Impaired Cerebral Vasoreactivity After Embolization of Arteriovenous Malformations: Assessment with Serial Acetazolamide Challenge Xenon CT

Embolization of a portion of the nidus of an arteriovenous malformation not only may alter hemodynamics within the nidus, but also may change blood flow dynamics in adjacent normal vessels. Sequential acetazolamide-challenge xenon CT cerebral blood flow studies were performed in eight patients before and after embolization of arteriovenous malformations to assess the hemodynamic effects on the major vascular territories supplying the malformation. Acetazolamide is a potent cerebral vasodilator, and its administration combined with cerebral blood flow studies allows assessment of cerebral vasoreactivity. In seven of the eight patients, one or more parenchymal areas exhibited a normal cerebral blood flow augmentation response to acetazolamide before embolization, but diminished acetazolamide flow augmentation was seen after embolization, indicating abnormal vasoreactivity. We found that the decrease in vasoreactivity peaked 6–10 days after embolization. In one of the eight patients, a temporary delayed neurologic deficit developed during a period of impaired cerebral vasoreactivity following embolization.

Our results suggest that embolization of an arteriovenous malformation can induce vasoreactivity changes in adjacent normal vessels. Because these changes appear to be somewhat time-dependent, an appropriate interval should be observed between embolization stages or before surgical resection of an arteriovenous malformation following embolization to allow hemodynamic equilibration to occur. Acetazolamide challenge combined with serial cerebral blood flow studies following embolization enables determination of this hemodynamic equilibration.


Arteriovenous malformations (AVMs) usually have chronic effects on blood flow to surrounding brain parenchyma. They do this by altering perfusion pressures in normal cerebral vessels secondary to the low resistance of the shunt [1–10]. We have previously used stable xenon CT cerebral blood flow (CBF) studies with acetazolamide challenge to identify parenchymal regions of low vascular reserve associated with AVMs [4]. Acetazolamide administration normally causes a global and symmetric increase in CBF because of temporary cerebral vasodilatation [4, 11–16]. Vascular areas that fail to augment CBF normally in response to acetazolamide challenge are presumed to have diminished vasoreactivity [4, 11].

Abrupt occlusion of the shunt through an AVM following surgical resection or substantial AVM embolization may cause edema or hemorrhage in the adjacent brain [17–23]. This phenomenon, termed normal perfusion pressure breakthrough syndrome, is thought to be due to an abrupt rise in perfusion pressure in arteriolar beds that have abnormal autoregulatory capabilities [24]. To determine changes in CBF and vasoreactivity induced by partial nidus embolization, we studied patients before and after AVM embolization with xenon CT CBF studies combined with acetazolamide challenge.
Subjects and Methods

We examined eight patients with supratentorial AVMs, five men and three women 16–55 years old. Although four of the eight patients had a history of intracranial hemorrhage, none of the patients had a history of acute or subacute hemorrhage. AVM size was categorized as small (less than 3 cm), medium (3–6 cm), and large (greater than 6 cm in greatest diameter) on the basis of angiography [25]. Each patient was studied with a baseline xenon CT CBF study and an acetaza8olamide challenge xenon CT CBF study immediately before and at various time intervals (from 1 to 26 days) following partial embolization of the AVM nidus. In two patients, more than one CBF study was performed following embolization. None of the eight patients required sedation for any xenon CT CBF study. However, anxiety attacks precluded completion of CBF studies in two patients not included in this study.

CBF studies were performed by using the stable xenon CT and acetaza8olamide-challenge method previously described [4, 11, 26–28]. All xenon CT CBF studies were performed by using a GE 9800 CT scanner equipped with a CBF hardware and software package (General Electric Medical Systems, Milwaukee, WI). Each examination consisted of a baseline two-level CBF study and a repeat two-level CBF study performed 20 min after the IV administration of 1 g of acetaza8olamide. To obtain identical supratentorial scanning levels, patients were not moved between the baseline and acetaza8olamide-challenge studies. Scanning levels identical to those used for preembolization CBF studies were chosen for postembolization CBF studies by matching postembolization unenhanced axial scout CT levels with unenhanced axial scout CT levels that accompanied the preembolization CBF studies. The basal ganglia/lateral ventricle configuration was used as a reference for choosing the first level of the CBF study. The second level was automatically chosen 3 cm superior to the first level. Scan angulation was kept constant for individual patients.

