Diffusion- and Perfusion-Weighted Imaging in Vasospasm After Subarachnoid Hemorrhage

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Background and Purpose—Better measures of cerebral tissue perfusion and earlier detection of ischemic injury are needed to guide therapy in subarachnoid hemorrhage (SAH) patients with vasospasm. We sought to identify tissue ischemia and early ischemic injury with combined diffusion-weighted (DW) and hemodynamically weighted (HW) MRI in patients with vasospasm after SAH.

Methods—Combined DW and HW imaging was used to study 6 patients with clinical and angiographic vasospasm, 1 patient without clinical signs of vasospasm but with severe angiographic vasospasm, and 1 patient without angiographic spasm. Analysis of the passage of an intravenous contrast bolus through brain was used to construct multislice maps of relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF), and tissue mean transit time (tMTT). We hypothesize that large HW imaging (HWI) abnormalities would be present in treated patients at the time they develop neurological deficit due to vasospasm without matching DW imaging (DWI) abnormalities.

Results—Small, sometimes multiple, ischemic lesions on DWI were seen encircled by a large area of decreased rCBF and increased tMTT in all patients with symptomatic vasospasm. Decreases in rCBV were not prominent. MRI hemodynamic abnormalities occurred in regions supplied by vessels with angiographic vasospasm or in their watershed territories. All patients with neurological deficit showed an area of abnormal tMTT much larger than the area of DWI abnormality. MRI images were normal in the asymptomatic patient with angiographic vasospasm and the patient with normal angiogram and no clinical signs of vasospasm.

Conclusions—We conclude that DW/HW MRI in symptomatic vasospasm can detect widespread changes in tissue hemodynamics that encircle early foci of ischemic injury. With additional study, the technique could become a useful tool in the clinical management of patients with SAH. (Stroke. 1999;30:599-605.)

Key Words: subarachnoid hemorrhage ■ cerebral ischemia ■ ultrasonography, Doppler, transcranial ■ magnetic resonance imaging ■ imaging, diffusion-weighted ■ imaging, hemodynamically weighted

Delayed cerebral ischemia due to vasospasm is one of the most devastating sequelae of subarachnoid hemorrhage (SAH) secondary to ruptured aneurysms. Usually, the diagnosis of vasospasm after SAH has been made by patient history and physical examination with CT,1 transcranial Doppler study (TCDs),2 and/or angiographic confirmation. The findings of headache, fever, elevated white blood cell count, drop in serum sodium, elevation in blood pressure, and delayed neurological deficit are helpful but not specific for vasospasm. In patients with SAH, there may be multiple causes for neurological impairment. It is often difficult to be certain whether ischemia due to vasospasm is in fact a contribution. A reliable test to detect brain ischemia is sorely needed in these extremely ill patients.

