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R W Tarr, D W Johnson, M Rutigliano, S T Hecht, S Pentheny, C A Jungreis, J A Horton and H Yonas

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Use of Acetazolamide-Challenge Xenon CT in the Assessment of Cerebral Blood Flow Dynamics in Patients with Arteriovenous Malformations

Robert W. Tarr^{1,2}
 David W. Johnson¹
 Michael Rutigliano³
 Stephen T. Hecht^{1,3}
 Susan Penhney¹
 Charles A. Jungreis^{1,3}
 Joseph A. Horton^{1,3}
 Howard Yonas^{1,3}

Arteriovenous malformations (AVMs) may cause symptoms related to a reduction of cerebral blood flow (CBF) to surrounding brain parenchyma. To evaluate this compromise of hemodynamic reserve (commonly referred to as steal phenomenon), we used acetazolamide challenge and stable-xenon CT (Xe/CT). Baseline Xe/CT studies in 13 patients with AVMs were followed by an acetazolamide challenge to the vascular reserve. Blood flow maps were quantitated by using region-of-interest (ROI) software. ROI findings were categorized into four groups on the basis of the presence or absence of normal baseline CBF and presence or absence of normal augmentation of CBF. ROIs were designated as near site (within the vascular territory supplying the AVM) or far site (outside the vascular territory supplying the AVM). One patient had a normal baseline and normal augmentation of CBF (group 1). The other patients had a combination of one or more of the other three categories. Ten patients had parenchymal areas that exhibited either a normal or low baseline CBF with decreased augmentation; both conditions were interpreted as decreased vascular reserve (groups 2 and 3). Eleven patients had parenchymal areas that showed a low baseline CBF and normal augmentation with acetazolamide (group 4), interpreted as having a decreased demand for CBF but having a normal vascular reserve. Decreased vascular reserve was found in 27% of the near-site areas and 17% of the far-site areas. No patients had only far-site abnormal vascular reserve.

We believe that compromised vascular reserve can best be evaluated with a challenge study, such as this acetazolamide-challenge Xe/CT study. Furthermore, this information may be used to identify those patients at risk for normal perfusion pressure breakthrough after AVM excision or embolization.

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Arteriovenous malformations (AVMs) may cause neurologic deficits by a variety of mechanisms. These include intraparenchymal hemorrhage, venous hypertension or thrombosis, and cerebral edema or gliosis caused by pressure effects from the AVM [1]. Another proposed mechanism for paroxysmal or progressive neurologic deficits in AVM patients is a steal phenomenon [1-9]. Physiologic studies have suggested there are areas of decreased blood flow in parenchyma adjacent to or at some distance from an AVM [3, 4, 6, 10-13]. However, the observation of decreased blood flow cannot necessarily be equated with a steal phenomenon. Decreased blood flow may be due to either decreased demand for flow or decreased flow reserve. In order to further elucidate the nature of the hemodynamic physiology associated with AVMs, we have used stable-xenon CT (Xe/CT) combined with acetazolamide challenge to assess cerebral blood flow (CBF) dynamics. Acetazolamide is known to produce a potent, generalized, cerebral vasodilatory response [14-18]. A repeat CBF study after IV administration of acetazolamide permitted assessment of CBF reserves.

Material and Methods

We examined 13 patients (nine men and four women) (age range, 16-52) with known supratentorial AVMs. Spetzler's classification was used to categorize AVMs as small (<3 cm

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¹ Department of Radiology, University of Pittsburgh, Presbyterian-University Hospital, Pittsburgh, PA 15213.

² Present address: Department of Radiology, Case Western Reserve University Hospitals of Cleveland, 2074 Abington Rd., Cleveland, OH 44106. Address reprint requests to R. W. Tarr.

³ Department of Neurosurgery, University of Pittsburgh, Presbyterian-University Hospital, Pittsburgh, PA 15213.

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in greatest diameter), medium (3–6 cm), or large (>6 cm) [19]. Although four of the thirteen patients had a history of intracranial hemorrhage, none had acute or subacute hemorrhage. Two patients had a history of prior embolization procedures, both of which had been performed more than 1 year before these Xe/CT CBF examinations. One patient had surgical ligation of a feeding artery from which an enlarging aneurysm had arisen 2 months before the CBF examination.

CBF analysis was done for each patient by means of the stable-Xe/CT method as described previously [20–23]. All Xe/CT CBF analyses were performed on a GE 9800 CT scanner equipped with a CBF hardware and software package (General Electric Medical Systems, Milwaukee, WI). Either a two-level or a three-level supratentorial baseline CBF examination was performed on each patient. Subsequently, 1 g acetazolamide was administered intravenously to each patient, followed by repeat Xe/CT CBF analysis 20 min later. The patient was not moved in the interval, and scanning levels identical to those for the baseline CBF analysis were used for the postacetazolamide CBF analysis.

