Is There a Role for Diffusion-weighted Imaging in Patients with Brain Tumors or Is the ''Bloom off the Rose''?

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Is There a Role for Diffusion-weighted Imaging in Patients with Brain Tumors or Is the "Bloom off the Rose"?

It was the day after the department's holiday party, the traditional time for our annual MR protocol meeting. We meet that day on the theory that everyone is either too mellow or hung over to argue much. Yet all eyes turned anxiously to me when someone suggested we remove diffusion-weighted imaging from our seizure protocol. After all, it was I who had whined to our MR vendor for almost 2 years that we had to have diffusion imaging capabilities immediately. When we had diffusion imaging equipment, it was I who had insisted that it be part of all our brain protocols. But at this meeting I shrugged and agreed. After a few years, it had become clear, even to a zealot like me, that diffusion-weighted imaging was not going to provide useful information in all disease processes.

There is a natural history for new diagnostic tests. The initial results are amazing, the praise overwhelming. The test is viewed as having almost magical qualities. After a while, reality sets in. The initial enthusiasm wanes as experience accumulates. This is where we are now with diffusion-weighted imaging. Many recent publications have documented the limitations of diffusion imaging. In this issue of the *AJNR*, Kono et al (page 1081) continue this trend. The authors used diffusion imaging to examine 56 patients with the three most common types of intracranial neoplasms: gliomas, metastases, and meningiomas. They found that there was much variation within each group and no significant difference in intensity among groups on either diffusion-weighted images or apparent diffusion coefficient (ADC) maps. Tumors in all three groups ranged from hyper- to hypointense. In addition, the authors could not distinguish between vasogenic edema and tumor infiltration by visual inspection of images. They concluded that diffusion and ADC images cannot be used to differentiate between tumor types or to assess tumor grade. A quick inspection of the images confirms that diffusion-weighted images and ADC maps do not provide much useful information when compared with conventional MR sequences. In some cases, the lesions are difficult to find, let alone characterize.

But all is not lost. As our knowledge of the virtues and limitations of a test increase, we develop a more mature, if demystified, appreciation of its value. This is true for diffusion-weighted imaging. There were positive findings in Kono et al's study that provide us with direction for future research and use of diffusion imaging in assessment of intracranial neoplasms.

The most important trend is toward the use of quantitative diffusion imaging techniques. When ADC was measured, there was a significant difference between grade 2 and grade 4 gliomas. High-grade gliomas had lower ADCs than did low-grade gliomas. Thus, quantification reveals significant differences that were not apparent upon direct visual (qualitative) inspection of either diffusion images or ADC maps. Assessment of ADC values has also yielded interesting results in evaluation of other process such as acute infarction and normal aging.

It has always been possible to measure the physical parameters that underlie an MR image (eg, T1, T2, magnetization transfer ratios [MTR]). However, this is a time-consuming process often requiring special image acquisition protocols and intensive postprocessing. Moreover, these measurements have not proven to be useful in routine clinical practice. There is no guarantee that things will be different with diffusion imaging, but it seems that diffusion measurements may be of more practical value than other physical parameters of MR. ADC maps are easily generated from routine fast diffusion-weighted imaging by use of software available on many MR systems. Therefore, diffusion values can be obtained without a great deal of effort. Second, ADC may be a more a direct indicator of changes in the brain than are other physical parameters, because in the majority of cases, these parameters evaluate submicroscopic, molecular-level phenomena. T1 and T2 reflect changes in the interactions between water protons, whereas MTR reflects interactions between somewhat larger "structures", macromolecules and their hydration shells. All of these processes occur below the level of basic biological structures. The degree of diffusion, on the other hand, is strongly affected by microscopic biological structures such as the number, type, and spatial arrangement of cells. These structures create barriers to the free diffusion of water. Therefore, changes in diffusion may more directly reflect changes occurring within and between cells.