Although angiography is considered to be the standard for the diagnosis of vasospasm, it is invasive, can be associated with significant morbidity after SAH,3 and does not provide information about whether the tissue is ischemic; ie, it does not distinguish between angiographic versus symptomatic vasospasm. In recent years, TCDs has shown promise in the diagnosis of angiographic vasospasm by virtue of its ability to detect noninvasively increased middle cerebral artery (MCA) blood velocity associated with arterial narrowing.2,4,5 Studies have shown that the time course of flow velocity acceleration due to arterial narrowing from vasospasm correlates well with clinical grade, CT localization of subarachnoid clot, and angiographic data.6,7,8 More recent reports have demonstrated that the sensitivity of TCDs for the diagnosis of cerebral vasospasm after SAH can be low.9,10 While TCDs can interrogate the major intracranial vessels, TCDs cannot address questions that concern collateral flow, microvascular compromise, or infarcted tissue. Moreover, TCDs cannot...
Table 1. *Comparison of Clinical Deficit With MRI and Angiographic Findings*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical Deficit</th>
<th>DWI Abnormalities</th>
<th>CBF/MTT Abnormalities</th>
<th>DWI/HWI Patterns</th>
<th>Angiographic Vasospasm</th>
<th>Clinical Deficit to MRI, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aphasia</td>
<td>Multiple foci of DWI+ in L and R ACA/MCA, and MCA/PCA watershed distribution</td>
<td>L MCA, ACA, R MCA</td>
<td>DWI &lt; HWI</td>
<td>Severe L M1 and M2, Moderate L and R A2 and R M2</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Aphasia</td>
<td>L perisylvian and L midbrain foci of DWI+</td>
<td>L MCA, ACA</td>
<td>DWI &lt; HWI</td>
<td>Severe distal L ICA, L M1, L A1, moderate R A1, L P1</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>L hemiparesis</td>
<td>Large stroke R operculum, Few foci of DWI+ in ACA/MCA watershed</td>
<td>R MCA, ACA</td>
<td>DWI &lt; HWI</td>
<td>Severe R M1 and A1</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>L hemiparesis</td>
<td>Few foci of DWI+ in R MCA distribution</td>
<td>R MCA</td>
<td>DWI &lt; HWI</td>
<td>Severe R M1</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Multiple brainstem signs, L hemiparesis</td>
<td>Small foci in the R pons, R parietal cortex, bilateral cerebellum</td>
<td>Bilateral cerebellar, R MCA</td>
<td>DWI &lt; HWI</td>
<td>Severe basilar, severe R M1, moderate L M1 and A1</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>Headache</td>
<td>None</td>
<td>None</td>
<td>No abnormalities</td>
<td>Severe R distal ICA, R M1</td>
<td>No deficits</td>
</tr>
<tr>
<td>7</td>
<td>Multiple brainstem signs, L hemiparesis</td>
<td>Small foci in the R perisylvian region, L cerebellum</td>
<td>L cerebellum, R MCA</td>
<td>DWI &lt; HWI</td>
<td>Severe basilar, moderate R M1</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>No abnormalities</td>
<td>None</td>
<td>No deficits</td>
</tr>
</tbody>
</table>

DWI+ refers to "positive" signal abnormality on DWI consistent with stroke.

### Differentiate between symptomatic and asymptomatic vasospasm

Many authors have suggested the use of noninvasive cerebral blood flow (CBF) studies, such as xenon-CT, to measure tissue perfusion as an alternative to angiography and TCDs in the diagnosis and management of vasospasm. In fact, noninvasive CBF studies have proven useful in the identification of patients with initially reduced CBF values, who despite good clinical grade, are at risk for the development of vasospasm.

We sought to use newly developed MRI techniques to map the hemodynamic disturbances in patients with vasospasm. DWI detects the decrease in the diffusibility of water that occurs in an early phase of permanent ischemic brain injury. HWI tracks a rapid bolus of intravenous gadolinium during its first pass through the brain, which provides information about cerebral blood volume and flow. We sought to determine whether DWI and HWI were feasible in intensive care unit patients who had undergone aneurysm clipping. Because vasospasm usually causes, at least initially, a reversible neurological deficit, we hypothesized that HWI abnormalities would be present in patients at the time they developed neurological deficit and before the appearance of matching DWI abnormalities. In addition, HWI should demonstrate territorial differences in brain vascular supply that correlate with patients’ clinical symptomatology and angiographic abnormalities. We hypothesized that DWI abnormalities that represent ischemic tissue injury, if present in treated patients, will be smaller than the regional blood flow abnormality. These techniques should be able to differentiate areas of brain that may be affected by ischemia secondary to vasospasm, infarction, postsurgical edema, or some combination thereof.

