Imaging in Stroke: The More You Look, The More You See

Cerebral imaging has both humbled and enlightened stroke clinicians over the last 30 years. Imaging techniques are used to assist in diagnosis, guide intervention, and facilitate research. Stroke is not the only cause of sudden focal neurologic deficit, and imaging must help distinguish tumors, extraaxial lesions, migraines, and seizures. Clinical stroke research has become dependent on imaging in an effort to sharpen the understanding of the dynamic processes involved. Clinicians have struggled to define cerebral function and blood flow, relying on positron emission tomography, single-photon emission computed tomography, or Xenon imaging to provide data. More recently MR has promised, and may yet deliver, rapid physiologic data with diffusion and perfusion imaging.

Clinicians have long used the arbitrarily defined terms *stroke* and *transient ischemic attack* (TIA) to refer to the sudden loss of neurologic function from a vascular mechanism. Symptoms resolving in less than 24 hours have been referred to as TIA. The underlying tissue physiology of ischemia, whether reversible injury or infarction, does not always correspond to the clinical terms of TIA or stroke. Patients with TIA are commonly found to have areas of tissue infarction when imaged carefully. Many stroke clinicians have come to favor a 1-hour time limit for TIAs, improving the correlation of clinical and physiologic terms. Neuroimaging has become tightly integrated in the study and management of cerebrovascular disease.

In the decade since the first MR diffusion imaging of stroke patients, the technique has evolved and become familiar to those involved in acute intervention. Diffusion-weighted imaging has come to be a sensitive early marker of infarction, and reversible diffusion abnormalities have been far less common clinically than in animal stroke models. Territories with perfusion and diffusion mismatch may define tissue at risk for infarction, but with potential for recovery. An alternate strategy with CT technology uses rapid CT for dynamic perfusion imaging, with similar goals in mind. It is hoped that acute imaging can better guide interventions such as intravenous or intraarterial thrombolysis. While most attention has been focused on acute intervention, it must be emphasized that the vast majority of patients are not seen in an appropriate timeframe for acute therapies. Less than 10% of all stroke patients are evaluated less than 3–6 hours following symptom onset, severely limiting the application of acute therapies.

The vast majority of stroke patients are seen in the subacute time frame, where diagnostic imaging also plays a vital role in directing management. In this issue of the *AJNR*, Augustin et al (page 1596) report on the use of diffusion-weighted imaging in subacute stroke. They observe that diffusion-weighted imaging adds sensitivity to the standard MR evaluation, allowing identification of lesions otherwise not detected. The specificity of diffusion imaging for recent infarction also increases the ability to detect new lesions in a background of chronic changes.

Secondary stroke prevention is a major component of management in all patients, and represents the major focus in the subacute group. While experience would suggest that small vessel disease leads to 20% of ischemic stroke cases, another 20% are caused by large vessel carotid and intracranial disease, and 60% of cases derive from thromboembolic events, decisions for each patient should relate to a specific demonstration of stroke etiology. The evaluation is often directed by the diagnostic imaging. Small, deep infarcts typical of small vessel lacunar disease are usually easily identified, and imaging adds greatly to diagnostic certainty compared to clinical impression alone. While these may not always be related to intrinsic small vessel disease associated with hypertension and diabetes, the odds are such that embolism becomes a much less likely cause. Peripheral cortical infarcts imply an embolic mechanism, and if in the anterior circulation, should lead to evaluation of the cervical carotid. In these cases, more information is helpful. If diffusion imaging reveals a clinically silent subacute infarct in the cerebellar hemisphere, then interpretation of a 70% stenosis in the cervical internal carotid is radically altered. What might be interpreted as symptomatic carotid disease now becomes multiple emboli in different territories and leads to a search for cardiac sources, and therapy may change from surgical intervention to systemic anticoagulation.

It is interesting that despite the sensitivity of current imaging, it is not possible to identify an appropriate lesion in all patients with acute stroke deficits. Optimal stroke care requires collaboration between the clinician and radiologist, for we are clearly far from total understanding of the process. Diffusion-weighted imaging makes an important contribution to stroke management, even in the subacute timeframe, and should become widely applied. As improvements in technology allow further investigation, the more information we will have to be considered and applied to patient care.

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MR Imaging of Brain Tumors: Toward Physiologic Imaging

A few short years ago, the introduction of contrast agents for MR imaging led to much excitement about the possibilities for evaluating the presurgical workup of patients with brain tumors. Tumor detection became much more feasible, blood brain–barrier (BBB) breakdown could be detected, and an assessment of the tumor vascularity (ie, its blood volume) became possible. Nonetheless, the mere observation of contrast enhancement does not provide answers to all the interesting questions facing the clinician helping patients with brain tumors. Where is the most malignant region within a tumor? Can we better predict the patient's prognosis, or better follow up on a patient after therapy? One reason these questions are difficult to answer is that contrast enhancement represents the combination of two parallel physiologic processes. Intravenously injected contrast agent arrives in the blood pool of a tissue, reflecting the tumor vascularization, and, in the presence of a BBB breakdown, it leaks into the interstitial space, reflecting the microvascular permeability.

