Cerebral hemodynamics and metabolism in patients with cerebral arteriovenous malformations: an evaluation using positron emission tomography scanning

TORU IWAMA, M.D., KOHEI HAYASHIDA, M.D., JUN C. TAKAHASHI, M.D., IZUMI NAGATA, M.D., AND NOBUO HASHIMOTO, M.D.

Departments of Neurosurgery and Radiology, National Cardiovascular Center, Suita, Osaka, Japan

Object. The purpose of this study was to evaluate cerebral hemodynamic and metabolic features in patients with arteriovenous malformations (AVMs) by using positron emission tomography (PET) scanning.

Methods. Twenty-four patients with supratentorial cerebral AVMs participated in PET studies in which 15O inhalation steady-state methods were used. The authors recorded the values of regional cerebral blood flow (rCBF), regional cerebral blood volume (rCBV), the regional oxygen extraction fraction (rOEF), and the regional cerebral metabolic rate of O2 (rCMRO2) at three designated regions of interest (ROIs) in each patient. These ROIs included perilesional (ROI-p), ipsilateral remote (ROI-i), and contralateral symmetrical (ROI-c) brain regions. To identify the factors that exert a direct effect on the hemodynamics of brains affected by AVM, we also separated the lesions according to their size and flow type shown on angiograms, and grouped the patients according to the presence or absence of progressive neurological deficits. We then compared the PET parameters at different ROIs in individual patients and evaluated the mean values obtained for all 24 patients according to AVM flow type and size, and the presence or absence of progressive neurological deficits.

Conclusions. Overall, mean rCBV and rOEF values were significantly higher in ROI-p than in ROI-c (p = 0.00046 and p = 0.015, respectively). No significant differences were seen between the ROI-i and ROI-c with respect to rCBF, rCBV, and rOEF. Mean rCMRO2 values were similar in the three ROIs; however, the mean rCBF was significantly lower in the ROI-p than in the ROI-i in patients with high-flow AVMs (p = 0.019), large AVMs (p = 0.017), and progressive neurological deficits (p = 0.021). Furthermore, the mean rOEF values were significantly higher in the ROI-p than in the ROI-i in patients with high-flow AVMs (p = 0.005), large AVMs (p = 0.019), and progressive neurological deficits (p = 0.017). The PET studies revealed hemodynamic impairment characterized by decreased rCBF and increased rOEF and rCBV values in the ROI-p of patients with large, high-flow AVMs regardless of whether they exhibited progressive neurological deficits.

Key Words • arteriovenous malformation • positron emission tomography • hemodynamics • perilesional region

Abbreviations used in this paper: AVM = arteriovenous malformation; CBF = cerebral blood flow; CBV = cerebral blood volume; CT = computed tomography; ICA = internal carotid artery; MR = magnetic resonance; NPPB = normal perfusion pressure breakthrough; PET = positron emission tomography; rCBF = regional CBF; rCBV = regional CBV; rCMRO2 = regional cerebral metabolic rate of O2; rOEF = regional O2 extraction fraction; ROI = region of interest; ROI-c = contralateral ROI; ROI-i = ipsilateral remote ROI; ROI-p = perilesional ROI; SPECT = single-photon emission CT.
enlisted 24 patients with AVMs to participate in preinterventional PET studies.

Clinical Material and Methods

Patient Population

During the last 6 years, we performed PET studies in 24 patients with supratentorial cerebral AVMs to evaluate their cerebral hemodynamic and metabolic conditions. Informed consent was obtained from all patients before enrollment in this study. The patients’ ages ranged from 11 to 61 years (mean 35 years) and there were 15 male and nine female patients. Clinical manifestations included progressive neurological deficits in six patients, epilepsy and/or transient ischemic attack in five patients, and intracerebral hemorrhage in four patients. In the remaining nine patients, the AVM was diagnosed incidentally. Although some patients exhibited mild neurological deficits, all lived independent lives. In all five patients with a history of epilepsy, the seizures were well controlled during the PET studies by administration of anticonvulsant medications. In the four patients with hemorrhage, the interval between injury and the PET study was 40 days, 55 days, 10 months, and 12 months. Table 1 presents a summary of our clinical and radiological findings.

