Postoperative Hemodynamic and Metabolic Changes in Patients With Subarachnoid Hemorrhage

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Positron emission tomography was performed using an oxygen-15 gas inhalation technique to measure regional cerebral blood flow, metabolic rate for oxygen, oxygen extraction fraction, and cerebral blood volume in 13 patients with subarachnoid hemorrhage during the period of delayed vasospasm after surgery as well as in 10 volunteers as controls. Compared with the controls, the patients showed decreased hemoglobin concentration and decreased total arterial oxygen content due to postoperative hemodilution. Global reductions in the metabolic rate for oxygen and in the tissue oxygen supply were noted even in the apparently normal cortex of the patients in spite of adequate blood flow and adequate oxygen extraction fraction. In addition, regional reductions in blood flow and in perfusion reserve were seen in the cortical territory corresponding to cerebral vasospasm. Our results indicate that two processes are involved in the pathophysiology of cerebral vasospasm: 1) generalized impairment of oxygen metabolism with a reduced tissue oxygen supply, even in the apparently normal cortex, and 2) additional impairment of regional perfusion in the territory of vasospasm. (Stroke 1989;20:1504-1510)

Cerebral vasospasm is one of the most important causes of cerebral dysfunction after aneurysmal rupture. It is generally believed that neurologic symptoms become overt as arteries narrow and blood flow falls below the ischemic threshold. However, cerebral function during vasospasm might be affected by factors other than low perfusion, such as possible toxicity from subarachnoid clots or changes in the patient's general condition due to postoperative management.

Cerebral vasospasm also differs from other causes of cerebral ischemia in its pathogenesis, in the duration and distribution of vascular narrowing, and in the reversibility of low perfusion. Thus, the hemodynamic and metabolic sequences during vasospasm may not necessarily be similar to those during acute ischemia, which have been described in humans in previous positron emission tomography (PET) studies.

The aim of our study was to investigate the pathophysiologic mechanism of cerebral dysfunction during the period of delayed vasospasm after subarachnoid hemorrhage (SAH), in addition to clarifying the problems of current postoperative management of SAH patients under usual clinical settings.

Subjects and Methods

We selected 13 SAH patients, nine women and four men, mean age 50 (range 25-70) years between June 1986 and June 1988. We also selected 10 persons without SAH, seven men and three women with a similar age range, to serve as controls.

The patients had SAH due to an initial aneurysmal rupture in the anterior circulation; no history of other intracranial, cardiopulmonary, or metabolic disease; no intracerebral hematoma either on admission or during their entire clinical course; and underwent successful neck-clipping of aneurysms without any complications related to either surgery or anesthesia. The diagnosis of SAH was confirmed by x-ray computed tomography (CT), and the aneurysms were demonstrated on initial angiograms taken the day of admission. Aneurysms were located...
in the anterior communicating artery in four patients, in the middle cerebral artery in four patients, and in the internal carotid artery (ICA) in five patients.

Twelve patients had successful aneurysm neck clipping ≤48 hours after the initial aneurysmal rupture. In one patient (Case 3), the aneurysm neck was clipped on Day 6 after SAH, which was the day of admission. All patients underwent a unilateral frontotemporal craniotomy for aneurysmal clipping. Postoperatively, all patients were carefully managed to maintain normal fluid balance.5,6 For this purpose, each patient was given plenty of colloid agents (dextran, plasma, or albumin; 300–800 ml/day, repeated every 6–8 hours) to maintain a systolic arterial blood pressure of 120–180 mm Hg, a central venous pressure of 3–8 cm H2O, and a normal electrolyte balance. Erythrocytes were transfused as needed in patients whose hematocrits were <30%. Thus, patients were considered to be in a state of isovolemic or slightly hypervolemic hemodilution.

Neurologic status was graded on admission using the Hunt and Hess Scale.9 Outcome after 3 months was determined using the Glasgow Outcome Scale.10 Symptomatic vasospasm was defined as a delayed neurologic deterioration that could not be attributed to hydrocephalus, intracerebral hematoma, electrolyte abnormalities, or surgical procedures. Postoperative angiography was carried out in 11 patients during the period of delayed vasospasm (≤3 weeks after SAH) and in two patients after remission of clinical vasospasm (4 weeks after SAH). Degree of angiographic vasospasm was classified according to the criteria of Fisher et al11 as −, no evidence of vasospasm; +, slight vasospasm; ++, moderate vasospasm; and ++++, severe vasospasm.

