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Cerebrovascular Hemodynamics in Arteriovenous Malformation Complicated by Normal Perfusion Pressure Breakthrough

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Catastrophic hyperemic states are known complications after the treatment of certain types of intracranial arteriovenous malformations (AVMs). A case is presented in which a large AVM was preoperatively embolized and later resected. There was clear intra- and postoperative evidence of edema and hemorrhage, which resulted in a fatal outcome. Regional cerebral blood flow (rCBF) data from this patient obtained with single photon emission computed tomography (SPECT) both before and after embolization were compared with data from four patients with similar size supratentorial AVMs treated and studied in a similar protocol who did not develop perfusion breakthrough. Pretreatment hemispheric rCBF was significantly reduced in this patient's ipsilateral hemisphere (50 ml/100 g/min) compared to the control group mean (83 ± 9.5 ml/100 g/min). A similar relative depression was found in the contralateral hemisphere. After therapeutic embolization, the ipsilateral rCBF increased by 33 ml/100 g/min and the contralateral hemispheric rCBF increased by 30 ml/100 g/min; this embolization-induced increase in rCBF was significantly higher than in the control group. Acetazolamide, known to increase rCBF in normal tissue by 35 ± 3%, resulted in a 56% augmentation of ipsilateral hemispheric flow before embolization in the reported patient vs. a 22 ± 10% increase for the control group. Postembolization, this hyperresponsiveness to acetazolamide remained unchanged. It is possible that these hemodynamic derangements may indicate a dissociation between the vasoconstrictive and vasodilatory reactivity in chronically hypoperfused territories adjacent to AVMs such that pharmacological or metabolic stimuli may induce further vasodilation, but sudden redistribution of large volumes of flow will not promote protective vasoconstriction. (*Neurosurgery* 22:503–509, 1988)

Key words: Arteriovenous malformation, Normal perfusion pressure breakthrough, Regional cerebral blood flow

INTRODUCTION

The high flow, low resistance arteriovenous shunt associated with intracranial arteriovenous malformations (AVMs) can lead to chronic hypoperfusion in surrounding brain tissue. Abrupt occlusion of the shunt has in some cases led to edema and hemorrhage in adjacent brain. This phenomenon was first described in an experimental model by Spetzler et al. in 1978 and was called the "normal perfusion pressure breakthrough" (NPPB) theory (18). Several other cases have been reported since 1978 (4, 9). It is likely that less fulminant episodes occur during the resection of certain types of AVMs. Large malformations, those with high flow, low resistance characteristics, and those with clinical or angiographic evidence of steal have been thought to pose increased risk (11, 16–18). We report a fatal case of NPPB after treatment by embolization and subsequent resection of a large AVM. Regional cerebral blood flow (rCBF) was measured using xenon-133 inhalation and single photon emission computed tomography (SPECT). Chronically reduced perfusion should result in maximal vasodilation and loss of the normal properties of vasoreactivity. For demonstration of these properties with rCBF measurements, hemodynamic or pharmacological manipulations are required. The administration of acetazolamide is known to augment rCBF in normal brain tissue (22). Chronic marginal perfusion with resulting maximal arteriolar vasodilation should preclude further increases in rCBF after pharmacological activation with acetazolamide. rCBF measurements obtained both in the resting state and after acetazolamide administration were performed preoperatively and after preliminary embolization of the patient's AVM. Quantitative hemispheric flow values from this patient at each stage were compared with those obtained from four other patients with large (5 cm or greater) supratentorial AVMs subjected to similar treatment and investigative protocols who did not develop NPPB.

MATERIALS AND METHODS

Dynamic single photon emission computed tomography

rCBF was determined by dynamically monitoring the cerebral transit of xenon-133 using the Tomomatic 64 SPECT (Medimatic A/S, Copenhagen, Denmark) designed by Stokely et al. (19). It consists of four detector arrays each containing 16 NaI (T1) scintillation crystals. The arrays are mounted in a hollow square configuration that rotates around the subject's head at 6 rpm. Special focused collimators define three transverse tomographic cross sections with centers 4 cm apart. Xenon-133 is administered in an air/oxygen mixture (10 mCi/litre) during the 1st minute of a 4-minute wash-in/wash-out procedure. The patient breathes room air during the remaining 3 minutes of the study, exhaling the mixture into a charcoal trap. During the 4-minute measurement period, activity in the lung is monitored by a scintillation probe placed on the chest, and this activity is assumed to correspond to the arterial blood concentration of xenon-133 in the brain. rCBF is calculated in ml/100 g/min according the the double-integral method described by Kanno and Lassen (7), Celsis et al. (3), and Smith et al. (15). The reproducibility and reliability of this method were evaluated in normal individuals by Devous et al. (5). Voxel flow values are displayed in a 64 × 64 matrix using a 16-shade scale that can be normalized to the highest flow value. Cerebral blood flow was also numerically recorded with