Subsequently, several strategies have been developed to separate these two parameters to achieve more useful, quantifiable information on tumor biology and behavior. Most work has been focused on quantification of the tumor's vascularity, or relative cerebral blood volume (rCBV), a parameter historically used in nuclear medicine studies such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) (1). rCBV has been studied extensively, and elevations in this parameter have been found to have a good specificity for tumor malignancy. PET and SPECT, however, are limited by poor spatial resolution, which results in insensitivity to small lesions; they are also insensitive to low-grade intraaxial brain tumors. Furthermore, PET still lacks sufficient availability to serve as a viable clinical approach for routine application.

MR imaging with T1-weighted first-pass techniques to assess a contrast agent's transit through the brain has been applied to this problem, but the low blood volume of cerebral tissue (less than 10%) makes it difficult to appreciate changes in signal intensity after contrast injection. Dynamic contrast-enhanced MR imaging gained popularity following the introduction of echo planar–capable systems with high-performance gradients. Fast imaging with high sensitivity to changes in magnetic susceptibility allows assessment of the T2* effect on contrast-enhanced images, which is much stronger than the T1 effect and extends over a wider area. Consequently, several studies have been performed using some kind of T2* echo-planar MR imaging to quantify the rCBV of tumor tissue (2, 3). These slightly different protocols for rCBV measurement require a standardized approach in order to make the results comparable across studies. One worthwhile approach is taken by Roland Bruening et al in their article *Effects of Three Different Doses of a Bolus Injection of Gadodiamide: Assessment of rCBV Maps in a Blinded Reader Study* in this issue of the *AJNR* (page 1603). The authors focus on one aspect of first-pass dynamic T2*-weighted MR imaging, the contrast agent dose. Their conclusions are valid and in agreement with anecdotal experience in day-to-day practice that the bolus injection of 0.2 mmol/kg body weight is an adequate dose of gadodiamide for the measurement of rCBV.

Unfortunately, life is not that simple and T2*-weighted imaging is influenced by parameters other than just the contrast agent dose. Thus, other factors influence the calculation of rCBV, including whether a spin-echo (SE) echo-planar sequence or a gradient-recalled (GRE) echo-planar sequence is used. Recently, from the famous brain/vein debate in fMR imaging, it has been found that GRE sequences could be dominated by large vessel contributions. On the other hand, using an SE sequence (or an asymmetric SE sequence) increases the relative contribution of small to large vessels, which may be more relevant in determining tumor type. In any case, one would expect a different dose dependence for an SE echo-planar sequence, which trades off the sensitivity of the GRE sequence against improved microvascular specificity. Quite important for echo-planar sequences and T2* measurements is a standardized echo time. Different dose response characteristics might be expected with varying echo times. Other sequence parameters may affect the T1 contribution, confounding the T2* effects. T1 saturation occurs with a shorter repetition time and higher flip angle; the more T1 effect the greater the contamination, particularly in the second half of a contrast agent bolus curve. Thus, there are many parameters to consider when attempting to standardize the acquisition of rCBV.

Furthermore, going back to the two contributing aspects of contrast enhancement, there is more to physiologic imaging of brain tumors than just rCBV calculations. One must not forget about the BBB breakdown in tumors. The resulting extravasation of contrast agent during the observation of the first pass leads to errors in the calculation of rCBV, as mentioned by the authors. While T1 effects cause the contrast agent curve not to return completely to baseline, the leakage of contrast agent into the interstitium yields a return above baseline. Thus, measures have to be taken to correct for this effect, particularly in high-grade tumors. In addition, instead of just correcting for the effect of BBB breakdown and the contrast agent

extravasation into the interstitum, the microvascular permeability can potentially be used as an independent variable in its own right. The rate of transendothelial diffusion is related to the integrity of the vascular wall in general and the BBB in particular, and these are reflections of tumor angiogenesis. Indeed, the feasibility of the approach to use dynamic contrast-enhanced MR for the noninvasive assessment of tumor microvascular characteristics has recently been demonstrated (4). Such a technique can be used not only to assess tumor characteristics, but potentially to monitor new cancer treatments, like angiogenesis inhibitors.