CBF data for baseline and postacetazolamide examinations at each level were analyzed by using multiple, contiguous, region-of-interest (ROI) circles aligned along the outer cortical ribbon of both hemispheres. A diameter of 2.0 cm was chosen for the ROI circles to optimize inclusion of the largest area of gray matter while excluding most white matter within individual ROIs. Recent, correlative, conventional contrast-enhanced CT or MR images were used to map the location of the AVM on the Xe/CT CBF images. Any ROI including the AVM and one ROI on either side of the AVM were not used in the quantitative analysis to exclude the AVM nidus, enlarged feeding vessels, or enlarged draining veins. In addition, parenchymal areas encompassed by ROIs were divided into near-site areas (vascular supply is equivalent to that of the AVM) and far-site areas (major vascular territory is separate from that supplying the AVM) on the basis of recent angiographic data. On the basis of flow data from the preacetazolamide examination, ROIs were placed in one of two categories: normal flow (≥ 35 ml/100 g/min) and low flow (< 35 ml/100 g/min). Similarly, on the basis of flow augmentation after administration of acetazolamide, these same parenchymal areas were placed in one of two categories: normal augmentation ($\geq 10\%$ increase in CBF) and decreased augmentation ($< 10\%$ increase in CBF).

Results

The presenting symptoms and AVM characteristics of the 13 patients studied are summarized in Tables 1 and 2. The observed blood flow patterns can be categorized into four general groups based on CBF analysis before and after the administration of acetazolamide.

Group 1. Normal preacetazolamide CBF (≥ 35 ml/100 g/min) and normal augmentation ($\geq 10\%$) of CBF after acetazolamide administration (Fig. 1).

TABLE 1: Reason for Presentation of 13 Patients with Arteriovenous Malformations

Reason for Presentation	Number of Patients
Seizure	6
Hemorrhage	4
Headaches	2
Progressive neurologic deficit	1

Note.—These 13 patients (nine men and four women) ranged in age from 16 to 52 years old.

TABLE 2: Location and Size of Arteriovenous Malformations (AVMs) in 13 Patients

Characteristic	Number of Patients
Location of AVM	
Frontal	4
Temporal	3
Parietal	6
Occipital	1
Deep gray matter	1
Size of AVM (greatest diameter in cm)	
Small (< 3)	1
Medium (3–6)	13
Large (> 6)	1

Note.—One of the 13 patients had three medium AVMs, one in each frontal lobe and one in the right temporal lobe.

Group 2. Normal preacetazolamide CBF (≥ 35 ml/100 g/min) and decreased augmentation ($< 10\%$) of postacetazolamide CBF (Fig. 2).

Group 3. Low preacetazolamide CBF (< 35 ml/100 g/min) and decreased augmentation ($< 10\%$) of postacetazolamide CBF (Fig. 3).

Group 4. Low preacetazolamide CBF (< 35 ml/100 g/min) and normal augmentation ($\geq 10\%$) of postacetazolamide CBF (Figs. 3 and 4).

The results of individual ROI parenchymal analysis of the CBF data are presented in Tables 3 and 4. The average standard deviation of blood flow measurements within individual ROIs was 17.2 ml/100 g/min. Nineteen percent (67/355) of all parenchymal areas surveyed showed decreased augmentation on the postacetazolamide examination, indicating decreased vascular reserve. Twenty-six percent (32/121) of the near-site regions showed decreased vascular reserve. Fifteen percent (35/234) of the far-site regions showed decreased vascular reserve. In addition, 27% (26/97) of near-site areas and 17% (32/191) of far-site areas with normal CBF on the baseline study showed decreased augmentation on the postacetazolamide study, indicating decreased vascular reserve. Sixteen percent (58/355) of all parenchymal areas showed decreased CBF on the baseline examination but normal augmentation on the postacetazolamide study, suggesting a relatively decreased demand for blood flow rather than lowered flow reserve.

Most of the patients exhibited complex blood flow patterns. Only one patient, who had a small AVM, had completely normal baseline blood flows and diffusely normal augmentation of blood flow after acetazolamide administration. Eight of the 13 patients had three or more types of flow patterns. Ten had flow patterns consistent with diminished vascular reserve. In addition, seven patients had evidence of decreased vascular reserve at far-site locations. Each of the seven patients with evidence of diminished vascular reserve in far-site territories also had decreased vascular reserve in near-site territories. In one patient (who had a left parietal AVM and progressively decreasing right-sided proprioceptive, stereognostic, and graphesthetic abilities), decreased vascular reserve was observed in the left parietal lobe. Eleven patients had parenchymal areas with decreased demand for blood flow (decreased flow on the baseline examination but normal augmentation of flow after acetazolamide challenge).

Fig. 1.—32-year-old man who presented with seizures.