### Subjects and Methods

#### Patient Selection

All patients admitted to our institution with SAH due to aneurysm rupture are admitted to the neuroscience ICU for preoperative and postoperative monitoring. After surgery, patients are routinely maintained in a relatively hypotensive and euvolemic state in anticipation of cerebral vasospasm. Daily clinical observations and TCDs measurements are used to detect vasospasm. Once vasospasm is detected, systolic blood pressure is elevated with phenylephrine, and hypervolemia (central venous pressure of 10 to 12 mm Hg) and hemodilution are instituted. If an ischemic deficit appears or progresses despite maximal medical therapy, then intra-arterial vasodilatation with papaverine and angiplasty are typically used. In this report, we describe 6 patients with symptomatic vasospasm and 1 with asymptomatic vasospasm admitted between March 1995 and October 1997 who were selected to have an MRI study to look for evidence of stroke. As a control, an eighth patient admitted in September 1995 had a similar functional MRI study (systolic blood pressure was 160 mm Hg and central venous pressure was 8 mm Hg at the time of the study) performed 1 day after surgery for SAH. At that time, the TCDs did not show any evidence of vasospasm. Every patient had a head CT scan after the MRI study and preceding the angiogram. We hypothesized that HWI would show larger abnormalities than DWI in treated subjects with symptomatic vasospasm. To test this hypothesis, each MRI study was visually assessed by a neuroradiologist blinded to the symptomatology. Each scan was ranked as DWI=HWI, DWI<HWI, or DWI>HWI. DWI and HWI (all parameters) abnormalities were compared for distribution and size of region involved. Each patient was also ranked as symptomatic or nonsymptomatic. The angiogram closest in time to the MRI was evaluated for the degree of vasospasm in each of the vessels of the circle of Willis. This study was initiated with the approval of the Subcommittee on Human Studies at Massachusetts General Hospital.

#### MRI Protocol

MRI is performed with a General Electric Signa 1.5-T MRI unit with an echoplanar retrofit from Advanced NMR Systems (Wilmington, Mass). We use the same acute stroke MR protocol, with 2 modifica-
Figure 1. Patient 1 is a 46 year old with SAH initially designated Hunt and Hess grade 2. He underwent clipping of a left anterior communicating aneurysm. His postoperative course was complicated by the development of a severe expressive aphasia and mild right hemiparesis on day 8 postictus. The presence of vasospasm was confirmed by TCDs and angiogram. The angiogram performed on day 8 showed severe left MCA vasospasm (M1 and M2 segments), moderate bilateral ACA (A2 segments), and right M1 vasospasm. MRI was performed on day 9 postictus before the repeat angiogram. Perfusion MR showed normal rCBV maps (B), but low rCBF and increased tMTT (C) in a, the high territory of the superior division of the left MCA; b, the lowest and most posterior territory of the inferior division of the left MCA; and c, the most posterior territory of the right MCA inferior division. DWI (A) showed foci of ischemic injury in the ACA/MCA watershed and MCA/PCA watershed territory. The MR image is distorted immediately around the aneurysm clip, in the region of the anterior communicating artery. Repeat angiograms on days 9, 10, and 11 demonstrated vasospasm. The patient was treated with daily intraarterial papaverine infusions for 3 days on days 9, 10, and 11 with resolution of angiographic vasospasm. His neurological status improved gradually, and at the time of discharge, he had only some mild word finding difficulties and no motor deficit.
clinical practice. Consequently, rCBF was determined by deconvolving the tissue concentration–time curve with an arterial input function. To determine rCBV, the tissue concentration–time curve is numerically integrated, as described. The latter is manually selected by choosing voxels over the MCA that supplies the unaffected hemisphere. This method sensitively captures information on asymmetry of flow to the affected hemisphere, but it is not quantitative. Maps of rCBF and tMTT are then created with our model-independent approach. To date, analysis of the hemodynamic data sets has been unable to provide absolute quantitative flow measurements.

Blood Pressure Management During MRI Study

All patients were studied during treatment with intravenous phenylephrine to maintain blood pressure within previously set limits. Blood pressure was monitored by intra-arterial catheters with high-resistance tubing that lead from the MR room to a transducer and monitor outside the room. Phenylephrine was infused through an intravenous pump located outside the MR room connected to the patient’s central line by 20 ft of tubing.