Microscopic features are, of course, precisely those used by pathologists to diagnose and differentiate neoplasms. In Kono et al's investigation, the authors evaluated the relationship between ADC values and tumor cellularity as determined by an automated quantitative evaluation of cell blocks. They demonstrated a good correlation ($r = -0.77$) between ADC and cellularity in gliomas. This is an encouraging finding, because cellularity is an important histologic determinant of glioma grade. The authors point out that other histologic features that are known to influence tumor grade may also contribute to ADC values, including nuclear cytoplasmic ratio, tumor matrices, and extent of fibrosis and

gliosis. Until now it has been difficult to assess the relative contributions of these factors to ADC. Kono et al report on an important first step toward more precisely determining the effects of histologic variables on ADC. In the future, correlation between quantitative assessment of histologic measures and ADC values may improve our ability to assess tumor grade.

The most disappointing finding in Kono et al's article is that diffusion-weighted images, ADC maps, and ADC measurement cannot be used to determine the extent of tumor infiltration and to differentiate infiltration from peritumoral edema as previously reported (1). This is one of the ''holy grails'' of glioma imaging, because determination of extent of infiltration could affect both treatment and prognosis. Because infiltration occurs within and along white matter tracts, diffusion tensor imaging may yield useful information in the future. Another avenue for future research is high-b-value diffusion-weighted imaging that could allow for a more accurate assessment of infiltration as well as open a window for imaging the intracellular environment within tumors.

As we proceed to evaluate diffusion-weighted imaging of tumors, it will be important to ask useful questions. These will vary depending on the type of lesion under investigation. In Kono et al's article, the authors evaluated the three major groups of intracranial neoplasms by using the same techniques. However, within each broad group there will be different issues that need to be addressed that will require a more customized approach.

For instance, the finding that ADC of meningiomas did not correlate with histologic subtype is not a significant concern, because subtype does not determine prognosis or alter therapy. The correlation between cellularity and ADC was weaker in meningiomas ($r = -.67$) than in gliomas, but this also is of little concern. In meningiomas, information that improves our ability to predict which tumors are malignant or atypical would be important as this would affect therapeutic decisions. In a recent publication, Filippi et al (2) demonstrated that low ADC values (less than those in normal brain) were seen most frequently in malignant or atypical meningiomas. If this finding is confirmed in a larger series, it could prove to be an important advance in the diagnosis of meningiomas. Correlations between specific histologic features associated with malignancy and ADC should be sought.

Diffusion changes in metastatic disease also need further investigation. In this publication, the authors evaluated 21 patients with metastatic disease from four different primary tumors. There is, in reality, no reason to group all of these metastatic diseases in a single category. The histologic features of each tumor type is different and therefore one would expect that each type would have its own range of ADC values. Combining different tumor types only obscures potential differences between types. Further studies of cases in each primary tumor will be needed to determine if diffusion-weighted imaging has any role in the assessment of these lesions.

Initially, Kono et al's findings seem disheartening, but on further thought they offer possibilities. The fact that diffusion images, ADC maps, and even measurement of ADC values did not allow for differentiation between gliomas, meningiomas, and metastases is neither a surprise nor a major problem. Clinical information and routine ''anatomic'' MR imaging findings allow for correct diagnosis in the vast majority of intracranial neoplasms. Cases wherein these findings are discordant with the pathologic diagnosis represent rare diseases or unusual manifestations of common diseases. Only a truly magical test could prove definitive in these circumstances. Diffusion-weighted imaging is not magical, but it may yet provide valuable information about intracranial neoplasms that will improve our understanding of these diseases and aid in their diagnosis and treatment planning. We need to look at each disease process separately, gather more cases, and ask the right questions.

At the end of our protocol party, we had removed diffusion-weighted imaging from a few specific protocols (chronic seizures, multiple sclerosis follow-up). We all agreed that diffusion imaging should stay in our ''rule out'' protocols. After all, the art of clinical diagnosis remains just that, and diffusion-weighted imaging takes less than 1 minute to perform. Feeling that we had completed our task like responsible adults, we headed off to the tavern, the Nimrods, extending the holiday spirit one more day.

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Intraarterial Signal on Fluid-attenuated Inversion Recovery Images: A Measure of Hemodynamic Stress?

Since its introduction in 1992 (1), fluid-attenuated inversion recovery (FLAIR) sequences have become a routine part of standard imaging protocols. An inversion pulse is used with long TR and TE to create heavy T2 weighting with CSF nulling, providing improved contrast adjacent to CSF and brain interfaces (2). Dependence on longitudinal relaxation provides another source of contrast, which several authors have exploited to study abnormalities in the CSF itself. For example, increased protein content and subarachnoid hemorrhage have been shown to be detectable using FLAIR sequences (3–5).