A, Lateral right internal carotid angiogram shows middle cerebral arterial supply to AVM.

B, Lateral left vertebral angiogram shows enlarged right posterior cerebral arterial supply to AVM.

C, Axial MR (2000/80/2) shows flow void signal in multiple vessels of AVM located in right posterior parietal lobe. No surrounding parenchymal abnormalities are present.

D, Precetazolamide Xe/CT CBF analysis shows globally normal blood flow values (numeric ROI data correspond to CBF in ml/100 g/min).

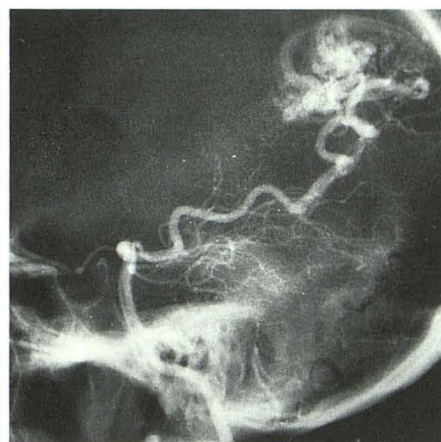
E, Precetazolamide contrast image of D (window level = 60; window width = 2). Blood flow values <60 ml/100 g/min are shown as black. Blood flow values ≥ 60 ml/100 g/min are shown as white. Arrows outline blood pool within AVM.

F, Postacetazolamide Xe/CT CBF analysis shows diffuse ($\geq 10\%$) augmentation of CBF (group 1).

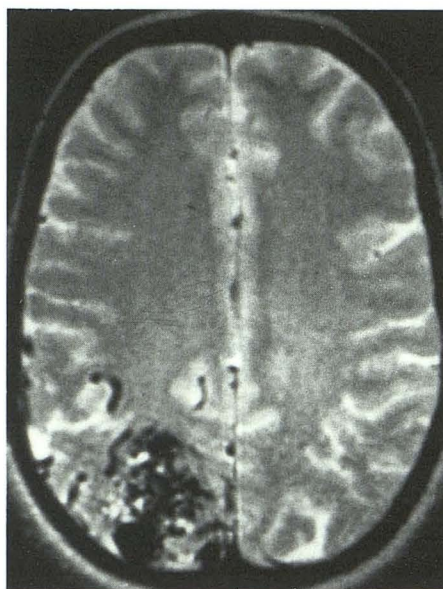
G, Postacetazolamide contrast image of F (window level = 60; window width = 2). Note that diffuse augmentation of CBF after acetazolamide administration is manifested as greater area of white pixels.