We conducted the initial PET studies during the period of delayed vasospasm in all patients and subsequently investigated the relations among the clinical data, the angiographic findings, and the PET data.

PET scans were performed using a Headtome III PET scanner (Shimadzu Co., Japan) with an image resolution of 8 mm at full-width half-maximum (FWHM) and a slice thickness of 11–13 mm FWHM.12 Three tomographic planes were established 1.5 cm apart, 4.5, 6.0, and 7.5 cm above and parallel to the orbitomeatal line. These planes were set to be the same as those in CT studies done just before the PET studies.

We measured baseline physiologic data in each patient before CT and PET and in each control before PET. Arterial oxygen saturation (SaO2) was derived from measured arterial oxygen tension (PaO2) using the equation of Hill.13 Total arterial oxygen content (CaO2) was then calculated as 1.39×hemoglobin concentration×SaO2+0.0031×PaO2. We measured regional cerebral blood flow (CBF), oxygen extraction fraction (OEF), and the metabolic rate for oxygen (CMRO2) using an oxygen-15–labeled gas steady-state technique as described by Frackowiak et al.14 Regional cerebral blood volume (CBV) was measured using the bolus inhalation of O-15–labeled carbon monoxide gas according to the method of Phelps et al.15 In each individual, we corrected overestimations of OEF and CMRO2 by CBV according to the method of Lammertsma and Jones.16 We also calculated the CBF:CBV ratio as an index of cerebral perfusion pressure17,18 and used CBF×CaO2 as an index of tissue oxygen supplied by arterial blood.19,20 Every individual was studied in a dark room without any sedation.

We chose 40–50 contiguous 14×14-mm (49-pixel) regions of interest (ROIs) on CBF images to encompass the entire cortical territory of the anterior circulation in each patient (Figure 1). The mean PET values were calculated from these ROI data in each patient for three cortical territories: 1) apparently normal cortex, an ICA territory in the cerebral hemisphere contralateral to the craniotomy and not the focus of clinical vasospasm or the territory of angiographic vasospasm; 2) territory of angiographic vasospasm, the cortical territory that corresponds to the extent of angiographic vasospasm greater than +++; and 3) territory of symptomatic vasospasm, the cortical territory that includes the focus of neurologic deficits. Patients with only mental disturbance and without focal neurologic deficits were excluded from analysis of this last territory, and we selected the first two territories only from patients that underwent angiography during the period of delayed vasospasm. We compared the applicable patients’ mean PET values for each of these three cortical territories with those of the 10 controls.

Statistical comparisons were made using Wilcoxon’s unpaired two-sample rank test, and significance was confirmed when p<0.05.

Results
The clinical characteristics at presentation and the neuroradiologic findings of the patients are summarized in Table 1. Angiographic vasospasm was demonstrated in nine of the 11 patients examined during the period of delayed vasospasm. Symptomatic vasospasm occurred in nine patients, two with only a transient mental disturbance (Cases 5 and 6) and seven with focal neurologic deficits (Cases 7–13). No patient had critical clinical vasospasm that resulted in death or a persistent vegetative state.

The baseline physiologic data for both the patients and the controls are shown in Table 2. The patients revealed significantly decreased in hematocrit, hemoglobin concentration, and CaO2 compared with the controls (p<0.005). The patients also revealed reductions in PaCO2 and arterial pH (p<0.05). No significant differences in age, PaO2, SaO2, or mean arterial blood pressure were seen between patients and controls.

The results of the PET studies are shown in Tables 3 and 4 and in Figure 2. Apparently normal cortex consisted of ICA territories in nine patients.
(Table 3). Significant reductions in both CMRO$_2$ and CBF×CaO$_2$ were observed in the nine patients despite their significant increase in CBF compared with the controls. No significant difference was seen in OEF, CBV, or the CBF:CBV ratio (Table 3, Figure 2).