All patients had undergone CT and MR imaging, as well as cerebral angiography before the PET studies. In maximum diameter, the AVM nidi ranged from 2 cm (three patients) to 8 cm (three patients). According to the system of Spetzler and Martin, there were five Grade V, seven Grade IV, seven Grade III, three Grade II, and two Grade I AVMs. We also divided the lesions into high-flow and non-high-flow types; we noted high flow when normal arterial structures around the AVM were faintly opacified on the angiogram. All angiograms were obtained by intrathecal mechanical injection of contrast medium (total volume 8–10 ml, injection speed 6 ml/second) through a catheter that had been placed in the ICA or the vertebral artery (Figs. 1 and 2). Of the 24 patients, 11 underwent surgical resection of the AVM after evaluation of the lesions.

Positron Emission Tomography Studies

The PET studies were performed as previously reported. We used a four-ring, seven-plane PET scanner (Headtome IV; Shimadzu Co., Kyoto, Japan). This unit has a transaxial resolution of 6.5 mm and an axial resolution of 4.5 mm full width at half maximum in clinical use. After the patients inhaled 15O-labeled CO2, O2, and CO, the values of rCBF, rCMRO2, rOEF, and rCBV were measured and arterial activity was corrected through a radial artery catheter. Blood gases were measured with the aid of a blood gas automatic analyzer (280 Blood Gas System; Ciba-Corning Diagnostics Corp., Medfield, MA). The patient’s blood pressure was monitored throughout the examinations.

Regions of interest were identified on a case-by-case basis by one investigator (T.I.); their placement was supported by data obtained from CT and MR imaging studies, and from PET images of CBV (Fig. 1). The first ROI, the ROI-p, was fed by the main trunk of the feeding artery and was close to the AVM, without including the nidi, major draining veins, or old hematoma cavity. The second ROI, the ROI-i, was located far from the AVM in the ipsilateral hemisphere. The third ROI, the ROI-c, mirrored the ROI-p in the contralateral hemisphere.

Analysis of PET Data

We recorded PET data from all 24 patients at the three ROIs chosen for this study (Table 2). We analyzed data obtained at each ROI with respect to the AVM size and flow type of the AVM, and the manifestation of progressive neurological deficits (Table 3). For statistical evaluation of the results, we used both the paired and unpaired Student t-tests and a Bonferroni correction when necessary. A probability value lower than 0.05 indicated a significant difference.

Perioperative Management

Of the 24 patients, 11 underwent surgical extirpation of the AVM. Patients with high-flow or Spetzler–Martin Grade IV and V AVMs received continuous intravenous barbiturate medications during and after surgery. In one patient with a high-flow, Grade V lesion (Case 4), we resected the AVM under conditions of hypothermia and hypotension by using a percutaneous cardiopulmonary support system.
were significantly higher in the ROI-p than in the ROI-c (p = 0.00046 and p = 0.015, respectively). The mean rCBV was also significantly higher in the ROI-p than in the ROI-i (p = 0.002), and there were no region-specific differences in rCMRO₂ values. The ROI-i and ROI-c did not exhibit significant differences with respect to the PET parameters evaluated in this study.

**Effect of AVM Flow Type on Brain Hemodynamics and Metabolism**

As shown in Table 3, in the nine patients with high-flow AVMs, the mean rCBF in the ROI-p was significantly lower than that in the ROI-c (p = 0.019). Also, both mean rCBV and rOEF values were significantly higher in the ROI-p than in the other ROIs. The mean rCMRO₂ values did not differ significantly among the three ROIs.

In the 15 patients in whom the AVMs were not high flow, the mean rCBF was somewhat lower and the mean rOEF somewhat higher in the ROI-p than in the other two ROIs; however, the mean rCBV was significantly higher in the ROI-p and the mean rCMRO₂ values did not differ significantly among the three regions.

Further comparisons showed that in patients with high-flow AVMs, the mean rCBF in the ROI-p was significantly lower than in patients harboring AVMs without high flow (p = 0.022). In addition, the mean rOEF was higher in the ROI-p of patients harboring high-flow AVMs (p = 0.052). With respect to the mean rCBV and rCMRO₂ values in the ROI-p, there was no significant difference between patients with high-flow lesions and those without high-flow AVMs. There was no significant difference in the mean values of rCBF and rOEF in the ROI-i between patients harboring high-flow AVMs and those without high-flow AVMs.