values characterizing the activity of the whole hemisphere. System resolution (full width at half maximum) measured with a xenon-133 line source in water varies from 1.7 cm at the center of each slice to 1.0 cm at the edge transversely.

Subjects are studied with their eyes open and ears unplugged. The room is dimly lit and background noise originates primarily from instrument cooling fans. Subjects breathe through a fitted mouthpiece with nostrils occluded by a spring clamp. Approximately 2 minutes of adaptation time is allowed before initiating the study. Each subject is asked to take a deep breath at the beginning of the study, after which no further communication occurs. Subjects are positioned in the tomograph so that the three transverse cross sections are located 2, 6, and 10 cm above and parallel to the canthomeatal line. Positioning is accomplished by marking a reference line on the subject's face that is aligned with the tomograph frame.

Vasoreactivity was evaluated by Vorstrup and Lassen by performing SPECT rCBF studies before and after the administration of acetazolamide, a cerebral vasodilator that acts via carbonic anhydrase inhibition on red cells and impairs removal of CO_2 from brain tissue (21, 22). A direct vasodilatory effect has also been postulated (6). For this study, the subject received a base line rCBF study and 30 minutes later acetazolamide (1.0 g) was injected i.v. rapidly. Ten minutes after this injection, a vasodilator-stimulated rCBF SPECT measurement was obtained. In normal subjects, acetazolamide leads to a 35 ± 3% increase in rCBF throughout the entire brain. Preserved vasoreactivity is associated with relatively unchanged or even increased regional/whole brain flow ratios for various brain regions.

Embolization

The patient underwent flow-directed left internal carotid embolization using 100 1- × 1-mm particles of polyvinyl alcohol sponge. The particles were introduced individually, utilizing repeated angiography and neurological examination to monitor progress. The procedure was terminated when the left middle cerebral artery was observed to be subtotally occluded at its bifurcation, leaving only lenticulostriate feeders to the AVM. The distal sylvian vessels were observed to fill via leptomeningeal collaterals.

Case report

A 67-year-old, right-handed man with a 4-year history of complex partial seizures developed bifrontal headache and dizziness. A computed tomographic (CT) scan revealed subarachnoid hemorrhage (SAH) associated with a large, enhancing lesion in the middle cerebral artery (MCA) distribution (Fig. 4). Cerebral angiography disclosed a 5-cm left frontoopercular and insular AVM fed heavily by MCA branches as well as an anterior cerebral contribution predominantly through the artery of Heubner (Fig. 1). Neurological examination revealed an alert man without signs of meningeal irritation or focal deficit. Thirty-frame per second angiography displayed an area on the left MCA that perhaps was an aneurysm.

Thinking that the SAH might be aneurysmal in origin, a left transsylvian exploration was performed on posthemorrhage Day 5, but satisfactory exposure of the M_1 trunk and bifurcation was precluded by a tight, swollen brain and a large sylvian varix. Additional retraction and dissection produced AVM bleeding, which was controlled by clips. The wound was closed after dural patching and the bone flap was left out because of brain swelling. The patient tolerated the procedure well, remaining neurologically intact. On postoperative Day 6 and posthemorrhage Day 11, the patient underwent flow-directed embolization of the left internal carotid artery (as previously described). A remarkable diminution of arterial input to the malformation was noted, and the large ascending frontal MCA branch was occluded (Fig. 2). Despite subtle word-finding difficulties and mild disorientation over the first 24 hours, the patient completely recovered. On posthemorrhage Day 23 and postembolization Day 12, the patient was taken to the operating room for definitive resection. The operative procedure was complicated by significant brain swelling requiring electroencephalogram burst suppression doses of etomidate as well as induced hypotension to 80 mm Hg systolic. Immediately after mobilization and excision of the AVM, significant hemorrhage from the margins ensued. A thorough inspection of the operative site, including the lateral ventricle as well as the entire middle cerebral (M_1) trunk failed to reveal residual AVM. Eventually, the bleeding abated after a 16-unit blood loss. Because of what was clinically an episode of normal perfusion breakthrough, the patient was placed in barbiturate coma during the ongoing hemorrhage.

