Cerebral circulation and metabolism in the acute stage of subarachnoid hemorrhage

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OBJECT. The mechanism of reduction of cerebral circulation and metabolism in patients in the acute stage of aneurysmal subarachnoid hemorrhage (SAH) has not yet been fully clarified. The goal of this study was to elucidate this mechanism further.

METHODS. The authors estimated cerebral blood flow (CBF), cerebral metabolic rate of oxygen (CMRO2), O2 extraction fraction (OEF), and cerebral blood volume (CBV) preoperatively in eight patients with aneurysmal SAH (one man and seven women, mean age 63.5 years) within 40 hours of onset by using positron emission tomography (PET). The patients’ CBF, CMRO2, and CBF/CBV were significantly lower than those in normal control volunteers. However, OEF and CBV did not differ significantly from those in control volunteers. The significant decrease in CBF/CBV, which indicates reduced cerebral perfusion pressure, was believed to be caused by impaired cerebral circulation due to elevated intracranial pressure (ICP) after rupture of the aneurysm. In two of the eight patients, uncoupling between CBF and CMRO2 was shown, strongly suggesting the presence of cerebral ischemia.

CONCLUSIONS. The initial reduction in CBF due to elevated ICP, followed by reduction in CMRO2 at the time of aneurysm rupture may play a role in the disturbance of CBF and cerebral metabolism in the acute stage of aneurysmal SAH.

KEY WORDS • subarachnoid hemorrhage • cerebral aneurysm • cerebral metabolism • positron emission tomography

Previous clinical investigations have revealed reduced CBF and cerebral metabolism in the acute stage of SAH. However, the mechanism of the reduction in CBF and cerebral metabolism is not yet clearly understood, particularly the primary process. Previous studies have indicated that CBF reduction is due to an elevation in ICP, metabolic reduction due to disturbance in brainstem-mediated O2 uptake, or metabolic reduction due to the direct effects of subarachnoid blood. However, the primary process involved in the reduction of CBF and cerebral metabolism remains controversial. In this study, we measured CBF and cerebral O2 metabolism in the acute stage of SAH by PET scanning, and studied the primary process of the reduction in CBF and cerebral metabolism in these patients.

Clinical Material and Methods

Patient Population

The patient population consisted of one man and seven women between the ages of 47 and 79 years (average 63.5 years). All patients experienced rupture of cerebral aneurysm, and all were admitted to our institution on the day of onset of rupture. The site of rupture was the ICA in four patients, MCA in three, and anterior cerebral artery in one. The extent of SAH in all patients was Grade 3 according to the CT classification system of Fisher, et al. The clinical severity of the rupture was evaluated using the Hunt and Hess classification system. According to that system, five patients were Grade II, one was Grade III, and two were Grade IV. Cerebral angiography revealed no findings indicative of cerebral ischemia such as stenosis, occlusion, or vasospasm of the cerebral arteries (Table 1).

Protocol for PET Scanning

After patients were sedated by continuous intravenous administration of flunitrazepam (0.01–0.02 μg/kg/min) to protect against rerupture of the aneurysm, PET scanning was performed. In all patients, PET scanning was performed within 40 hours (mean 16 hours) of aneurysm rupture (Table 1). We measured CBF, OEF, and CBV by using 15O2-labeled water, 15O2-labeled molecular O2, or 15O2-labeled CO as previously reported by using a Headstone V monitor (Shimazu Co., Ltd., Kyoto, Japan). The CMRO2 and CBF/CBV ratio were also calculated.

Analysis of PET findings was performed using 34 circular ROIs that were 16 mm in diameter and located symmetrically in the cortical regions as shown in Fig. 1. The mean value of 17 ROIs in each cerebral hemisphere was...
defined as the hemispheric value, and the mean value of 34 ROIs was defined as the global value. The CBF, OEF, CBV, CMRO2, and CBF/CBV levels in our patients were compared with values obtained in 16 healthy volunteers (seven women and nine men between 40 and 69 years of age, mean 54.4 ± 7.4 years). For the global value, statistical significance was established at the probability level of 0.01 by using unpaired t-tests. For the hemispheric value, statistical significance was established at 1 standard deviation from normal control values. During PET scanning, arterial blood gas analysis revealed normal PCO2 and PO2 levels in each patient, and systolic blood pressure was maintained below 140 mm Hg.

Informed written consent was obtained from the family of each patient. The protocol was approved by the Clinical PET Study Committee of the Research Institute for Brain and Blood Vessels in Akita, Japan.

Results

As shown in Table 2, the mean global CBF in our patients was 34.2 ± 8.4 ml/100 ml/min, which was significantly lower than control values (t = 3.266, p = 0.035). The mean global CMRO2 was 2.3 ± 0.3 ml/100 ml/min, which was significantly lower than control values (t = 6.164, p < 0.001). The mean global OEF was 0.47 ± 0.03, which did not differ significantly from control values (t = 0.95, p = 0.3826). The mean global CBV was 3.1 ± 0.4 ml/100 ml/min, which did not differ significantly from control values (t = 0.03, p = 0.9746). The mean global CBF/CBV ratio was 11.7 ± 2.8 ml/100 ml/min, which was significantly lower than control values (t = 2.825, p = 0.0099; Fig. 2).