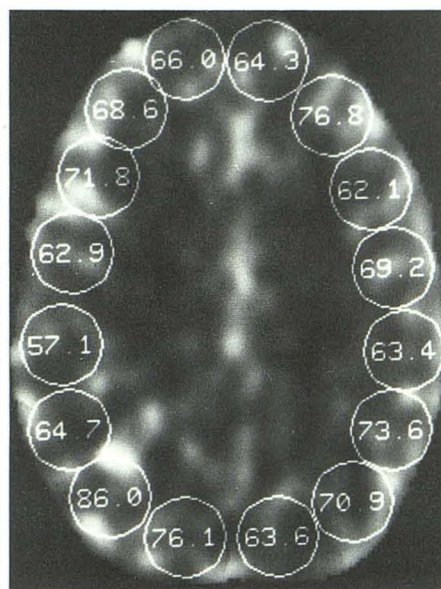
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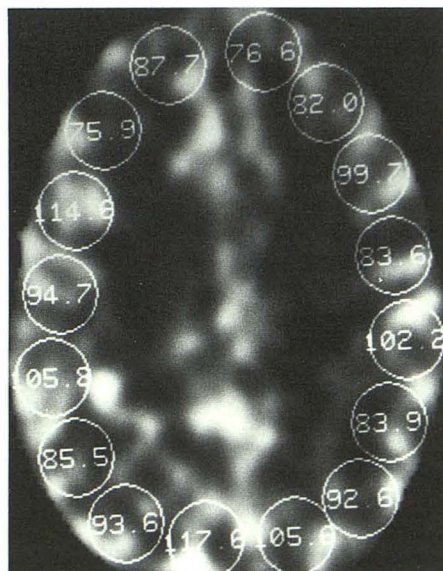
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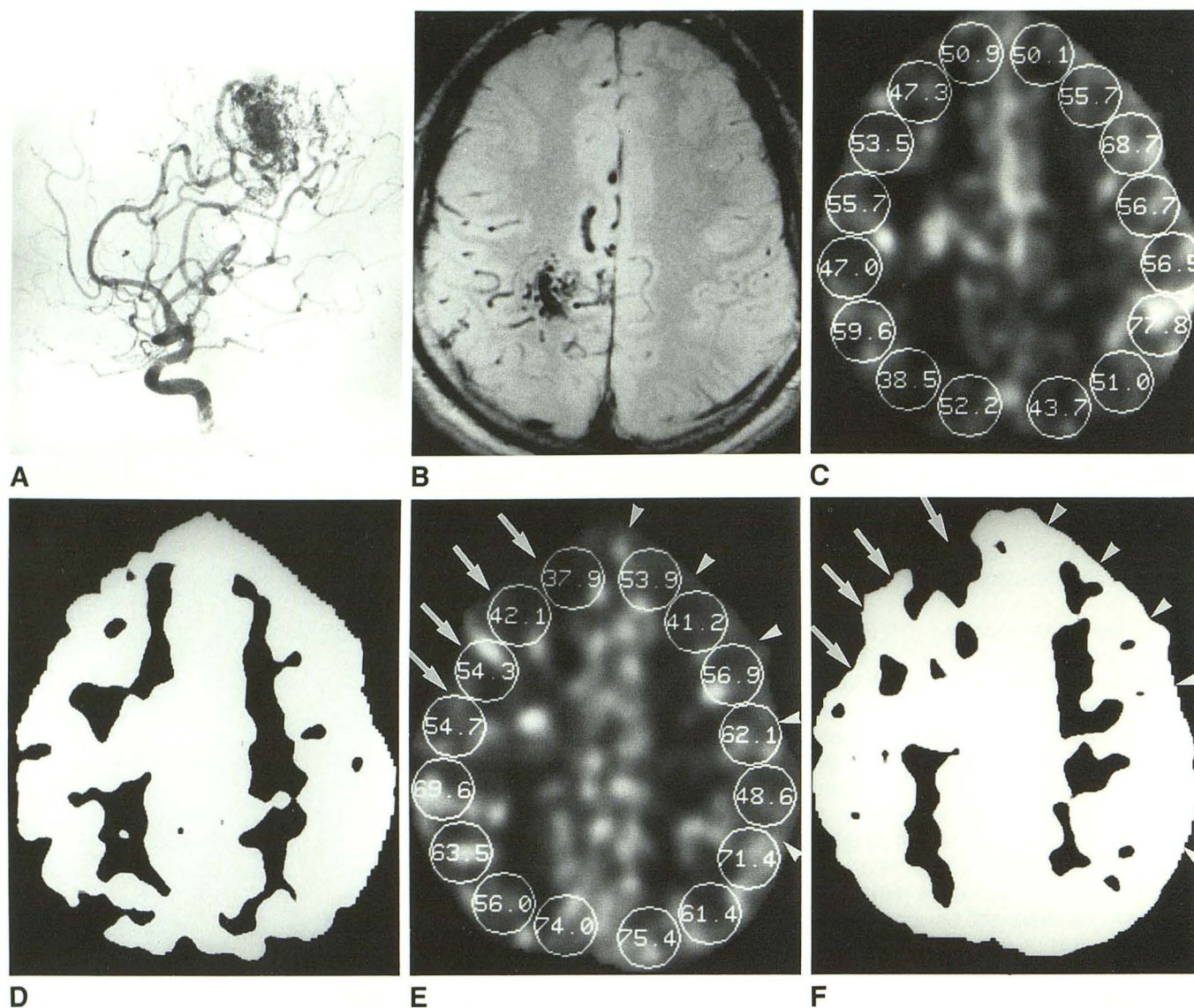


Fig. 2.—20-year-old man who presented with intractable seizures.

A, Lateral right internal carotid angiogram shows pericallosal and middle cerebral arterial supply to AVM.

B, Axial MR (2000/20/1) shows AVM extending into right centrum semiovale. No surrounding parenchymal reaction is present.

C, Preacetazolamide Xe/CT CBF analysis at level of centrum semiovale shows regionally normal blood flow values (numeric ROI data correspond to CBF in ml/100 g/min).

D, Preacetazolamide Xe/CT contrast image of C (window level = 35; window width = 2) shows diffuse cortical blood flow values ≥ 35 ml/100 g/min. Blood flow values < 35 ml/100 g/min are shown as black; blood flow values ≥ 35 ml/100 g/min are shown as white.

E, Postacetazolamide Xe/CT CBF analysis shows cortical regions in both near sites (arrows) and far sites (arrowheads) that fail to show normal ($\geq 10\%$) augmentation of blood flow. These regions represent areas that have decreased vascular reserve (group 2).

F, Postacetazolamide contrast image of E (window level = 35; window width = 2) shows failure to augment; even a slight decrease in CBF is seen in several parenchymal areas, indicating diminished vascular reserve. Arrows indicate near sites, and arrowheads indicate far sites; these correspond to same areas as in E.