Preembolization angiographic data were used to determine which major vascular territories (anterior cerebral, middle cerebral, and/or posterior cerebral) had vascular pedicles that supplied the AVM. The vascular territories that had feeding pedicles to the AVM were defined as near-site regions on the CBF studies. Near-site CBF data at each level were analyzed by using multiple contiguous 2.0-cm-diameter region-of-interest (ROI) circles aligned along the cerebral cortex [4]. The ROI diameter of 2.0 cm was chosen to maximize gray matter and minimize white matter inclusion with the individual ROIs. ROIs including the AVM nidus or draining veins were excluded from quantitative analysis. Individual ROIs encompassing identical near-site parenchymal areas were analyzed from baseline CBF and flow augmentation after acetaza8olamide challenge before and after embolization. Blood flow values for consecutive studies were adjusted for changes in carbon dioxide tension by assuming a change of 3% increase in CBF per 1 mm Hg increase in carbon dioxide tension [29, 30]. The preembolization study was used as the reference for this adjustment. Baseline CBF for each parenchymal area encompassed by an ROI was categorized as low (less than 35 ml·100 g−1·min−1), normal (35–75 ml·100 g−1·min−1), or high (greater than 75 ml·100 g−1·min−1) [31]. Flow augmentation after acetaza8olamide challenge was categorized as normal (10% or more increase in CBF) or decreased (<10%). Comparable ROIs for each level were analyzed for flow characteristics on pre- and postembolization studies.

Supraselective partial nidus embolization was performed with a 2.4-French Tracker catheter and 0.016-in. (0.41-cm) steerable guidewire system (Target Therapeutics, Inc., Los Angeles, CA), introduced coaxially through a diagnostic angiographic catheter. Real-time digital fluoroscopic road-mapping was used for catheter guidance. Digital subtraction microangiography and provocative sodium amyal testing were used to ensure safe catheter position in feeding pedicles.

Provocative sodium amyal testing was evaluated with detailed neurologic examination. Pedicle embolization was performed under continuous real-time subtracted fluoroscopic monitoring, using either polyvinyl alcohol (PVA) or a combination of PVA, silk suture material, and coils. Embolization of a pedicle was terminated when flow to the AVM was reduced significantly or became stagnant. The number of pedicles embolized in each patient varied from one to three. Patients were maintained on steroids for 24 hr prior to and 72 hr after embolization procedures.

Results

Table 1 summarizes patient, AVM, and flow data. We analyzed a total of 169 pre- and postacetaza8olamide near-site parenchymal areas (individual ROIs) before and after embolization. The mean standard deviation of blood flow measurements within individual ROIs was 19.1 ml·100 g−1·min−1. Before embolization, the mean near-site baseline CBF for the eight patients was 49.9 ml·100 g−1·min−1 with an interpate standard deviation 5.5 ml·100 g−1·min−1. Following embolization, the mean near-site baseline CBF was 56.8 ml·100 g−1·min−1 with an interpate standard deviation of 16.1 ml·100 g−1·min−1.

Acetaza8olamide-induced flow augmentation of ≥10% was categorized as normal. The mean flow augmentation in those parenchymal areas categorized as normal was 49.1 ± 28.6%. Before embolization, the mean acetaza8olamide-induced flow augmentation in all near-site parenchymal areas was 36.1 ± 20.9%. After embolization, the mean acetaza8olamide-induced flow augmentation of 15.8 ± 24.9% was significantly diminished (t test, p < .001).

The results of analyzing individual ROI parenchymal areas of acetaza8olamide-induced flow augmentation are presented in Table 2. Before embolization, 78% (132/169) of near-site parenchymal areas demonstrated normal (≥10%) acetaza8olamide-induced flow augmentation, whereas following embolization 58% (98/169) demonstrated normal acetaza8olamide-induced flow augmentation. Forty percent (53/132) of parenchymal areas that had had normal acetaza8olamide-induced flow augmentation prior to embolization exhibited diminished (<10%) augmentation after embolization. The proportion of parenchymal areas showing diminished augmentation after

### TABLE 1: Summary of Patients with Supratentorial Arteriovenous Malformations (AVMs) Who Underwent Xenon CT Cerebral Blood Flow Imaging Before and After Embolization

<table>
<thead>
<tr>
<th>AVM Size/Case No.</th>
<th>Presenting Symptom</th>
<th>No. of Vascular Territories Supplied by AVM</th>
<th>No. of Pedicles Embolized</th>
<th>Time of CBF Study (No. of Days Postembolization)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small (&lt;3 cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Headache</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Seizures</td>
<td>2</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>Hemorrhage</td>
<td>2</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>Headache</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>Hemorrhage</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>Seizures</td>
<td>3</td>
<td>2</td>
<td>1, 5, 12</td>
</tr>
<tr>
<td>Large (&gt;6 cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Hemorrhage</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>Hemorrhage</td>
<td>3</td>
<td>3</td>
<td>6, 9</td>
</tr>
</tbody>
</table>
hemorrhage (42%) was significantly greater than the proportion prior to embolization (22%) (chi-square, \( p < .001 \)).