**Effect of AVM Size on Brain Hemodynamics and Metabolism**

In 11 of the 24 patients, the AVM measured more than 5 cm. As shown in Table 3, in this group, the mean rCBF in
the ROI-p was significantly lower than that in the ROI-c (p = 0.017). On the other hand, in the ROI-p, the mean rCBV was significantly higher than those values in the other two ROIs and the mean rOEF was significantly higher than that in the ROI-c. There was no significant difference in the mean rCMRO₂ values among the three ROIs.

In the 13 patients with AVMs smaller than 5 cm, the only significant difference among the three ROIs was found in the mean rCBV value; it was significantly higher in the ROI-p than in the ROI-i (p = 0.007) and ROI-c (p = 0.009). There was no significant difference in mean rCMRO₂ values among the three ROIs.

Although we found that in the ROI-p of large AVMs the mean rCBF was lower and rCBV and rOEF were higher than those values measured in patients with smaller AVMs, these differences were not statistically significant. Furthermore, the size of the AVM had no significant effect on mean rCMRO₂ values in the ROI-p or on the values of any PET parameter in the ROI-i and ROI-c.

**Relationship Between Progressive Neurological Deficits and Brain Hemodynamics and Metabolism**

As shown in Table 3, in the six patients with progressive neurological deficits, the mean rCBF in the ROI-p region was significantly lower than those in the ROI-i and ROI-c (p = 0.04 and p = 0.021, respectively). The mean rOEF value in the ROI-p was significantly higher than that measured in ROI-c (p = 0.017). There was no significant difference in mean rCMRO₂ values among the three ROIs.

In the 18 patients who presented with manifestations other than progressive neurological deficits, the mean rCBV was the only PET parameter whose value in the ROI-p was significantly different, that is, higher, than those measured in the ROI-i (p = 0.003) and ROI-c (p = 0.004). The mean rCMRO₂ values were not significantly different among the three ROIs.

**Clinical Results of AVM Resection**

Of the 11 patients who underwent surgical resection, one had a high-flow, Spetzler–Martin Grade V AVM, three had Grade IV AVMs that did not exhibit high flow, and three had high-flow Grade III or II AVMs (Table 1). These seven patients received intravenous barbiturate medication during and after the operation. Although different degrees of postoperative brain edema were observed in this group, none of the patients experienced critical brain swelling. The other four patients underwent simple AVM resection and there was no surgical complication in any surgically treated patients.

**Discussion**

**Hemodynamics and Metabolism in the ROI-p**

Various degrees of hypoperfusion have been reported in brains affected by AVMs. Intracranial steal phenomenon, venous hypertension, mass effect from the nidus, seizure activity, and neurogenic depressed tissue activity have been suggested as possible causes of this hypoperfusion.6,8,10,11,15,17,23,25 Hyperemic complications sometimes occur after AVM resection.2–4,10,17,23–26

Hyperemic complications have been proposed as underlying mechanisms in severe brain swelling.

Both the CBF and hemodynamic reserve have been studied in patients with AVMs to assess their correlation with postoperative hyperemic complications and cerebral hemodynamic disorders.2–4,10,17,23–26 Most of these were SPECT studies or Xe-enhanced CT studies in which there was acetazolamide loading. As previously reported, PET studies6,8,14,27 did not evaluate the combination of cerebral hemodynamics and metabolism and factors affecting the hemodynamic status of patients with AVM. We measured rCBF, rCBV, rOEF, and rCMRO₂ in three ROIs in the brains of 24 patients with AVMs and assessed the possible effect of the size and angiographically determined type of the AVM and the presence of progressive neurological deficits on these parameters. We found that in the ROI-p, the rCBF value was lower and the rCBV and rOEF values were higher than those measured in the ROI-c. Between the ROI-i and ROI-c, however, there were no significant differences with respect to the PET parameters that we examined.

Previous reports showed decreased rCBF in areas surrounding the AVM,2,4,8,10,11,14,15,17,19,23–26 especially larger AVMs.28 Our detailed analysis revealed that patients with angiographically defined high-flow AVMs manifested the greatest decrease in rCBF in the ROI-p (high-flow AVMs compared with nonhigh-flow, p = 0.022). There were no hyperemic complications after AVM resection.2–4,10,17,23–26

J. Neurosurg. / Volume 97 / December, 2002

1317
In our series, four patients presented with cerebral hemorrhage; however, in these patients rCBF was not significantly lower than that measured in patients without hemorrhage, possibly because their hemorrhages were not severe and the patients manifested no neurological deficits.