An immediate angiogram failed to disclose residual AVM (Fig. 3). CT scanning at that time showed diffuse left hemis-

FIG. 1. Lateral (*A*) and anteroposterior (*B*) left carotid angiogram obtained after SAH revealing an AVM irrigated by the left MCA and the anterior cerebral artery.

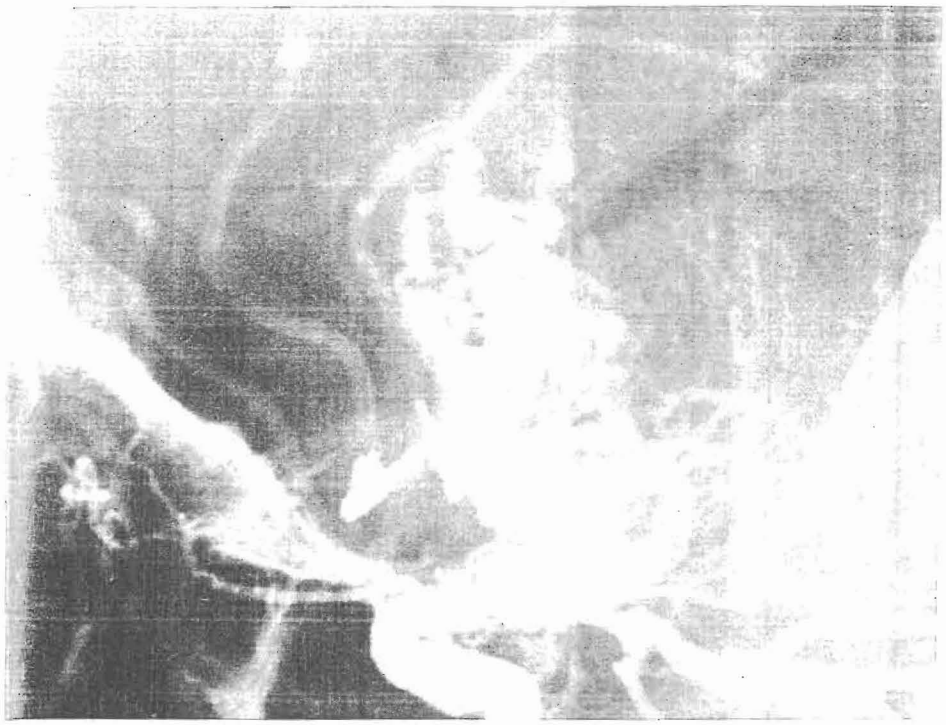

FIG. 2. Repeat left carotid angiogram (lateral projection) on posthemorrhage Day 11 after flow-directed embolization of the AVM.