In seven of the eight patients, one or more parenchymal areas had normal acetazolamide-induced flow augmentation prior to embolization, but exhibited diminished acetazolamide-induced flow augmentation after embolization. Delayed onset of a temporary left upper extremity paresis developed in one patient (case 6) following embolization (Fig. 1). This patient underwent embolization of three pedicles supplying a right parietal AVM. The deficit developed 24 hr after embolization, at which time a CBF study demonstrated increased baseline CBF and diminished acetazolamide flow augmentation in the near-site right middle cerebral artery distribution. The deficit gradually improved and was completely resolved by 12 days after embolization. Interval CBF studies were performed on days 5 and 12 following embolization. On day 5 the CBF study demonstrated decreased acetazolamide flow augmentation in the near-site right middle and anterior cerebral arterial distributions. Baseline flows remained slightly elevated in these distributions compared with the preembolization study. By 12 days after embolization the symptoms had resolved and a CBF study demonstrated normal baseline flows and acetazolamide flow augmentation in the right middle and anterior cerebral arterial distributions.

Figure 2 presents postembolization data on the percentage of parenchymal areas with diminished acetazolamide flow augmentation responses before embolization and normalization of acetazolamide responses after embolization. The percentage of areas showing normalization of acetazolamide response was significantly greater on days 11–26 (66%) than on days 1–5 (7%) or days 6–10 (0%) after embolization (chi-square, \( p < .001 \)). The percentage of areas demonstrating normalization of acetazolamide response did not vary significantly with AVM size or number of pedicles embolized (chi-square, \( p > .05 \)).

### Discussion

Previous studies have shown that untreated AVMs may have marked effects on parenchymal hemodynamics, both at sites near the AVM and at sites far removed from the lesion [4]. These flow effects of untreated AVMs are often complex within individual patients [4]. One of these effects is an inability of the cerebral vasculature in some regions to respond appropriately to acetazolamide. Acetazolamide is a potent cerebral vasodilator that normally increases global CBF by 5–90% [4, 11–13]. In some untreated AVM patients, the failure to augment CBF appropriately in response to acetazolamide may be due to chronic arteriolar dilatation from lowered perfusion pressures in normal arterial beds [4, 32, 33]. This diminished capacity for CBF augmentation, though evident on acetazolamide CBF studies, may be subclinical [4]. Although clinically silent, the inability to respond appropriately to a vasodilatory challenge suggests impaired vasoreactivity in a vascular bed.

Particle embolization of a portion of an AVM nidus progressively decreases flow through the pedicle being embolized. This progressive alteration in flow is accompanied by an increase in feeder pedicle arterial pressure [34–36]. In addition, nidus embolization may be accompanied by a marked redistribution of regional CBF [37]. These abrupt changes occur in arterial beds that are chronically adjusted to a parallel low-pressure shunt.

In this study, we observed changes in cerebral vasoreactivity that occurred after embolization. These changes were complex and varied among individual patients. In selected near-site parenchymal areas there was a diminished ability of the cerebral vasculature to dilate normally in response to acetazolamide. Although none of the patients in our series received pedicle pressure monitoring during embolization, it is reasonable to hypothesize that the diminished vasodilatory response following embolization resulted from perfusion pressure changes and flow redistribution. These abrupt changes may alter the normal vasomotor responsiveness to vasodila-
tory challenges. Possibly, the increased intravascular pressure that occurs in selected vascular pedicles following embolization induces a protective increased vasoconstrictive response. Vessels that experience this increased vasomotor tone may initially be incapable of dilating normally in response to acetazolamide. In this series, we found that diminished vasoreactivity was more prominent in the first 10-day period after embolization. The vasoreactivity changes observed after embolization did not vary significantly with preembolization AVM size or number of pedicles embolized. Previous authors have noted that flow redistribution and abnormal vasoreactivity after AVM embolization or resection may predispose to parenchymal edema or hemorrhagic complications [17, 20, 33, 37].