Results

HW/DW imaging results and angiographic findings are illustrated in Table 1 for 8 patients. In 6 cases, the patient had neurological symptoms suggestive of clinical vasospasm. In each, the tMTT maps showed large regions of delayed or slow flow in the clinically appropriate vascular territory consistent with angiographically demonstrated vasospasm. In these 6 cases, DWI showed small, usually multiple, regions of ischemic injury within the region of abnormal tMTT. The rCBV maps were normal in all patients except in 1 patient in a region containing a large, angiography-related stroke (T2 abnormal). In one case (patient 8), DW/HW imaging was performed in a patient with SAH postclipping of a right MCA bifurcation aneurysm in whom angiogram did not show vasospasm. The MR study was normal in all respects. In all patients (6 of 8) with an abnormal neurological examination due to symptomatic vasospasm, the abnormality seen on rCBF and tMTT was much larger than the abnormality seen on the DWI sequence or rCBV (when present). In one patient (patient 6), angiographic and TCD studies suggested vasospasm but the patient remained asymptomatic even at low systolic blood pressure. HW/DW MRI studies were normal. The mean time between the onset of clinical deficit and the MRI study was 10.5 hours (between 9 and 12 hours).

Figures 1 through 3 document imaging findings in cases 1, 2, and 6, whereas Table 1 compares the clinical picture with

Figure 2. Patient 2 is a 33-year-old male with SAH initially designated as Hunt and Hess grade 1. His CT showed extensive SAH. His admission angiogram did not reveal an aneurysm. Five days after admission he developed severe word finding difficulty and mild right arm weakness. Vasospasm was diagnosed by TCDs. The angiogram demonstrated severe vasospasm of the left M1 segment, the left A1, the P1 segment of the left PCA, and the left distal internal carotid artery (ICA). A small aneurysm at the left ICA bifurcation was also seen. He was taken to the operating room immediately after the angiogram, and after surgery his vasospasm was aggressively treated with hypertension, hypervolemia, and hemodilution with resolution of the neurological symptoms. His MR study was done on day 9 postictus. Perfusion MR showed normal rCBV maps (B) but low rCBF (C) and increased tMTT (D) in the entire left MCA territory. DWI (A) showed only a hazy hyperintense signal in the posterior parietal lobe and a midbrain lesion. His angiograms demonstrated vasospasm on days 8 and 13. He was discharged to home 20 days later after a normal neurological examination.
the MRI and angiographic findings in all patients. In all symptomatic patients, the CT scans performed immediately before the angiogram and immediately after the MRI showed ischemic changes in the areas of abnormal DW signal. These lesions persisted and were seen on the discharge head CT scans, whereas the territories that were abnormal on the rCBF and tMTT but normal on DWI appeared normal on the discharge studies. The apparent diffusion coefficient was reduced in all of the DWI lesions.

Discussion

Vasospasm after SAH is generally considered to be caused by periarterial blood clot. In 1980, Fisher and colleagues showed that the amount and location of subarachnoid blood seen on the initial CT scan is a strong predictor of vasospasm. Their system for grading the amount of subarachnoid clot is the most widely used feature for the estimation of the risk for vasospasm in individual patients.

When studied 10 to 12 days after SAH, 60% to 70% of patients with severe cisternal accumulation of blood have angiographic vasospasm. However, angiographic vasospasm does not always correlate with symptomatic vasospasm. Ischemic neurological deficit due to arterial narrowing occurs in ~30% of patients. In patients with SAH, neurological function is often severely impaired as a result of the initial hemorrhage, cerebrovascular surgery, hydrocephalus, or fever, as well as potential ischemia due to vasospasm. There is a need for sensitive and more specific methods of diagnosing clinically significant vasospasm. Ideally, treatment decisions about the use of hypertensive, hypervolemic therapy, or vasodilation through angioplasty or papaverine should be made with information about the state of the intracranial arteries, brain blood flow and metabolism, and degree of ischemic injury. Angiography is still the standard by which arterial vasospasm has been diagnosed in patients after SAH, but it is time consuming, is not without clinical risk, and does not give direct information about tissue perfusion.