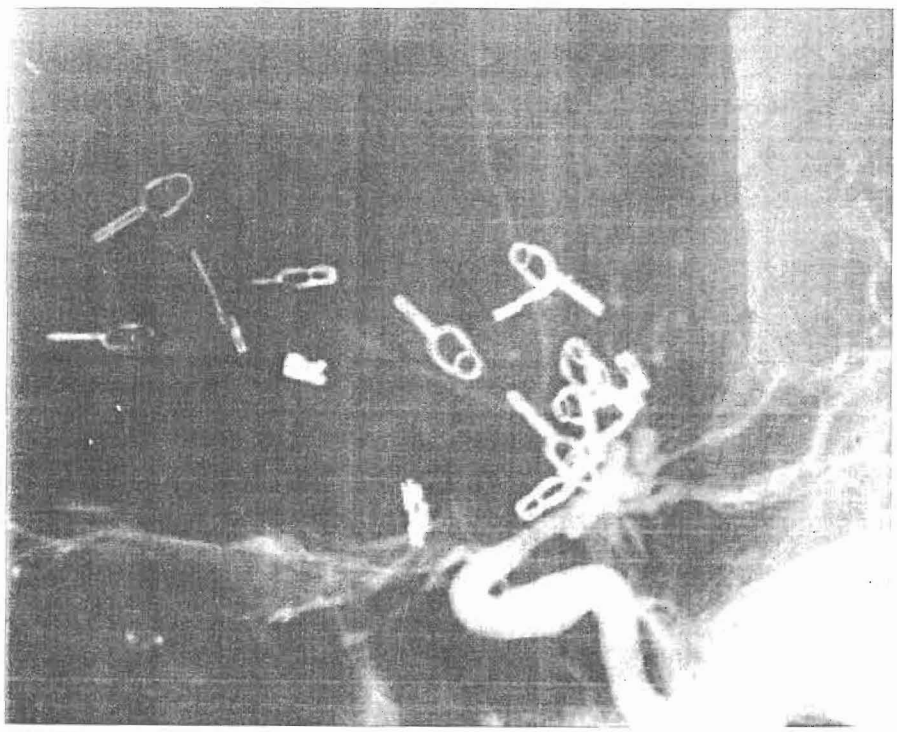

FIG. 3. Immediate postoperative left carotid angiogram confirming complete resection of the AVM.

pheral swelling with minimal shift of midline structures. Swan-Ganz monitoring was used to sustain cardiac parameters during the intermittent use of pressors to support rigidly a systolic blood pressure of not more than 100 mm Hg. During this period, the CT images remained unchanged. Forty-eight hours postoperatively, after withdrawal of the barbiturate drip, the patient became hemodynamically unstable, requiring pressors; subsequently, the left pupil dilated.

He was taken to the operating room despite lack of change on repeat CT scan (Fig. 4). Inspection of the operative site disclosed minimal clot, but severe brain edema. A left frontal lobectomy was performed and, upon reversal of anesthetic, both pupils were found to be dilated and fixed. A repeat CT scan showed diffuse low density in the entire diencephalon (Fig. 4). The patient soon developed diabetes insipidus followed by the adult respiratory distress syndrome and died

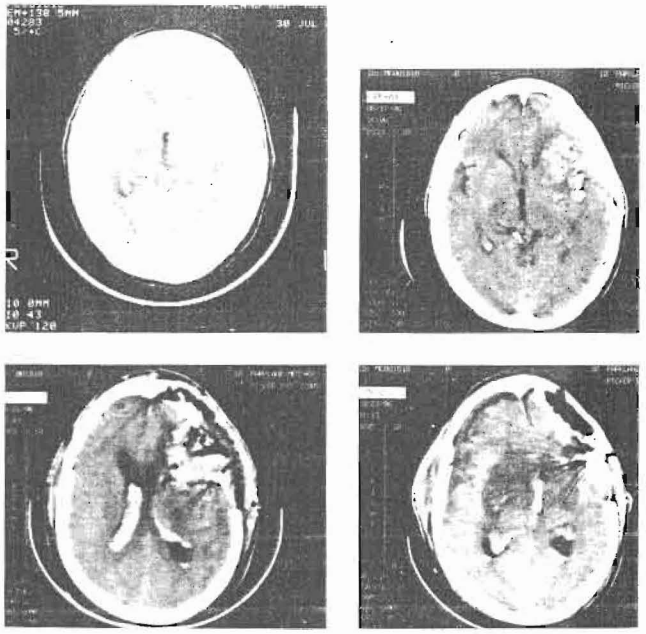

FIG. 4. CT scans obtained during the patient's hospital course: *Top left*, enhanced CT scan 1 week after the ictus shows SAH with an enhancing parasylvian mass. *Top right*, after flow-directed embolization, the CT scan reveals an accumulation of polyvinyl alcohol foam particles within the substance of the malformation. *Bottom left*, immediately after clinical deterioration 48 hours postoperatively, a CT scan reveals clot within the resection site associated with moderate ventricular hemorrhage and significant frontal mass effect. *Bottom right*, final CT scan obtained when the patient developed diabetes insipidus and brain stem dysfunction showing remarkable bilateral diencephalic low density and shift from right to left.

from cardiovascular collapse. The family requested that no autopsy be performed.

rCBF measurements (Table 1)

SPECT images obtained as base line and after acetazolamide administration both before and after therapeutic embolization are shown in Figure 5. Hemispheric rCBF was measured bilaterally to evaluate the hemodynamic impact of the AVM. Data obtained were statistically compared to four "control" patients with similar size supratentorial AVMs who were similarly treated but did not develop evidence of perioperative hyperemia.