Illustrative Cases

Case 1

This 62-year-old woman experienced rupture of a right MCA aneurysm. At admission her clinical classification was Grade II according to the Hunt and Hess system, and the extent of SAH was Grade 3 according to Fisher’s classification. Figure 3 consists of CT and PET images; PET scanning was performed 7 hours after the initial rupture. The CMRO2 in this patient was significantly reduced in the right hemisphere. However, CBF and CBV levels did not differ significantly from control values. The OEF was significantly reduced bilaterally. On the other hand, the CBF/CBV ratio did not differ significantly from control values. Luxury perfusion was observed bilaterally in this patient.

Case 4

This 76-year-old woman experienced rupture of a right ICA aneurysm. At admission her clinical classification was Grade II according to the Hunt and Hess system. The extent of SAH was Grade 3 according to Fisher’s CT classification. Figure 4 consists of CT and PET images; PET scanning was performed 4 hours after the initial rupture. The CBF and CMRO2 were significantly reduced bilaterally in this patient. However, the OEF and CBV levels did not differ significantly from control values. The CBF/CBV ratio was significantly reduced bilaterally. In this patient, matched perfusion was observed bilaterally.

Case 6

This 53-year-old woman experienced rupture of a left MCA aneurysm. Her clinical classification at admission was Grade III according to the Hunt and Hess system. The extent of SAH was Grade 3 according to Fisher’s CT classification. Figure 5 consists of CT and PET images; CT scanning revealed a hematoma in the left sylvian fissure, and PET scanning was performed 14 hours after the initial rupture. The CBF and CMRO2 were significantly reduced bilaterally, whereas the OEF was significantly higher in...
the left hemisphere. On the other hand, the CBF/CBV ratio was significantly reduced bilaterally. In this patient, misery perfusion was observed in the left hemisphere.

**Discussion**

This is the first report in which cerebral circulation and metabolism have been measured in the acute stage of SAH by PET scanning performed just before surgical intervention. Our results indicated that global values of CBF, CMRO₂, and CBF/CBV ratio were reduced in acute aneurysmal SAH. Because measures were recorded after patients received intravenously administered flunitrazepam, the lower CBF and CMRO₂ values may reflect its sedative action. However, the reduction in the CBF/CBV ratio in acute SAH is likely independent of a sedative effect. Forster, et al.,8 studied the effect of benzodiazepine on CBF and CBV responsiveness to CO₂ in healthy volunteers. During administration of the drug, CBF decreased and CBV responsiveness to CO₂ increased in both normocarbia and hypercarbia. Based on these results, the investigators concluded that benzodiazepine decreases both CBF and CBV. However, their results indicated that benzodiazepine administration does not affect the CBF/CBV ratio. As reported previously, cerebellar deactivation caused by a supratentorial brain lesion is associated with metabolic suppression and subsequent CBF reduction. Under these conditions, no significant change in the CBF/CBV ratio was observed.28 These results support the hypothesis that CBF reduction caused by either neuronal suppression or sedative agents is not associated with vasodilation, which is often found in brain areas in which decreased perfusion pressure is observed. We speculate that the global reduction in the CBF/CBV ratio in our patients reflects a unique hemodynamic failure caused by increased ICP following aneurysm rupture.

In two patients (Cases 1 and 6), uncoupling between CBF and CMRO₂ was observed. The patient in Case 1 had luxury perfusion, and the one in Case 6 had misery perfusion. There was also evidence of impaired cerebral perfusion in the acute stage of aneurysmal SAH in these two patients. The cause of this impaired cerebral perfusion was thought to be acute elevation in ICP at the time of aneurysm rupture. Once ICP becomes elevated to the level of mean arterial blood pressure because of aneurysm rupture, the cessation of flow lasts for a few minutes, leading to the development of cerebral anoxia and disturbance of cerebral metabolism.1,21 Transcranial Doppler examination