Where do we have to go with the physiologic imaging of brain tumors? The trend is definitely toward standardization of established techniques like T2*-weighted dynamic contrast-enhanced MR imaging. But standardization should also include other parameters that might confound these measurements. This will then allow comparison of results from different centers. Physiologic imaging should incorporate many tools, not only one physiologic parameter like blood volume. We should be evaluating the vascular permeability of a tumor, a reflection of tumor angiogenesis, as well as cellular metabolic profiles obtained using MR spectroscopy, and integrating this information within the context of our anatomic maps. In this way, the information we contribute can be used by physicians and in clinical trials in a meaningful way.

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MR Angiography for the Diagnosis of Vasospasm after Subarachnoid Hemorrhage. Is It Accurate? Is It Safe?

There are about 30 000 cases of subarachnoid hemorrhage in the United States each year. Roughly two thirds of the patients who survive the hemorrhage will develop angiographically detectable vasospasm; of these patients, approximately one half will become symptomatic. The imaging changes can be detectable as early as day 3 and are maximal at about 1 week. Symptomatic vasospasm is associated with high morbidity and mortality, each in the range of 30% (1, 2).

The pathophysiology of vasospasm is incompletely understood, but both direct vessel constriction and impairment of vasodilatation appear to be involved. The total amount of the subarachnoid hemorrhage, as well as the presence of a focal clot encasing a given segment of vessel, are known risk factors for vasospasm (2).

Fortunately, there are a number of therapies that can positively affect the grim statistics associated with vasospasm. Hypervolemic hypertensive therapy is an accepted and widely employed treatment. Calcium channel–blocking agents, balloon angioplasty, intraarterial papaverine, subarachnoid thrombolysis, and papaverine infusion also appear to have efficacy (1).

At our center, and at many centers in the United States, early treatment of ruptured aneurysms associated with subarachnoid hemorrhage is advocated to allow for aggressive therapy to prevent and treat vasospasm. Thus, by the time vasospasm develops, an aneurysm clip or endovascular coils are often present, resulting in additional challenges for diagnostic imaging.

Cerebral angiography is the standard of reference for diagnosing vasospasm; however, it is associated with a small, but definite, risk of stroke. Transcranial Doppler sonography is widely employed for screening purposes in the intensive care unit, although a number of technical problems exist; in one recent study, test results were inconclusive for the detection of angiographically significant vasospasm in about 50% of patients (3). CT angiography has shown some promise as a screening test (4). Brain perfusion examinations are also useful, and may ultimately represent the best correlation with the degree of symptomatic vasospasm (5).

In this issue of the *AJNR*, Grandin et al (page 1611) examine the feasibility of diagnosing vasospasm in the presence of subarachnoid hemorrhage using three-dimensional time-of-flight MR angiography (MRA) performed on a 0.5-T imaging system. MRA was compared to digital subtraction angiography by use of only maximum intensity projection images obtained within 24 hours of each other. Prevalence of angiographic vasospasm in this sample was 26%. High signal intensity ascribed to methemoglobin was observed adjacent to vessels in 16% of cases, and was felt to be limiting in about 5% of cases. The ability of MRA to detect significant vasospasm correlated highly with that of dig-

ital subtraction angiography. Nonetheless, although no false-negative evaluations were present in the anterior cerebral artery distribution, false-negative rates of about 5%, as well as reduced sensitivity, were noted when data for the internal carotid and middle cerebral arteries were analyzed separately.

This is a technically challenging application for time-of-flight MRA. Two difficulties are immediately apparent. First, since vessels are screened for vasospasm in the subacute period, the increased signal associated with methemoglobin within residual subarachnoid hemorrhage adjacent to arteries can result in false-negative results. Indeed, the vessels that lie encased in subarachnoid clot are likely to be the vessels most severely affected by vasospasm. Although Grandin et al do not feel that subarachnoid hemorrhage was a significant source of false-negative readings in their study, I continue to be concerned about this source of error. Evaluation of source images or projection schemes using integration in addition to ray projection may reduce this error.

The second difficulty with using time-of-flight MRA for the detection of vasospasm involves the presence of aneurysm clips or endovascular coils, which often results in nonvisualization of adjacent arteries on MRA images. These vessels near the ruptured aneurysm often are most severely affected by vasospasm. In this trial, only a small number of studies were performed after aneurysm clipping. This would not be the case in many centers, and the presence of artifact associated with aneurysm clips could only increase the risk of missing significant stenosis.

Vasospasm associated with subarachnoid hemorrhage is a highly prevalent condition with a potentially devastating outcome, for which a number of effective therapies exist. In this setting, time-of-flight MRA does not represent a good alternative to conventional angiography. Nonetheless, MRA, preferably performed at high field strength, and possibly in combination with MR perfusion imaging, may have a place as a screening examination if a very low false-negative rate can be demonstrated. Grandin et al have taken an important first step in assessing this potential.

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