Ipsilateral hemisphere. As seen in Table 1, before treatment the patient had a base line hemispheric rCBF of 50 ml/100 g/min, which is significantly depressed relative to the mean of the control group (83 ± 9.5 ml/100 g/min). A dramatic increase in base line hemispheric rCBF after emoblization was noted. An increase by 33 ml/100 g/min was significantly different from the mean change of the control (−1.5 ± 7 ml/100 g/min). In evaluating vasoreactive phenomena, the patient was found to have a 56% increase in hemispheric flow after acetazolamide before embolization as compared to the control group's increase by 22 ± 10%. After embolization, the patient continued to respond to acetazolamide with a 54% increase as compared to the control group increase of 29 ± 8%.

Contralateral hemisphere. Base line hemispheral pretreatment blood flow was also depressed in the patient's contralateral hemisphere (52 ml/100 g/min) relative to the control contralateral hemispheric mean (80 ± 10 ml/100 g/min). Interestingly, the base line rCBF also increased dramatically in the contralateral hemisphere by 30 ml/100 g/min after embolization. This increase was also significantly greater than

TABLE 1
rCBF[a]

	Patient	Control Patients				
		1	2	3	4	Mean ± SD
Ipsilateral hemisphere						
pre (base line)	50	87	71	80	93	83 ± 9.5
post (base line)	83	94	69	80	82	81 ± 10
(post-pre) (base line)	+33	+7	−2	0	−11	−1.5 ± 7
pre (acetazolamide)	78	95	95	100	111	100 ± 7.5
post (acetazolamide)	128	120	97	101	100	104.5 ± 10
(post-pre) (acetazolamide)	+30	+25	+2	+1	−11	4. ± 15
vasoreactivity (pre)	28 (56%)	8 (9.2%)	24 (33.8%)	20 (25%)	18 (19.4%)	22% ± 10%
vasoreactivity (post)	45 (54%)	26 (27.6%)	28 (40.6%)	21 (26.3%)	18 (21.9%)	29% ± 8%
Contralateral hemisphere						
pre (base line)	52	87	66	79	87	80 ± 10
post (base line)	82	91	75	82	92	85 ± 8
(post-pre) (base line)	+30	+4	+9	+3	+5	5 ± 3
pre (acetazolamide)	83	95	95	107	113	102.5 ± 9
post (acetazolamide)	130	123	105	115	106	112 ± 8
(post-pre) (acetazolamide)	+47	+28	+10	+8	−7	10 ± 14
vasoreactivity (pre)	31 (59.6%)	8 (9.2%)	29 (43.9%)	28 (35.4%)	26 (29.9%)	30% ± 15%
vasoreactivity (post)	48 (58.5%)	32 (35.2%)	30 (40%)	33 (40.2%)	14 (15.2%)	33% ± 12%

[a] Abbreviations: pre = hemispheric blood flow before embolization; post = hemispheric blood flow after embolization; (post-pre) = difference between post- and preembolization blood flow values; vasoreactivity (acetazolamide − base line). All rCBF values are expressed in ml/100 g/min.