**TABLE 1.** Clinical Characteristics of 13 Patients With Aneurysmal Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Case/age/sex</th>
<th>Aneurysm location</th>
<th>Hunt and Hess grade on admission</th>
<th>Operation Day</th>
<th>Side</th>
<th>Glasgow Outcome score at 3 months</th>
<th>Symptomatic Vasospasm</th>
<th>Angiographic Extent</th>
<th>Day of positron emission tomography</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/25/F</td>
<td>L ICA</td>
<td>III</td>
<td>1</td>
<td>L</td>
<td>GR</td>
<td>–</td>
<td>+</td>
<td>L MCA</td>
</tr>
<tr>
<td>2/57/F</td>
<td>L MCA</td>
<td>II</td>
<td>1</td>
<td>L</td>
<td>GR</td>
<td>–</td>
<td>++</td>
<td>L MCA</td>
</tr>
<tr>
<td>3/70/F</td>
<td>L ICA</td>
<td>II</td>
<td>6</td>
<td>L</td>
<td>GR</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4/53/M</td>
<td>ACoA</td>
<td>I</td>
<td>1</td>
<td>R</td>
<td>GR</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5/39/F</td>
<td>ACoA</td>
<td>II</td>
<td>1</td>
<td>L</td>
<td>GR</td>
<td>+ (delirium, confusion)</td>
<td>++</td>
<td>B MCA, B ACA</td>
</tr>
<tr>
<td>6/52/F</td>
<td>R MCA</td>
<td>II</td>
<td>1</td>
<td>R</td>
<td>GR</td>
<td>+ (drowsiness)</td>
<td>+++</td>
<td>R MCA, R ACA</td>
</tr>
<tr>
<td>7/38/M</td>
<td>ACoA</td>
<td>II</td>
<td>0</td>
<td>L</td>
<td>SD</td>
<td>+ (tetraparesis, aphasia, stupor)</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>8/41/F</td>
<td>L ICA</td>
<td>II</td>
<td>0</td>
<td>L</td>
<td>MD</td>
<td>+ (R hemiparesis)</td>
<td>+</td>
<td>L MCA</td>
</tr>
<tr>
<td>9/55/M</td>
<td>ACoA</td>
<td>III</td>
<td>1</td>
<td>L</td>
<td>GR</td>
<td>+ (R hemiparesis)</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>10/45/F</td>
<td>R MCA</td>
<td>II</td>
<td>0</td>
<td>R</td>
<td>MD</td>
<td>+ (L hemiparesis)</td>
<td>+++</td>
<td>R MCA</td>
</tr>
<tr>
<td>11/60/F</td>
<td>R MCA</td>
<td>II</td>
<td>0</td>
<td>R</td>
<td>MD</td>
<td>+ (L hemiparesis)</td>
<td>+</td>
<td>R MCA</td>
</tr>
<tr>
<td>12/58/M</td>
<td>R ICA</td>
<td>II</td>
<td>1</td>
<td>R</td>
<td>MD</td>
<td>+ (L hemiparesis, hemianopsia)</td>
<td>+++</td>
<td>R MCA</td>
</tr>
<tr>
<td>13/60/F</td>
<td>L ICA</td>
<td>III</td>
<td>0</td>
<td>L</td>
<td>MD</td>
<td>+ (R hemiparesis, dysphasia)</td>
<td>++</td>
<td>L MCA</td>
</tr>
</tbody>
</table>

F, female; M, male; L, left; R, right; B, bilateral; ICA, internal carotid artery; MCA, middle cerebral artery; ACoA, anterior communicating artery; ACA, anterior cerebral artery; GR, good recovery; SD, severe disability; MD, moderate disability; NA, not applicable because angiogram not performed.
The territory of angiographic vasospasm consisted of MCA territories in five patients and ICA territories in two (Table 4). Significant reductions in both CMRO$_2$ and CBF×Ca$_o_2$ as well as in the CBF:CBV ratio were observed in the seven patients compared with the controls, while OEF revealed a wide range of values. We also observed a significant increase in CBV in the patients, although no significant differences in CBF were seen (Table 4, Figure 2).