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**TABLE 2**

Results of PET scanning in eight patients with SAH and 16 control volunteers*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>CBF†</th>
<th>CMRO₂†</th>
<th>OEF</th>
<th>CBV†</th>
<th>CBF/CBV†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50.8/45.8‡</td>
<td>2.9/2.6</td>
<td>0.37/0.37</td>
<td>3.2/3.4</td>
<td>15.9/13.5‡</td>
</tr>
<tr>
<td>2</td>
<td>30.5/30.8</td>
<td>2.8/2.5</td>
<td>0.47/0.52</td>
<td>2.8/2.5</td>
<td>10.9/12.3</td>
</tr>
<tr>
<td>3</td>
<td>35.9/34.3</td>
<td>2.5/2.4</td>
<td>0.46/0.45</td>
<td>3.3/3.0</td>
<td>10.8/11.4</td>
</tr>
<tr>
<td>4</td>
<td>29.4/30.0</td>
<td>2.0/1.9</td>
<td>0.44/0.44</td>
<td>2.8/2.6</td>
<td>10.5/11.5</td>
</tr>
<tr>
<td>5</td>
<td>29.8/30.7</td>
<td>2.0/2.0</td>
<td>0.47/0.47</td>
<td>2.5/2.9</td>
<td>12.7/12.0</td>
</tr>
<tr>
<td>6</td>
<td>17.5/23.6‡</td>
<td>2.1/2.3</td>
<td>0.58/0.49</td>
<td>3.3/3.9</td>
<td>5.7/6.6</td>
</tr>
<tr>
<td>7</td>
<td>41.9/47.1</td>
<td>2.1/2.1</td>
<td>0.47/0.48</td>
<td>3.7/3.7</td>
<td>11.7/11.7</td>
</tr>
<tr>
<td>8</td>
<td>37.6/37.0</td>
<td>2.4/2.4</td>
<td>0.51/0.52</td>
<td>2.6/2.6</td>
<td>15.5/15.2</td>
</tr>
<tr>
<td>mean ±  SD</td>
<td>34.2 ± 8.4‡</td>
<td>2.3 ± 0.3</td>
<td>0.47 ± 0.4</td>
<td>3.1 ± 0.4</td>
<td>11.7 ± 2.8</td>
</tr>
<tr>
<td>controls</td>
<td>46.1 ± 8.6</td>
<td>3.3 ± 0.4</td>
<td>0.45 ± 0.4</td>
<td>3.0 ± 0.4</td>
<td>16.3 ± 4.1</td>
</tr>
</tbody>
</table>

* Values are given for the left/right hemispheres. Abbreviation: SD = standard deviation.
† Values are given as ml/100 ml/min.
‡ Statistically significant (p < 0.01). This level of probability was required because of multiple comparisons.
Cerebral circulation and metabolism in acute SAH

has demonstrated that blood velocity in the MCA is almost zero in the first minutes after SAH, during the period of high ICP. The cause of CBF/CBV reduction in our patients was considered to be cerebral ischemia that occurred during the course of recovery from elevated ICP caused by aneurysm rupture.

Experimental studies also provide supporting evidence. After the aneurysm ruptures, as soon as hemostasis is achieved, the pressure-buffering system begins to function, followed by a decrease in ICP and a concomitant increase in cerebral perfusion pressure, which is invariably succeeded by a rapid elevation in CBF and reactive hyperemia. Duration of prolonged elevation of ICP, which causes ischemia due to low perfusion pressure, may affect the degree of the brain damage that causes disturbance of consciousness. The longer high ICP continues, the more ischemic brain damage may occur. Further study with a larger number of cases, in which a variety of modalities such as ICP monitoring are used, would settle this important issue.

The PET findings in Case 1, in which CBF was not reduced significantly despite a significant reduction in OEF, indicate reactive hyperemia (luxury perfusion). In contrast, PET scanning in Case 6 revealed misery perfusion. A CT scan revealed a hematoma on the left sylvian fissure, and elevated ICP was considered. Under these conditions, CBF was reduced by the elevated ICP, but CMRO₂ might be preserved in the acute stage. The cause of misery perfusion in Case 6 was considered to be cerebral ischemia caused by elevated ICP resulting from the hematoma in the sylvian fissure. In such cases, focal neurological signs may be seen.

Previous PET studies performed in the acute stage of aneurysmal SAH have demonstrated a significant reduction in global CMRO₂ compared with age-matched control volunteers. In this PET study, no significant change was demonstrated in OEF or CBF/CBV ratio to suggest primary reduction in CMRO₂, with a secondary reduction in CBF due to reduced metabolic demands, and therefore, we cannot speculate on the mechanism. Although global CBF was lower than control values, this difference was not significant. Our results and those reported in previous studies may be attributable to differences in the duration from onset of rupture to time of PET study. Our studies were all performed within 40 hours of onset of rupture (mean 16 hours). In contrast, previous PET studies were performed between 1 and 4 days after onset, with half the patients undergoing PET scanning more than 3 days after rupture. This delay in evaluation may reflect a change in cerebral circulation over time due to recovery from the initial ischemia. Thus, cerebral circulation may be matched with cerebral metabolism in the early period.

Experimental reports have shown that cerebral perfusion pressure in first-time hemorrhage does not usually

J. Neurosurg. / Volume 93 / December, 2000

1017
drop to the point of perfusion arrest and does not correlate with neurological outcome. Moreover, direct and toxic effects of subarachnoid blood on brain tissue mediated by a brainstem mechanism may influence cerebral energy metabolism, and chemical mediators derived from subarachnoid blood also reportedly play a possible role. This mechanism may account for the reduced CMRO₂ in patients with low-grade SAH who showed matched perfusion, but cannot explain the reduction in the CBF/CBV ratio or the uncoupling of CBF and CMRO₂ in the present study.

Conclusions

Patients with aneurysmal SAH presented with impaired cerebral circulation and metabolism in the acute stage. Although the effects of ruptured intracranial aneurysms on cerebral circulation and metabolism represent complex interactions of several different factors (such as hydrocephalus, intracranial hemotoma, sedative effects, and chemical mediators derived from aneurysm rupture), the initial impairment due to SAH appears to be derived from the initial ICP elevation, which caused cerebral ischemia followed by CMRO₂ reduction.

References


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