Discussion

The mechanisms by which an AVM can alter CBF locally or in distant areas of the brain can be grouped into two general categories: (1) decreased flow reserve and (2) decreased flow demand. The mechanisms causing decreased flow reserve have previously been labeled the steal phenomenon, a somewhat misleading term. Rather than primarily transferring flow away from vascular territories, AVMs probably alter perfusion gradients in higher-resistance vasculature that supplies normal parenchyma [4, 7, 13]. The altered

intracranial hemodynamics may result in symptoms caused by critical hypoperfusion. In the normal situation, cerebral arteries exhibit autoregulation, and perfusion remains relatively constant despite wide changes in mean arterial pressure. The minimum mean arterial blood pressure that allows autoregulation to remain intact is approximately 50–60 mm Hg [24]. Mean arterial pressure in normal nutrient vessels arising from AVM feeding vessels may be below the minimum needed for autoregulation [4, 13]. These vessels are dilated as much as they can be, any further decrease in perfusion pressure will actually cause a decrease in blood flow. Also,

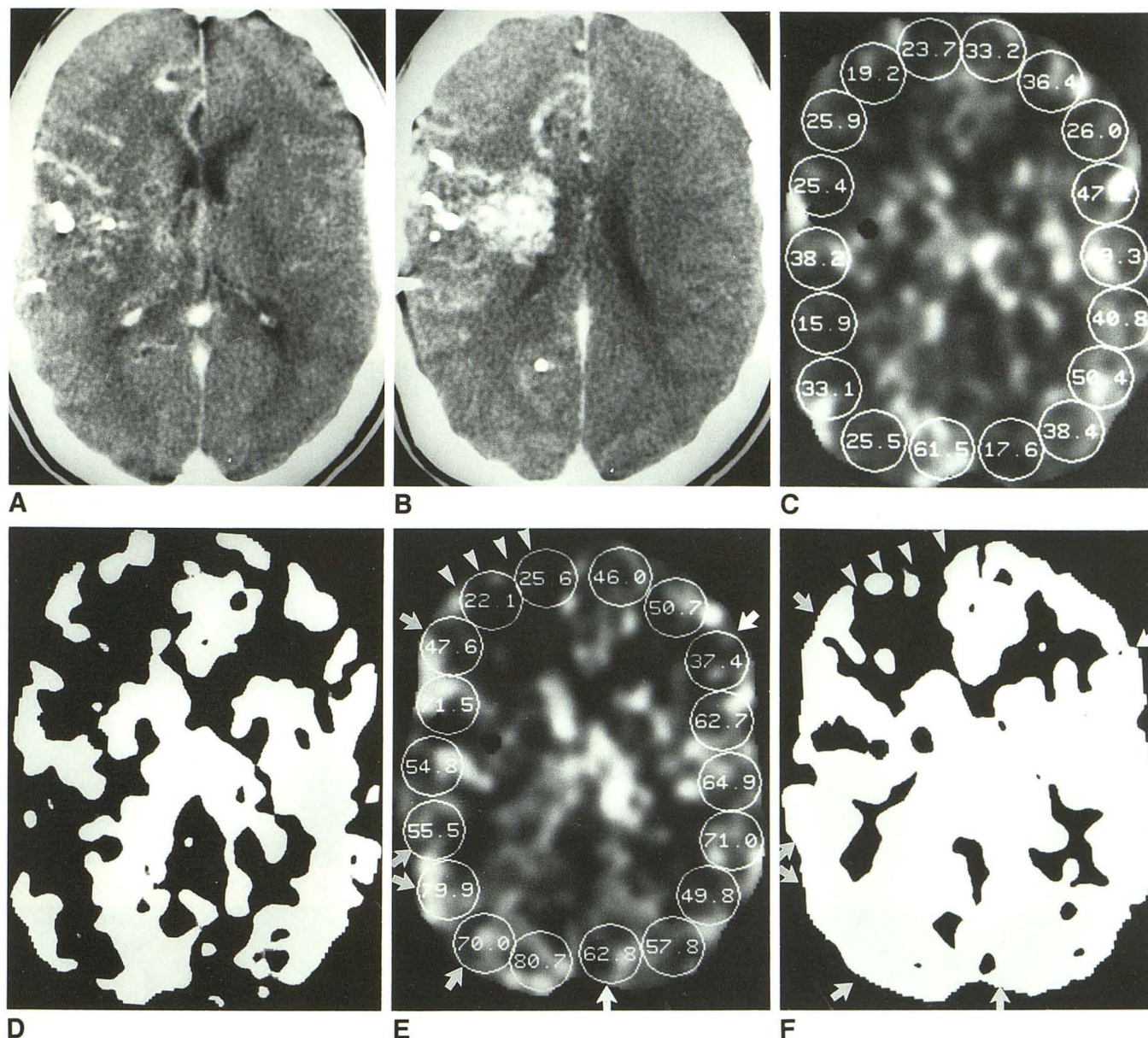


Fig. 3.—36-year-old woman who underwent partial particulate embolization of a right parietal AVM more than 1 year before these studies. A and B, Contrast-enhanced CT scan shows AVM nidus in right centrum semiovale. Multiple, small, metalliclike densities represent embolic material. C, Preacetazolamide Xe/CT CBF analysis shows low blood flow values (<35 ml/100 g/min) in multiple cortical parenchymal sites. D, preacetazolamide contrast image of C (window level = 30; window width = 2) again shows multiple cortical areas with low blood flow. Black areas represent flows <30 ml/100 g/min. E, Postacetazolamide