
<tr>
<td>Sham-operated</td>
<td>1.0447 ± 0.0005</td>
<td>1.0445 ± 0.0004</td>
</tr>
<tr>
<td>Normal</td>
<td>1.0443 ± 0.0002</td>
<td>1.0443 ± 0.0002</td>
</tr>
</tbody>
</table>

Hemispheres trisected; cortical ribbon obtained from coronal section at level of the main cortical branch of the middle cerebral artery. MCAo, middle cerebral artery occlusion. Values are mean ± SEM g/cm\(^3\).
conclusions can be drawn about any long-term effects on the clinical outcome or lesion size. The short period of time to sacrifice was chosen because previous use of this model had shown the onset of significant cerebral edema as soon as 3 hours after vessel occlusion.\(^{13,14}\)

SG was chosen as the parameter to measure because previous work showed this value to be essentially interchangeable with water content in various forms of experimental cerebral edema.\(^{15}\) In turn, water has been shown to be a significant component of cerebral edema induced by cerebral infarction.\(^{16,17}\)

These observations indicate that rapid injection of hyperosmolar angiographic contrast medium, such as 1768 mosm/l meglumine diatrizoate, results in a significant removal of water from the cerebral cortex of the areas perfused by the injected artery. Such effects are not restricted to areas perfused by the occluded branch, but also include adjacent areas with open tributaries. We suggest that the blood–brain barrier may continue to be a competent selectively permeable structure in the majority of the tissue sampled in this model.

Endothelial damage is a well-known byproduct of diatrizoate exposure. Morettin et al\(^{18}\) demonstrated significant cellular swelling, denudation, platelet aggregation, and fibrin deposition within 1 hour after a 3-minute exposure to 60% diatrizoate. Repeated small injections of 50% diatrizoate have been shown to cause interendothelial tight junction breakdown and increased pinocytosis.\(^{8}\) The contrast medium exposure in each of these examples is of a considerably greater magnitude than in our model. Thus, with relatively small contrast medium exposures, comparable to human internal carotid angiography, this model behaves as though there is some preservation of the blood–brain barrier. The proposed mechanism of dehydration would then be an osmotic gradient induced by the contrast medium. Histologic study of the vasculature in this model will be necessary to document this hypothesized preservation of endothelium.

In conclusion: the early administration of the hyperosmolar angiographic contrast medium meglumine diatrizoate into a hemisphere with a major vessel occlusion did not result in a significant enhancement of cortical edema and, in fact, reduced its water content.

References


Keywords
- meglumine diatrizoate
- cerebral angiography
- specific gravity
- cerebral edema
- stroke
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