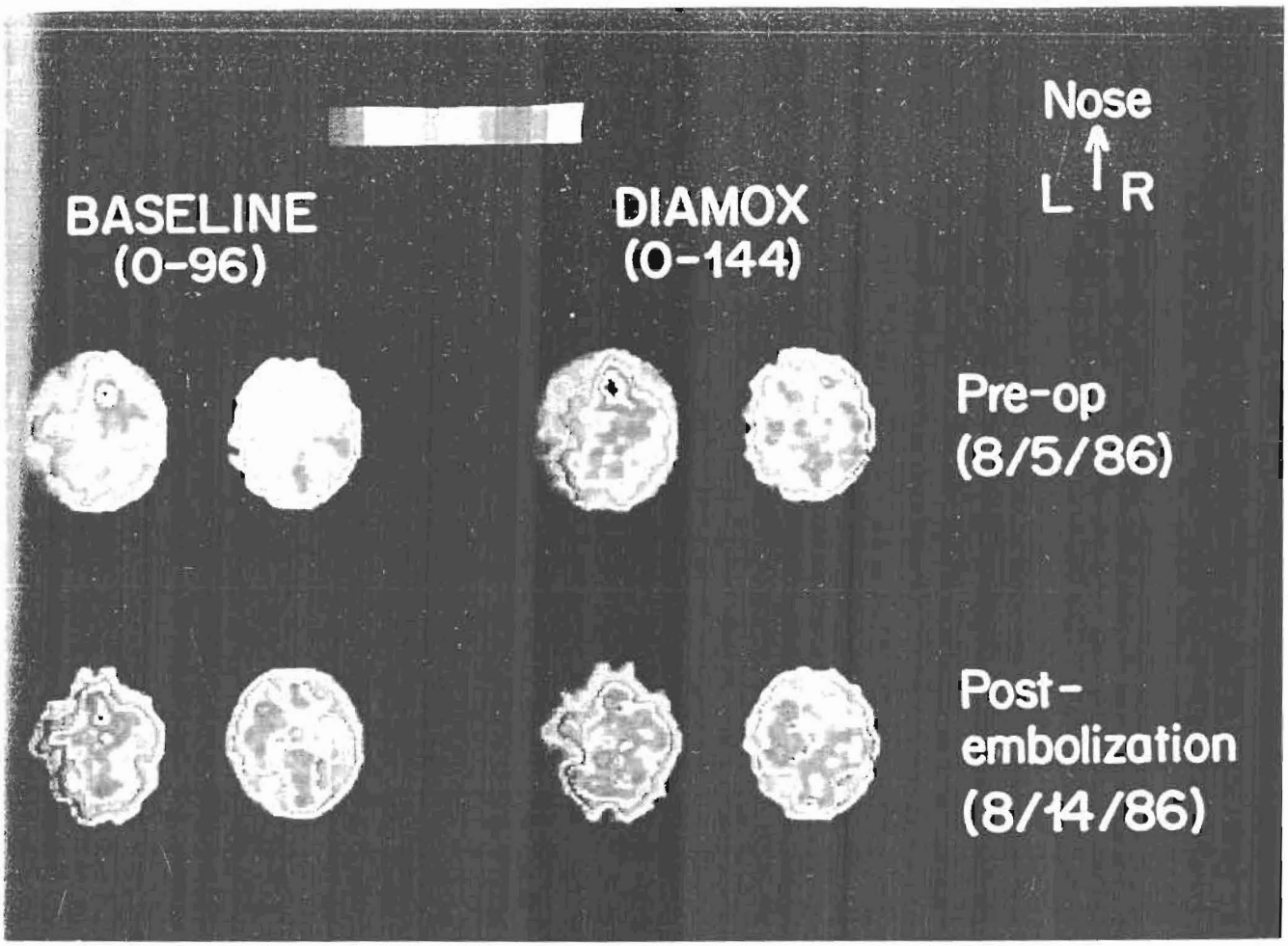

FIG. 5. Preoperative—12 days post-SAH (August 5, 1986): SPECT rCBF images obtained both at rest (base line) and after the administration of acetazolamide (1.0 g) illustrate hemispheral symmetry with a striking increase in bilateral perfusion after acetazolamide (See Table 1 for actual hemispheric values).

Postembolization—3 weeks post-SAH and 10 days postembolization (August 14, 1986): After recovery from a mild neurological deficit due to the embolization procedure, repeat rCBF images show significantly increased bilateral hemispheral flow with preserved responsiveness to acetazolamide (see Table 1).

in the control groups. The differences in vasoresponsiveness to acetazolamide between the patient and the control group were not significant in the contralateral hemisphere.

DISCUSSION

Symptoms of cerebral ischemia are well-known presenting complaints of patients harboring intracranial AVMs. Most think that the extremely high flow, low resistance characteristics of these lesions selectively direct blood through the malformation, resulting in hypoperfusion of the surrounding brain (17). Nornes and Grip described decreased metabolite delivery to this tissue associated with excessive venous pressures (11). Several characteristics have been implicated in the development of hemorrhage and edema at the time of resection. These include clinical and radiographic evidence of hypoperfusion adjacent to the AVM, large size, high flow characteristics, and long, tortuous feeding arteries (10, 11, 14, 17, 18, 23). When severe, these hemodynamic crises can be disabling or fatal, although successful treatment has been described with induced hypotension and barbiturate coma (1, 4, 8). Pertuiset et al. attempted to prevent this complication in high risk patients with deranged autoregulatory capacity by partially occluding the cervical carotid artery at the time of excision (13).