Xe/CT analysis shows persistent low flows in border zone between right anterior cerebral artery and middle cerebral artery (arrowheads indicate border zone). These low flows indicate limited vascular reserve (group 3). Other parenchymal areas that showed low flow on baseline examination show normal augmentation of CBF after administration of acetazolamide (arrows), indicating a decreased baseline demand for blood flow (group 4). (ROI values correspond to CBF in ml/100 g/min.) F, Postacetazolamide contrast image of E (window level = 30; window width = 2) again shows evidence for decreased vascular reserve in border zone between anterior cerebral artery and middle cerebral artery. Other areas with previously low blood flow show normal augmentation of blood flow. Arrows and arrowheads correspond to same areas as in E.

In D and E, blood pool in region of body of lateral ventricles is due to partial volume averaging of enlarged draining veins.

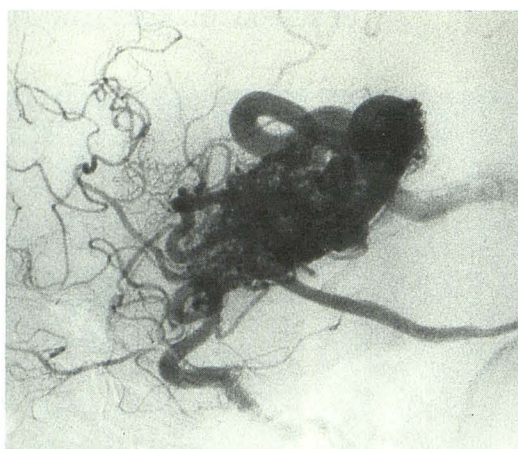
because these vessels cannot vasodilate further, they cannot augment CBF in response to acetazolamide.

Alternatively, AVMs may decrease flow to normal brain parenchyma by decreasing demand for flow because of either neuronal loss or decreased neuronal metabolic activity. The extent of neuronal loss may be microscopic and not detectable by macroscopic imaging techniques such as CT and MR.

Also, neuronal loss near an AVM may affect blood flow demand far removed from the AVM by the principle of intracerebral diaschisis [25, 26]. According to this principle, loss of afferent or efferent axons in one area can cause cell body loss or decreased cell body activity in remote cortical or subcortical regions owing to loss of association fibers between these areas. Although baseline demand for blood flow