Demonstration of elevated blood flow velocity and increase in turbulent flow by TCDs can provide an early clinical awareness of vasospasm that involves the circle of Willis. Because this method is noninvasive and can be repeated as often as necessary, it is commonly used to monitor for cerebrovascular vasospasm after SAH. However TCDs can fail to detect vasoconstriction if vasospasm occurs beyond insonated arteries, such as in the distal M2 portion of the

neosynephrine was used to increase the SBP to 120 mm Hg. No abnormalities were seen on the DWI, rCBV, rCBF, or tMTT maps. Hypertension, hypervolemia, and hemodilution were then discontinued without any change in the neurological examination. Despite persistence of elevated TCDs velocities in the right MCA stem, the patient was discharged to home October 29, 1997, and was neurologically intact with a SBP ranging from 110 to 140 mm Hg. TCDs velocities remained elevated and severe headache continued, and the patient was readmitted November 13, 1997. A repeat angiogram (A) shows a severe distal right ICA stenosis, and the repeat MRI study with DWI (B), rCBF, and tMTT (C) maps was entirely normal. A diagnosis of right ICA dissection vs persistent stenosis because of vasospasm was made, and the asymptomatic patient was discharged on coumadin.
MCA, in the A2 (anterior cerebral artery, ACA), in the P2 (posterior cerebral artery, PCA), or in the vertebrobasilar system. In severe vasospasm, decreases in CBF can occur that lead to a drop in blood velocity. Increased intracranial pressure or brain edema can increase the pulsatility of the waveform, which makes interpretation of higher velocities difficult. Patient movement, suboptimal insolation windows, aberrant vessel course, and clip artifacts may obscure the detection of pathological signals. Systemic hemodynamic, rheological, and metabolic factors may also confound the interpretation of flow velocity. Many studies have stressed the low sensitivity of TCDs to detect vasospasm. In addition, TCDs cannot differentiate between symptomatic and asymptomatic vasospasm and cannot detect changes in CBF with hypertensive, hypervolemic treatment.

A number of techniques are available for the measurement of regional CBF, including radioactive xenon clearance (using the intravenous or inhalational technique), stable xenon CT, single photon emission CT (SPECT), and positron emission tomography (PET). Several of these methods have been applied to patients with presumed vasospasm and appear very sensitive to the early detection of vasospasm. In most patients with SAH, these noninvasive techniques can help to delineate the location and severity of vasospasm and may help predict the development of vasospasm. SPECT has been used to study patients with cerebral ischemia after SAH. PET has provided physiological information by demonstrating that vasospasm is accompanied by increased oxygen extraction and increased blood volume, presumably secondary to arterial dilatation, to allow maintenance of adequate cerebral metabolic rate. The 133Xe technique has been used for clinical research and clinical studies for >20 years, has been repeatedly validated, and provides CBF measurements that are stable and reliable. The Xe/CT technique has limitations and possible disadvantages. These include the exposure to a relatively high level of radiation that allows the study of only 2 slices and the possible increase in intracranial cerebral pressure.

New MRI techniques recently validated in ischemic stroke experimental and human studies have considerable potential for aiding the diagnosis and treatment of acute ischemic stroke. DWI demonstrates regions of early ischemic injury. In animal experiments, DWI becomes abnormal in <30 minutes in an ischemic zone. In humans, DWI has also been abnormal in very early studies (40 minutes) after ischemic stroke. In humans, hemodynamic imaging in acute ischemic stroke is thought to identify regions of ischemia, whereas DWI is highly sensitive and specific in the diagnosis of irreversible ischemic injury. In ischemic stroke patients, rCBV is generally significantly reduced in the region of DWI abnormality or T2 abnormality in a more mature infarct. In many stroke patients, the region of abnormal rCBV is larger than the initial region of abnormal DWI, and the stroke enlarges into and may exceed the area of abnormal rCBV. rMTT and rCBF maps are based on additional analysis of the kinetics of blood flow as measured by the use of an intravascular tracer. The arrival and clearance time of the bolus of gadolinium are important physical features that underlie the calculated rCBF and tMTT. In patients with acute ischemic stroke, regions of decreased rCBF and increased tMTT are often found to encompass the DWI and rCBV abnormalities. In acute stroke patients, we have seen that infarct may or may not extend into these regions with normal rCBV but low rCBF and increased tMTT.