More recently, investigators have noted increased intensity in cerebral blood vessels in the setting of acute ischemia (6, 7). The presence of hyperintense vessels on FLAIR images is thought to indicate the presence of slow flow or stasis in small arteries, veins, and collateral vessels. The mechanism of increased intravascular signal on FLAIR images is most likely due to a combination of slow flow (with resultant decreased intravoxel phase dispersion and time-of-flight effects), flow-related enhancement (slow, but not static flow), and T1 shortening in some cases (development of methemoglobin).

The hyperintense vessel signal (HVS) in FLAIR imaging is analogous to the finding of intravascular enhancement (IE) in the setting of acute stroke, described by several investigators (8–11). In the case of IE, the bright vessels are also due to a combination of slow flow, flow-related enhancement, and perhaps T1 shortening attributable to methemoglobin; however, the presence of an intraluminal T1 shortening substance (eg, gadolinium chelate) also contributes. Correlation with angiography suggested that IE was associated with angiographic slowing. Mueller et al (10) found that 64% of patients showing IE had significant symptoms, whereas those patients without IE had mild or no symptoms. Associations with cerebrovascular occlusive disease have also been reported in which patients are asymptomatic. Essig et al (11) found that IE was present in 59% of patients with acute (within 48 hours) infarct, correlating positively with extent of infarction; but IE was also present in 65% of patients with high-grade stenosis or occlusion of one or both carotid arteries who were asymptomatic at the time of the study, correlating positively with degree of carotid stenosis in this instance. They also found low vascular reactivity to carbon dioxide stimulation, and concluded that IE in such patients may indicate impaired reserve and increased risk of future infarction.

What then is the significance of IE or HVS in the acute or chronic setting? The mechanisms of IE and HVS are related, and in some ways identical. As for studies describing IE, sufficient pilot data are available to suggest that the presence of HVS on FLAIR images represents altered hemodynamics. The correlation with angiographic slowing and HVS is at least one indicator that this is probably true. In this issue of the *AJNR*, Toyoda et al (page 1021) present a retrospective study of 60 patients with hyperacute cerebral ischemia caused by major intracranial arterial occlusion. They found that HVS on FLAIR sequences was present in 58 (97%) of 60 patients in this selected population, and present in 25 (100%) of 25 patients studied within 3 hours of symptom onset. Cosnard et al (6) reported a prospective study of 53 patients who underwent MR imaging within 6 hours of onset of suspected acute stroke (6). In the 42 patients with confirmed infarct, HVS was seen in 26 (62%). Infarct volumes were larger in stroke cases with HVS on FLAIR images than in those without HVS. Kamran et al (12) found HVS in 30 (45%) of 66 MR studies obtained within 24 hours in acute stroke patients. A recent study at our institution (12) showed HVS on FLAIR images in 27 (84%) of 32 acute cerebrovascular events and in 26 (41%) of 61 studies in patients with chronic cerebrovascular disease. Perfusion was also assessed in this population by using a continuous arterial spin labeling MR perfusion method (13), which demonstrated regional hypoperfusion in 22 (69%) of 32 acute studies and 33 (54%) of 61 chronic studies. Perhaps more importantly, as many as 20% of patients with evidence of regional hypoperfusion did not show HVS in the acute setting.

For potential measures of ‘‘hemodynamic stress’’, it is important to be aware of exactly what is being measured. Hyperintensity in arteries and collateral vessels may represent slow flow, but its presence might represent an adequate compensatory response to proximal stenosis or occlusion. For example, Pantano et al (14) suggest that marked IE and increased cerebral blood volume might indicate good compensatory hemodynamic response via collaterals in middle cerebral artery occlusion in the setting of acute stroke. There are limited data addressing the question of prognosis in the setting of acute infarct without HVS, although acute stroke patients without HVS tended to have smaller stroke volumes in Cosnard et al’s study (6). In Kamran et al’s study (7), six patients without HVS demonstrated internal carotid or middle cerebral artery occlusion but good leptomeningeal collaterals and no evidence of slow flow on angiograms.