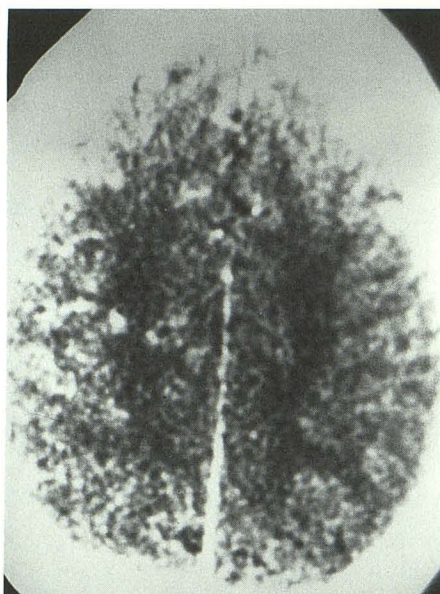
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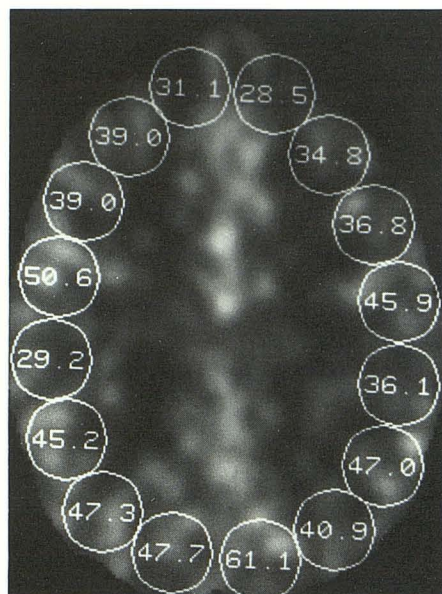
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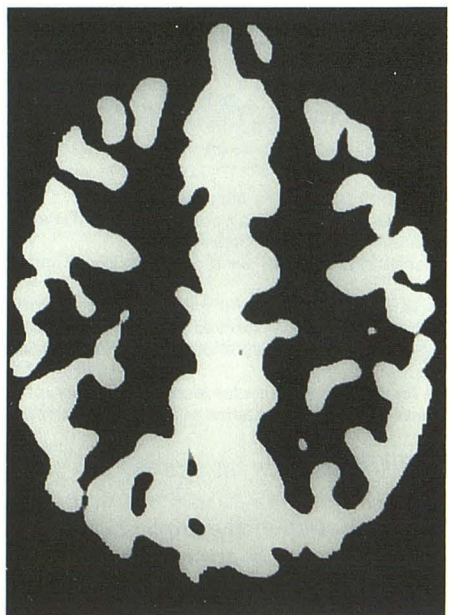
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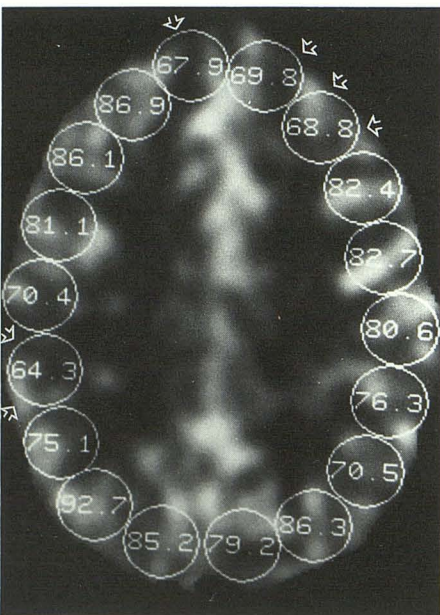
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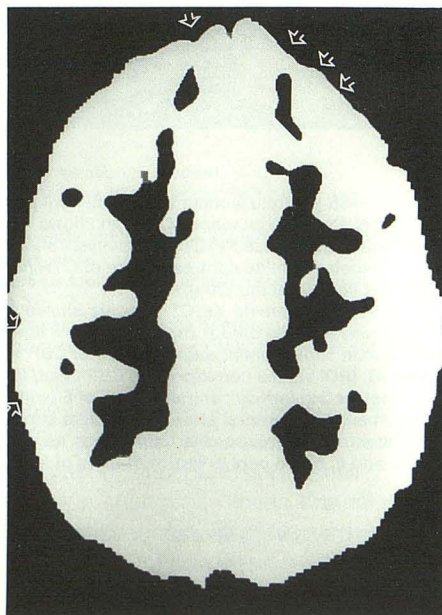
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TABLE 3: Two × Two Analysis of Near-Site ROIs

Postacetazolamide	Preacetazolamide		Total ROIs
	Normal CBF (≥35 ml/100 g/min)	Low CBF (<35 ml/100 g/min)	
Normal CBF augmentation (≥10%)	71	18	89
Decreased CBF augmentation (<10%)	26	6	32
Total ROIs	97	24	121

Note.—ROI = region of interest; CBF = cerebral blood flow. Numbers indicate the number of ROIs exhibiting either normal or low CBF combined with normal or decreased augmentation of CBF after acetazolamide. Near-site ROIs are those that are within the vascular territory that is supplying the arteriovenous malformation.

TABLE 4: Two × Two Analysis of Far-Site ROIs

Postacetazolamide	Preacetazolamide		Total ROIs
	Normal CBF (≥35 ml/100 g/min)	Low CBF (<35 ml/100 g/min)	
Normal CBF augmentation (≥10%)	159	40	199
Decreased CBF augmentation (<10%)	32	3	35
Total ROIs	191	43	234

Note.—ROI = region of interest; CBF = cerebral blood flow. Numbers indicate the number of ROIs exhibiting either normal or low CBF combined with normal or decreased augmentation of CBF after acetazolamide. Far-site ROIs are those outside the vascular territory that is supplying the arteriovenous malformation.

may be low, vessels supplying these regions remain capable of autoregulating and, therefore, can dilate or constrict in response to physiologic challenges.

Acetazolamide is a potent cerebral vasodilator, but the specific action by which acetazolamide produces a vasodilatory response is not known. The acute parenteral administration of acetazolamide inhibits carbonic anhydrase in red blood cells, decreasing the removal of CO₂ from blood and tissues. Some authors have suggested that an increased CO₂ in blood and brain may cause cerebral vasodilatation [16, 17]. Others have suggested that acetazolamide may cause vasodilatation by inhibiting carbonic anhydrase in the media of blood vessel walls [18] or by a direct action on vascular smooth muscle independent of its action on carbonic anhydrase [15]. Although the average magnitude of measured CBF increase reported after administration varies between 5% and 90% and depends somewhat on the patient's age and the dose administered, flow augmentation is normally diffuse and symmetric regardless of magnitude [14, 15]. An asymmetry of flow augmentation has been observed previously in patients with hemodynamically significant occlusive cerebral vascular disease [27, 28]. Acetazolamide administration does not have any permanent or serious sequelae, but it can cause temporary mild symptoms, such as circumoral and peripheral numbness, headaches, fatigue, giddiness, and nausea [14]. None

of the patients in our series developed related symptoms after acetazolamide administration.