Our results in patients with vasospasm show that DWI can detect small regions of early ischemic injury within large regions of abnormal rCBF and tMTT. Widespread decreases in rCBF and tMTT occurred in each patient throughout regions supplied by vessels with demonstrated angiographic vasospasm. In contrast, the rCBV maps were relatively normal except in the case in which a large infarct had already occurred. These MR data are concordant with PET data that demonstrate a mismatch between blood flow and blood volume in regions affected by vasospasm after SAH. One interpretation of this pattern in patients with vasospasm and in patients with acute ischemic stroke is that increased collateral flow through maximally dilated microcirculation preserves cerebral blood volume in regions with reduced CBF.

In acute stroke patients, this pattern of normal rCBV, decreased rCBF, and increased tMTT occurred around large regions of decreased rCBV and abnormal DWI. In contrast, in these patients with vasospasm after SAH, this less severe decrease in rCBF with preserved rCBV was found to be the predominant abnormality. In this study, large brain regions with decreased rCBF and increased tMTT were seen in all patients with clinically symptomatic vasospasm, and the regional location of these HWI abnormalities correlated well with the angiographic findings. Our patients were receiving hypertensive treatment during the scans for their suspected symptomatic vasospasm, and the effect of the treatment on the hemodynamic pattern is unknown. In these patients who were treated aggressively to prevent infarction, the large areas of abnormal rCBF/tMTT did not evolve into stroke and were normal on the follow-up studies. In most patients, the neurological signs and symptoms correlated better with the anatomy of the blood flow abnormality rather than with the small regions of infarct. The flow reductions were also most likely longstanding given the long duration between symptom onset and scan. This underlies the sensitivity of HWI to detect levels of ischemia that cause neurological deficits but which are not severe enough to cause all such regions to infarct. The specificity of these patterns for vasospasm in patients after SAH requires study of a larger patient cohort. HWI abnormality was not seen in 1 patient with angiographic and Doppler evidence of narrowing, but who remained without ischemic deficits even when blood pressure was unsupported. HWI abnormality was not seen in another patient after SAH who did not have a spasm on angiogram or clinical signs of vasospasm.

An advantage of MR imaging over other blood flow techniques is its ability to couple HWI with DWI, the latter a sensitive method that detects even small regions of ischemic injury. In this study, ischemic injury occurred as small foci of DWI hyperintensity in 6 of 6 patients with symptomatic vasospasm. Large infarcts, as in patient 3 and in patients with acute ischemic stroke, are associated with DWI abnormality in regions of reduced rCBV. It remains to be studied whether
reduced rCBV occurs at some time as a necessary event to cause infarct in regions that initially demonstrate only reduced rCBF and increased MTT.

In this initial study, we demonstrate the ability of MRI to measure widespread vasospasm-related changes in tissue hemodynamics that surround small regions of ischemic tissue injury. The ability to detect these changes raises more questions than it answers but provides a potentially valuable tool to approach the important issues in vasospasm management. As a result of these early findings, serial HWI in patients with SAH should be studied for its ability to recognize a particular hemodynamic pattern that reliably accompanies symptomatic vasospasm. It will also be important to know if a particular HWI abnormality predicts which SAH patients will suffer infarction due to vasospasm. Early, serial studies are needed to determine whether reliable hemodynamic changes on HWI precede clinically significant vasospasm. Because it can be performed repeatedly, HWI also offers a potential method to determine whether various treatment options improve or worsen cerebral perfusion abnormalities. Finally, this study raises the question of whether HWI can someday be used as a guide to decide on best therapy for an individual SAH patient. This may be the most important long-term goal worthy of systematic study.

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References


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