With intraoperative Doppler studies, Nornes et al. measured flow in feeding arteries up to 550 ml/min and found that total AVM flow can reach 900 ml/min (11, 12). Also, using an open technique, Barnett et al. measured local cortical blood flow in cerebral tissue immediately adjacent to AVM margins and at sites 2 to 4 cm from the margin (2). They noted that, before excision, the cortical flow was significantly depressed 2 to 4 cm away from the margin. Interestingly, the CO_2 reactivity was also impaired at these "remote" sites. After excision of the AVM, significantly increased flow was noted in tissue remote from the margins.

In this report, pilot rCBF data from four patients treated for symptomatic, large (greater than 5 cm), supratentorial AVMs with aggressive transfemoral intravascular embolization before surgical excision are compared to data from a patient who developed a classical and fatal episode of hemorrhage and edema after operation. In addition to pretreat-

ment and postembolization rCBF measurements with SPECT, cerebral vasoreactivity was evaluated at the same time by administering acetazolamide, which is known to augment rCBF in normal tissue. Realizing that this group of patients is too small to allow definitive conclusions, we were surprised to find several unique hemodynamic characteristics in the single patient who clearly developed fatal postoperative hyperemic complications:

1. The patient had significantly depressed hemispheric rCBF before treatment, both ipsilateral and contralateral to the AVM, compared to the control group.
2. Therapeutic embolization resulted in dramatic increase in rCBF in both hemispheres, whereas changes measured in the control group were slight.
3. Acetazolamide augmented rCBF both before and after embolization significantly more than in control patients in the hemisphere ipsilateral to the AVM.

It is possible that the depression in base line rCBF values bilaterally in this patient was simply a manifestation of true intracerebral steal. The extremely large ascending frontal branch of the left MCA captured most of the left internal carotid flow; conceivably, the contralateral hemisphere could have participated in irrigation of the AVM across anterior cerebral and posterior cerebral collateral channels. The preoperative angiogram documented patency of the circle of Willis, and some perfusion of the AVM was noted during injection of the right internal carotid and of both vertebral arteries.

The substantial increase in hemispheric flow bilaterally after embolization and subtotal MCA occlusion is consistent with recent measurements of cortical blood flow after resection of AVMs (2). Assuming that high flow feeding arteries can carry 2 to 3 times the normal MCA flow volume, at the time of embolization or excision the production of an extremely high resistance system necessitates redistribution of a large volume of internal carotid blood flow. In this patient, this redistribution could have occurred via the anterior cerebral and posterior communicating arteries and may have occurred into a chronically vasodilated and relatively lower resistance runoff bed. Perhaps the difference in magnitude of the redistribution reflected both the thoroughness of the embolization procedure and a large volume of brain tissue whose vessels lacked the capacity to vasoconstrict due to chronic hypoperfusion. Data from occlusive cerebrovascular disease suggest that chronically hypoperfused tissue should contain maximally dilated vasculature incapable of further vasodilation due to the administration of acetazolamide (20). If the mechanism of ischemia in AVM patients is simply a steal phenomenon with competitive vasodilation in hypoperfused tissue, it seems paradoxical that the rCBF in this patient was augmented so dramatically after acetazolamide administration. If this effect had been noted only on postembolization studies, it would have been tempting to postulate that the large additional quantity of blood that suddenly became redistributed simply overwhelmed the hemispheric circulation, and a mechanically passive but pharmacologically responsive arteriolar bed resulted. This unusual response to acetazolamide, however, was also seen in the pretreatment study when hemispheric rCBF was reduced.