The territory of symptomatic vasospasm consisted of ICA territories in seven patients (Table 4, three with progressive neurologic symptoms and four with symptoms that had peaked in severity by the time of the PET study). This territory overlapped primarily with that of angiographic vasospasm and produced similar results, that is, significant reductions in CBF, CMRO$_2$, and CBF×Ca$_o_2$ as well as in the CBF:CBV ratio, with an increase in CBV and widely varying OEF values for the seven patients compared with the controls (Figure 2). However, patients with progressive symptoms (Cases 7, 9, and 13) revealed increased OEF, while those with neurologic deficits that had already peaked in severity (Cases 8, 10–12) revealed reduced or normal OEF values (Figure 3).

**Discussion**

We have demonstrated a significant reduction in CMRO$_2$ after SAH even in apparently normal cortex despite unchanged CBF and OEF values, a phenomenon that might appear to be contradictory on gross inspection. However, using the equation $\text{CMRO}_2 = \text{CBF} \times \text{Ca}_o_2 \times \text{OEF}$ to express the relation between the PET parameters, we see that the rate of oxygen supply to cerebral tissue is not determined simply by CBF but by the product CBF×Ca$_o_2$, whereas OEF indicates the rate of tissue oxygen uptake. Our patients certainly revealed a significantly reduced CBF×Ca$_o_2$ value because of the significant decrease in Ca$_o_2$, which was calculated as $\text{Ca}_o_2 = 1.39 \times \text{hemoglobin concentration} \times \text{Sao}_2 + 0.0031 \times \text{Pao}_2$.

As this equation suggests and as our results confirm, this decline in Ca$_o_2$ was caused solely by a decrease in hemoglobin concentration. Furthermore, it is likely that the decrease in hemoglobin concentration was due to postoperative management, in which we attempted to maintain fluid balance mainly by intravenous infusion of plasma expanders, rather than by erythrocyte transfusion, to cope with blood loss during surgery or due to the SAH itself. Thus, the patients were considered to be in a hemodilutional state, although this was not the focus of our management regimen.

Experiments have shown that a hematocrit of approximately 33% provides an optimal trade-off between blood viscosity and oxygen carrying capacity, which forms the theoretical foundation for current hemodilution therapy. However, the optimal hematocrit in pathologic situations has been determined simply by CBF but by the product CBF×Ca$_o_2$, whereas OEF indicates the rate of tissue oxygen uptake. Our patients certainly revealed a significantly reduced CBF×Ca$_o_2$ value because of the significant decrease in Ca$_o_2$, which was calculated as $\text{Ca}_o_2 = 1.39 \times \text{hemoglobin concentration} \times \text{Sao}_2 + 0.0031 \times \text{Pao}_2$.

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TABLE 4. Mean±SD Values in Cortical Territories of Delayed Vasospasm in Patients With Aneurysmal Subarachnoid Hemorrhage and 10 Controls by Positron Emission Tomography

<table>
<thead>
<tr>
<th>Case</th>
<th>Angiographic vasospasm</th>
<th>Symptomatic vasospasm</th>
<th>Controls ICA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L MCA</td>
<td>B ICA</td>
<td>L MCA</td>
</tr>
<tr>
<td>2</td>
<td>39.9</td>
<td>23.3</td>
<td>39.3</td>
</tr>
<tr>
<td>5</td>
<td>40.3</td>
<td>39.9</td>
<td>40.4</td>
</tr>
<tr>
<td>6</td>
<td>42.4</td>
<td>40.4</td>
<td>40.3</td>
</tr>
<tr>
<td>10</td>
<td>39.4</td>
<td>40.3</td>
<td>39.4</td>
</tr>
<tr>
<td>11</td>
<td>53.7</td>
<td>39.4</td>
<td>53.7</td>
</tr>
<tr>
<td>12</td>
<td>37.8</td>
<td>39.4</td>
<td>37.8</td>
</tr>
<tr>
<td>13*</td>
<td>39.3</td>
<td>39.3</td>
<td>39.3</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>41.8±5.4</td>
<td>41.8±7.9</td>
<td>41.4±4.4</td>
</tr>
</tbody>
</table>

CBF, cerebral blood flow; OEF, oxygen extraction fraction; CMRO<sub>2</sub>, cerebral metabolic rate for oxygen; CBV, cerebral blood volume; L, left; R, right; B, bilateral; MCA, middle cerebral artery; ICA, internal carotid artery.