In our study, four separate groups of flow patterns were detected on the basis of local flow values recorded before and after the administration of acetazolamide. Eight of the 13 patients in our study showed multiple types of flow patterns, thus reflecting the complexity of the hemodynamic effect of an AVM on surrounding brain parenchyma. Parenchymal areas that show normal or low preacetazolamide CBF and decreased augmentation after administration of acetazolamide (groups 2 and 3) are areas that have reduced blood flow reserve owing to lowered perfusion pressure. Blood flow may be normal in the baseline state, but because arterioles in these areas are maximally dilated, they are unable to vasodilate further in response to acetazolamide. This results in either a failure to augment or even a slight decrease in blood flow after acetazolamide challenge. Ten of the 13 patients examined in our study showed some evidence of decreased vascular reserve. Also, seven patients had decreased vascular reserve both in vascular territories near the AVM and in vascular territories far removed from the AVM. This finding suggests that AVMs may not only affect the local hemodynamic balance but may also affect the hemodynamic balance of the entire brain. Eleven patients in our series had parenchymal areas that had low CBF before administration

◀Fig. 4 (Facing page).—20-year-old woman with persistent headaches.

A and B, Anteroposterior (A) and lateral right internal (B) angiograms show middle cerebral artery and lenticulostriate artery supply to AVM.

C and D, Contrast-enhanced CT scans at levels of thalamus (C) and supraventricular centrum semiovale (D) show AVM with no other parenchymal abnormalities.

E, Preacetazolamide Xe/CT CBF analysis at level of supraventricular centrum semiovale shows multiple areas of low cortical CBF (<35 ml/100 g/min). (ROI values correspond to CBF in ml/100 g/min.)

F, Preacetazolamide contrast image of E (window level = 30; window width = 2) shows multiple cortical areas, with flows <30 ml/100 g/min represented as black pixels.

G, Postacetazolamide Xe/CT CBF analysis shows normal augmentation of (≥10%) CBF in areas with low baseline CBF (arrows), indicating decreased baseline demand for blood flow in these regions (group 4).

H, Postacetazolamide contrast images of G (window level = 30; window width = 2) again shows diffusely normal augmentation of CBF in regions with low baseline CBF (arrows) (group 4).

of acetazolamide and normal augmentation afterward (group 4). These are areas that have decreased demand for cerebral blood flow. Although the baseline demand for blood flow is lowered, blood vessels in these areas are still capable of dilating and thus augmenting blood flow in response to acetazolamide.

Although the present Xe/CT technology is quantitative, it is still subject to pixel-to-pixel anatomic variation of blood flow and inclusion of white matter and sulci within individual ROIs, yielding a significant standard deviation for local blood flow measurements. However, comparison of a preacetazolamide study and a postacetazolamide study enables assessment of areas of normal or abnormal CBF augmentation that reflect areas of normal or marginal vascular reserve, respectively.

The importance of detecting areas of diminished vascular reserve associated with AVMs has been suggested by Barnett et al. [13]. They have previously demonstrated areas of low flow and decreased CO₂ reactivity in AVM patients during intraoperative monitoring and have suggested that this subgroup of patients may be at higher risk for normal perfusion pressure breakthrough syndrome after AVM excision [29].

The theory of normal perfusion pressure breakthrough has been discussed previously [29–31]. The decreased perfusion pressure in arteries feeding an AVM may result in chronic arteriolar dilatation. This dilatation causes medial atrophy, loss of contractile strength, and therefore loss of normal autoregulatory capability. A rapid rise in perfusion pressure in these arteries may occur after AVM resection or substantial AVM embolization. Because of the inability to regulate the increased flow, significant parenchymal edema or hemorrhage may occur.

On the basis of the results of this study, acetazolamide-challenge Xe/CT CBF mapping seems to offer a noninvasive method for the preoperative identification of a subset of AVM patients with decreased autoregulatory capabilities. Once these patients are identified, precautionary measures (such as staged embolization before surgery or maintenance of low systemic arterial pressure during the early postoperative period) may be reasonable approaches to reduce the risk of cerebral edema or hemorrhage after AVM resection. In addition, these patients may benefit from monitoring of arterial-feeder pressure to prevent rapid alterations of perfusion pressures during therapeutic embolization [32].

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