It seems possible that, in the altered hemodynamic circumstance of intracranial AVM, a paradoxical dissociation could exist between the vasoconstrictive and vasodilatory capacities of adjacent vessels. In spite of chronic hypoperfusion, further vasodilation may be prompted by metabolic or pharmacological stimuli, whereas these same vessels may have been rendered either transiently or permanently unable to constrict when faced with increased perfusion pressure. Further studies are in progress with larger numbers of patients to determine whether this unfortunate patient suffered a unique hemodynamic catastrophe or whether it might be possible to identify noninvasively with SPECT high risk groups in whom serial embolization procedures or protracted postembolization intervals might allow reversal of these abnormal rCBF patterns.

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COMMENTS

The authors present a most interesting case report with the unhappy complication of intracerebral hemorrhage and edema that is attributed to NPPB bleeding after excision of a large left cerebral AVM.

Of particular interest are the preoperative cerebral blood flow measurements showing preserved vasoreactivity to acetazolamide testing, an unexpected finding if indeed the postoperative hemorrhage was due to NPPB and the theories regarding the pathophysiology of this entity are correct. In explanation of this, the authors propose a paradoxical dissociation between the vasoconstrictive and vasodilatory capacities of the adjacent vasculature, an interesting but unproven concept.

Certainly, the blood flow measurements in this case are of major importance. It might be questioned whether the effect of craniotomy without bone flap replacement might have an effect on their validity. Also, no blood pressure measurements are given for correlation with the CBF measurements. While the depression in the base line cerebral blood flow measurements in the case report is attributed to intracerebral steal, it is also possible that this reduction is simply a reflection of recent SAH and increased intracranial pressure.

In spite of the questions that are raised, the observations and the deductions of the authors regarding this case are of great interest and indicate the need for further clinical and laboratory studies of the vasoreactivity in AVM and the hemodynamics that are operative in cases of presumed NPPB.

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Batjer et al. present a well-documented case of NPPB in a patient with a large AVM that was aggressively embolized and resected. As the authors discuss, this complication occurs most commonly in patients undergoing resection of large, high flow lesions. These large AVMs frequently demonstrate vascular steal from the surrounding brain. When the vascular steal is severe, angiography may demonstrate a virtual absence of flow to branches supplying the normal brain. Intraoperative pressure measurements and cerebral blood flow studies have verified the presence of areas of hypoperfusion in patients with such lesions. The vessels in these areas of chronic hypoperfusion may lose the ability to autoregulate cerebral blood flow in response to changes in arterial pressure. When an AVM surrounded by such areas is aggressively embolized or resected, the sudden increase in arterial pressure to normal levels may lead to hyperperfusion, edema, and hemorrhage (i.e., NPPB).

Batjer et al. present CBF evidence that, although vessels in areas of hypoperfusion surrounding the AVM may be unable to respond to sudden increases in perfusion pressure with appropriate constriction, they are capable of further dilation in response to changes in the tissue CO_2 produced by acetazolamide. In fact, the patient described had a greatly exaggerated response to acetazolamide challenge both before and after embolization. As the authors suggest, this exaggerated response to acetazolamide may be a marker of increased risk for NPPB, although further studies are needed to verify this association.

In the case described by the authors, the patient underwent an aggressive single stage transfemoral embolization procedure before AVM excision. The marked swelling and edema encountered at craniotomy for resection suggest that autoregulation may have already been disturbed. Resection of the AVM may then have precipitated the full-blown picture of NPPB with diffuse hemorrhage. In this instance, when swelling and edema were encountered, the authors would have been better advised to back out and close, delaying further intervention for 1 to 2 weeks.

To reduce the risk of NPPB, we have developed a strategy for the surgical management of large AVMs that involves a stepwise reduction of blood flow through the lesion, using staged intraoperative embolization procedures combined with vessel ligation (4). The gradual increases in cerebral perfusion pressure and blood flow produced by this staged approach seem to be well tolerated by the surrounding brain. Using a strategy of staged operative embolization, we have been able to resect completely 22 of 24 large AVMs (greater than 6 cm) with no mortality and only 1 severe disabling sequela.

Additional protection against NPPB seems to be offered by the intraoperative use of barbiturates (3). We perform all surgical procedures for AVMs with the patient under deep barbiturate anesthesia. Barbiturates reduce cerebral metabolism and blood flow and may help the brain to adjust to the changes in hemodynamics induced by the embolization and excision of an AVM. Barbiturates have also been effective in the management of NPPB, with several authors reporting successful outcomes in patients who were treated by the rapid induction of barbiturate coma (1, 2).

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