*Progressive symptoms at time of positron emission tomography.

†p<0.05, respectively, different from control by Wilcoxon's unpaired two-sample rank test.

![Bar graphs of mean±SD values in various territories of 13 patients with aneurysmal subarachnoid hemorrhage and 10 controls by positron emission tomography. CBF, cerebral blood flow; OEF, oxygen extraction fraction; CMRO<sub>2</sub>, cerebral metabolic rate for oxygen; CBV, cerebral blood volume. •, p<0.05; **, p<0.01 different from control by Wilcoxon's unpaired two-sample rank test.](http://stroke.ahajournals.org/Downloaded from)
not yet been established.\textsuperscript{24,25} Moreover, it has been suggested that the improvement in CBF brought about by hemodilution is nothing more than a physiologic response to the decrease in Cao\textsubscript{2}, at least in normal brain.\textsuperscript{19} Therefore, we cannot conclude whether the "hemodilution" seen in our patients, which indeed increased CBF, contributed to the improved oxygen supply to their brains. Our study does emphasize that such "hemodilution" can occur easily in SAH patients when they are managed as we did, but it remains necessary to confirm the optimal hematocrit for maximum oxygen delivery to the brain after SAH. Then, CBF×Cao\textsubscript{2}, rather than simply CBF, should be an important index of tissue oxygen supply.

It should also be noted that several investigators have similarly observed a global reduction in CMRO\textsubscript{2} after SAH and have interpreted this reduction as evidence of a direct toxic effect of subarachnoid clots.\textsuperscript{4,26,27} If only the relation between CBF and CMRO\textsubscript{2} were evaluated, our results might lead us to conclude that primary metabolic failure is reflected by a decrease in the tissue oxygen requirement relative to the oxygen supply. However, once we take into account the underlying decline in Cao\textsubscript{2}, we must consider the possibility that a CMRO\textsubscript{2} reduction is secondary to the tissue oxygen supply shortage.\textsuperscript{28} In some patients (Cases 1, 2, and 13; Table 3), CMRO\textsubscript{2} seemed to be maintained by a compensatory rise in OEF, whereas no elevation in OEF was seen in those patients with reduced CMRO\textsubscript{2}. These findings suggest that such metabolic suppression depends on individual differences, including the severity of SAH or the clinical stage.

In the cortical territories of vasospasm, we noted regional reductions in CBF as well as greater reductions in the CBF×Cao\textsubscript{2} value, while OEF varied widely. We also noted greater increases in CBV and greater reductions in the CBF:CBV ratio than in the apparently normal cortex. As for the paradoxical increase in CBV, it has previously been suggested that this may be due to the dilatation of intraparenchymal vessels, which react to the vasoconstriction of extraparenchymal vessels.\textsuperscript{26–29} It has been described elsewhere that the CBF:CBV ratio provides a sensitive index of the cerebral perfusion reserve.\textsuperscript{17,18} During acute ischemia, this ratio declines early in parallel with a decrease in perfusion pressure, causing OEF to increase as a compensatory mechanism (misery perfusion). In contrast, established infarcts are characterized by an either normal or decreased OEF, implying that the blood flow is adequate for the tissue's residual metabolic demands (luxury perfusion or matched low perfusion).\textsuperscript{7,8}

Based on these views, our results indicate that regional ischemia, that is, a reduced blood flow with a decreased perfusion pressure, certainly exists in the cortical territory of vasospasm. As for the widely ranging values of OEF, it is likely that these adverse ischemic sequences were intermingled in our measurements since the PET studies were not necessarily performed only during the early stages of delayed vasospasm. This explanation is supported by the fact that patients with progressive symptoms revealed a pattern of classic misery perfusion; after the severity of symptoms peaked, luxury perfusion or matched low perfusion were demonstrated (Figure 3).

It is difficult to propose an ischemic threshold that manifests neurologic deficits based on our gross analysis of a single set of measurements at one point during ischemia. Nevertheless, we can infer from the generalized hemodynamic and/or metabolic dysfunction that the threshold CBF in our patients is higher than that in patients with acute ischemia. Serial observations and a more detailed analysis of the data are necessary to investigate these aspects.

**Acknowledgments**

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