Increased rCBV values have been recorded in the hemisphere ipsilateral to the AVM,2,27 and, in cases in which the AVM was large, in the contralateral hemisphere.27 According to earlier PET studies,3,8,27 the rCMRO2 value was within normal limits or slightly decreased, and the rOEF value was within the normal range in patients with AVM. We found that rCBV was significantly increased in the ROI-p, regardless of the size or angiographically defined flow type of the AVM, or the presence of progressive neurological deficits. In our study population, although the rCBV in the AVM-affected brains.

Although rCMRO2, the slightly lower in the ROI-p compared with the other two ROIs, the differences were not significant. Our findings coincide with those of others,5,27 but differ in that we found that rOEF was significantly higher in ROI-p than in the ROI-c in patients with high-flow AVMs (p = 0.005), large AVMs (p = 0.019), and progressive neurological deficits (p = 0.017). Also, rOEF tended to be higher in the ROI-p than in the ROI-i. As was the case with rCBF, the AVM flow type had a greater effect on rOEF than did the size of the AVM.

Previous SPECT and acetazolamide-loading studies confirmed various degrees of impairment of hemodynamic reserves in perilesional regions of AVMs.2,3,10,17,26,28 Differences in hemodynamic reserves may be attributable to differences in AVMs such as size of the nidus, shunt volume and flow, and pressures in feeding arteries and draining veins. Although we did not directly address the issue of hemodynamic reserve in our series, the elevation of rOEF that we observed suggests that increased O2 extraction plays a role in the compensatory mechanism for hyperperfusion in AVM-affected brains.

In summary, our PET results demonstrated decreased rCBF, increased rCBV and rOEF, and unchanged rCMRO2 values in the perilesional regions (ROI-p) of patients with high-flow, large AVMs. These changes are incompatible with changes attributable to decreased neurological activities and mass effect for the following reasons. If hemodynamic and metabolic changes were due to decreased neurological activity of brain tissues, we should have recognized a decrease in rCMRO2. Similarly, if they were due to the mass effect of the nidus, we should not have recognized an increase in rCBV. Therefore, we propose that intracranial steal and venous hypertension are the primary factors lead-
### Table 3

Relevance of radiological and neurological features to PET parameters in brains affected by AVMs*

<table>
<thead>
<tr>
<th>Radiological &amp; Neurological Features</th>
<th>No. of Patients</th>
<th>ROI-p</th>
<th>ROI-i</th>
<th>ROI-c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CBF†</td>
<td>CBV‡</td>
<td>OEF</td>
</tr>
<tr>
<td>HF</td>
<td>9</td>
<td>30.92±6.79</td>
<td>6.68±5.09</td>
<td>0.532±0.066</td>
</tr>
<tr>
<td>p value vs ROI-c</td>
<td>0.019</td>
<td>0.047</td>
<td>0.005</td>
<td>NS</td>
</tr>
<tr>
<td>p value vs ROI-i</td>
<td>0.075</td>
<td>0.054</td>
<td>0.029</td>
<td>NS</td>
</tr>
<tr>
<td>non-HF</td>
<td>15</td>
<td>39.58±10.96</td>
<td>6.48±1.85</td>
<td>0.472±0.094</td>
</tr>
<tr>
<td>p value vs ROI-c</td>
<td>NS</td>
<td>0.0008</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>p value vs ROI-i</td>
<td>NS</td>
<td>0.004</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>size of AVM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>11</td>
<td>33.60±6.42</td>
<td>7.74±4.42</td>
<td>0.522±0.103</td>
</tr>
<tr>
<td>p value vs ROI-c</td>
<td>0.017</td>
<td>0.006</td>
<td>0.019</td>
<td>NS</td>
</tr>
<tr>
<td>p value vs ROI-i</td>
<td>NS</td>
<td>0.021</td>
<td>0.072</td>
<td>NS</td>
</tr>
<tr>
<td>&lt;5 cm</td>
<td>13</td>
<td>38.65±12.61</td>
<td>5.54±1.62</td>
<td>0.471±0.069</td>
</tr>
<tr>
<td>p value vs ROI-c</td>
<td>NS</td>
<td>0.009</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>p value vs ROI-i</td>
<td>NS</td>
<td>0.007</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>p value &gt;5 cm vs &lt;5 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>clinical presen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PND</td>
<td>6</td>
<td>30.34±5.10</td>
<td>8.00±5.93</td>
<td>0.533±0.083</td>
</tr>
<tr>
<td>p value vs ROI-c</td>
<td>0.021</td>
<td>0.057</td>
<td>0.017</td>
<td>NS</td>
</tr>
<tr>
<td>p value vs ROI-i</td>
<td>0.04</td>
<td>0.078</td>
<td>0.059</td>
<td>NS</td>
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<tr>
<td>others</td>
<td>18</td>
<td>38.33±11.00</td>
<td>6.07±1.93</td>
<td>0.482±0.089</td>
</tr>
<tr>
<td>p value vs ROI-c</td>
<td>NS</td>
<td>0.004</td>
<td>0.097</td>
<td>NS</td>
</tr>
<tr>
<td>p value vs ROI-i</td>
<td>NS</td>
<td>0.003</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>p value vs PND vs others</td>
<td>0.052</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Significance of probability values is shown if lower than 0.1. Abbreviations: Angio flow = AVM flow based on angiographic findings; NS = not significant; presen = presentation.
†Values are expressed as milliliters per 100 g per minute.
‡Values are expressed as milliliters per 100 g.
ing to the hemodynamic changes we observed. Studies are underway to identify which mechanism plays the greater role in the hemodynamic changes we documented in perilesional regions of our patients with AVMs.