The diminished vasodilatory capacity after embolization was subclinical in the majority (seven of eight) of our patients. However, in one of our patients (case 6), a delayed neurologic deficit developed in a time course related to elevated baseline CBF and abnormal acetazolamide response (Fig. 1). The timing of the deficit, the elevated baseline CBF, and the blunted acetazolamide response suggested that the deficit in this case was related to either CBF redistribution, diminished local vasomotor responsiveness, or a combination of both. Baseline flow values and acetazolamide response normalized and the symptoms resolved by 12 days after embolization.

Not all near-site parenchymal areas demonstrated diminished vasoreactivity following embolization. In fact, some parenchymal areas showed normalization of previously diminished responsiveness to acetazolamide. The percentage of parenchymal areas demonstrating normalization of acetazolamide response varied among individual patients, but was greatest more than 10 days after embolization. It is possible that vessels supplying these areas were maximally dilated owing to decreased perfusion pressure before embolization. Since they were maximally dilated they were incapable of dilating further in response of acetazolamide. In time, vasomotor responsiveness may be restored following embolization owing to normalization of intravascular pressure.

Though quantitative, the xenon CT CBF technique is subject to anatomic pixel-to-pixel variation in blood flow. The
HEMODYNAMICS AFTER EMBOLIZATION OF AVMs

**Fig. 1.—Continued.**

E and F, Serial contrast-mode xenon CT CBF studies at lateral ventricular (E) and supraventricular (F) levels. Window width = 2, window level = 60. CBF ≥ 60 ml·100 g⁻¹·min⁻¹ is white; CBF < 60 ml·100 g⁻¹·min⁻¹ is black. embo = embolization, AC = acetazolamide challenge.

G and H, Line graphs depict mean R ACA (squares) and R MCA (crosses) cerebral blood flow (CBF) before and at various times after embolization (EMBO) at ventricular (G) and supraventricular (H) levels. Before embolization (pre-Embo), precetazolamide or baseline (BL) CBF is normal. Acetazolamide challenge (AC)-induced flow augmentation is greater in R MCA than in R ACA distribution at supraventricular level. One day after embolization, left upper extremity paresis developed. Interval CBF study showed elevated baseline CBF and diminished AC response in R MCA distribution. By 5 days after embolization, AC response in R MCA distribution at ventricular level and both R MCA and R ACA distributions at supraventricular level have become paradoxical: CBF decreased in response to AC. By day 12, both blunted AC response and neurologic deficit have resolved.
hemodynamic such as with acetazolamide, can aid in determining when changes caused by procedures serially have occurred that recruitment embolization allows of the AVM nidus through between malformations. However, Some azolamide-induced activity that is time-dependent. vascular hemodynamic changes may be induced by acetazolamide-induced local CBF augmentation that reflects normal or abnormal vasoreactivity, respectively.

Our results suggest that the local hemodynamic changes induced by embolization may affect normal vessels in the vascular territories of arteries that supply the AVM. These hemodynamic changes may result in an abnormal vasoreactivity that is time-dependent. It is less pronounced 10 days or more after embolization. These results support the concept of staged AVM embolization [38].

The timing of multistaged AVM treatment is controversial. Some authors have recommended a short time interval between embolization and surgery to prevent the reconstitution of the AVM nidus through collateral circulation [38–40]. We have observed that recruitment rarely occurs quickly after partial nidus embolization [41]. Therefore, we believe that our results support a time delay between successive stages of embolization or between embolization and surgery to allow the cerebral vasculature to accommodate the hemodynamic changes caused by embolization. The timing of staged procedures should be individualized owing to the variability of hemodynamic effects among individual patients. However, serial CBF studies combined with a vasoreactivity challenge, such as with acetazolamide, can aid in determining when hemodynamic equilibration has occurred following embolization.

ACKNOWLEDGMENTS

We thank Margaret Sachse and Debra Lee Stokes for editorial assistance.

REFERENCES

HEMODYNAMICS AFTER EMBOLIZATION OF AVMs

32. Murphy JP. Cerebrovascular disease. Chicago: Year Book Medical, 1954
35. Jungreis CA, Horton JA. Pressure changes in the arterial feeder to a cerebral AVM as a guide to monitor therapeutic embolization. AJNR 1989;10:1057–1060