Effect of Surgical Resection or Embolization of the AVM on Brain Hemodynamics and Metabolism

The hemodynamics in the perilesional regions after AVM treatment are of interest because they address the issue of hyperemic complications in the acute stage after excitation of arteriovenous shunts, and the issue of recovery from hemodynamic impairment during the chronic stage after treatment. Batjer and colleagues observed postoperative hyperemia in the region affected by the intracranial steal phenomenon and reported abnormally enhanced vasoreactivity to acetazolamide loading. On the other hand, a patient presented by Ogasawara, et al., manifested decreased vasoreactivity to acetazolamide before, and marked hyperperfusion after, AVM excision.

In our series, 11 patients underwent surgical extirpation of the AVM. The seven patients with high-flow type and/or Grade IV or V AVMs received a prophylactic, continuous intravenous administration of barbiturates during and after the operative procedure. Of these seven patients, six manifested preoperative rOEF values higher than 0.5 in the perilesional regions. Although none of these patients suffered any morbidity attributable to postoperative hyperemic complications, all exhibited varying degrees of brain edema.

In one patient (Case 4) with a large, high-flow type Grade V AVM, intraoperative monitoring of cortical CBF with a laser Doppler system (Unique Medical Co., Ltd., Osaka, Japan) showed a continuous increase during the resection procedure. She required administration of barbiturates for 10 days following the operation to control brain swelling.

In the other four patients who were surgically treated, the AVM was neither the high-flow type nor Grade IV or V and, preoperatively, the rOEF values in these patients were not elevated in the perilesional regions. These four patients underwent AVM resection and there were no surgical complications. Although the occurrence of NPPB cannot be predicted with any degree of certainty, our findings suggest that patients with elevated rOEF values, those with angiographically confirmed high-flow, large, and higher Spetzler–Martin grade AVMs should be considered to be at increased risk for postoperative NPPB.

Embolization and spontaneous regression of AVMs reportedly resulted in improved hemodynamics in the perilesional region. We also obtained hemodynamic improvement in patients with progressive neurological deficits who had undergone AVM embolization. Although some investigators reported cerebral hemodynamic changes after surgical resection of AVMs, it is likely that the operative procedure has its greatest effect on the perilesional regions and it is difficult to evaluate the hemodynamic changes attributable only to the elimination of the AVM. Although we did not address postoperative hemodynamic changes in our series, evaluation of large numbers of surgically treated patients may show that operative intervention improves the hemodynamic status of patients with AVMs.

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References

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Address for Dr. Hashimoto: Graduate School of Medicine, Kyoto University, Japan.

Address reprint requests to: Toru Iwama, M.D., Department of Neurosurgery, Gifu University School of Medicine, 40 Tsukasamachi, Gifu, Gifu 500-8705, Japan. e-mail: tiwama@cc.gifu-u.ac.jp.