In Toyoda’s study, perfusion ‘‘abnormalities’’ are reported to correspond to HVS regions. While perfusion parameters like cerebral blood volume, de-

layed time-to-peak, increased transit time, reduction of peak curve height, and delayed washout may reflect an abnormality, clinical relevance in the acute or chronic setting is not yet clear. For example, a proximal stenosis may cause a delay in peak signal change and a reduction in curve height, but how much of a delay signifies brain tissue at risk? Moreover, calculation of the area of HVS is semiquantitative. A grading system based on extent of HVS in the sylvian fissure and over vascular territories has been proposed (7), but the vessels evaluated are primarily over cortical surfaces, whereas areas of hypoperfusion using perfusion techniques are more directly measurable. Subcortical ischemia may not be well represented by HVS (6).

One might try instead to use a method measuring absolute CBF, determining a CBF value below which brain is at risk and below which tissue damage is not reversible. Xenon CT data suggest that recovery from decreased perfusion does not occur below 12 cc/100 g/min (15), and in some cases as low as 6 cc/100 g/min (16). MR perfusion and positron emission tomography techniques may also be used for quantitation of CBF. On the other hand, perfusion abnormalities are only part of the pathophysiology of ischemia, and assessment of other parts of the pathway such as oxygen extraction fraction may be just as important (17, 18). Metabolic disturbances can also be addressed with proton spectroscopy, where a simple measurement like the ratio of *N*-acetyl aspartate to choline may be an indicator of tissue at risk (19).

In the acute setting, the primary goal of stroke imaging is to guide treatment strategy. With this in mind, the practical significance of a sign like HVS on FLAIR needs to be examined critically. In the broadest sense, the ultimate goal is early detection of a significant mismatch in energy supply and demand, in the hopes that discovery occurs prior to development of irreversible metabolic derangements so that interventions such as thrombolysis will have maximal probability of success. Even with tests addressing different aspects of the ischemic cascade, clinical examination still plays a crucial role in the decision to treat or not to treat. With evidence that HVS or IE or both can be seen in asymptomatic chronic cerebrovascular disease, these signs may be misleading in the acute setting.

Not only is the ischemic cascade complex, but it is also a dynamic process. A combined approach will most likely be necessary, and relative serial measurements may be more practical than absolute measurements (20). Thus, instead of replacing an examination like dynamic contrast-enhanced perfusion MR imaging or predicating its performance on the presence or absence of HVS on FLAIR images, it may be helpful to combine these findings and perhaps others, such as oxygen extraction fraction. The prognostic value of signs like HVS and tests addressing hemodynamic impairment needs to be evaluated with a large prospective study in acute and chronic settings to become clinically useful.

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What Role Does Functional MR Imaging Play in the Diagnosis or Prediction of Future-onset Alzheimer's Disease?

In this issue of the *AJNR,* Bozzao et al (page 1030) evaluated the sensitivity and specificity of functional MR (fMR) imaging in presumed Alzheimer's disease (AD) by comparing fMR results with those of minimally invasive contrast-enhanced perfusion scanning, diffusion-weighted scanning, and conventional MR imaging.

Significant differences were shown in regional CBV (rCBV) values derived by perfusion scanning when mildly and moderately impaired patients with a presumed diagnosis of AD were compared with a group of healthy aged-matched control subjects. Regional CBV values of presumed specificity measured as high as 91%. The authors also applied an atrophy correction to the perfusion measures, which reduced the strength of the results, but all the correlations remained significant. Diffusion scanning did not yield any significant correlations, and no correlates were found for white matter lesions (referred to by the authors as ''lesion load'').

This study exemplifies the exciting transition that we are witnessing in brain behavior research in which complex brain function such as brain metabolism and blood flow are being evaluated by minimally invasive techniques such as fMR imaging. Positron emission tomography (PET), until now considered the penultimate of brain behavior research, requires intravenous injection of a positron emitter as well as arterial cannulization of the patient. During a 20-minute uptake period, a positron-emitting molecule such as the glucose analog F18 fluoro-deoxy-D-glucose or carbon 11 deoxy-D-glucose is trapped at the stage of phosphorylation while emitting positrons. Each positron collides with a negatively charged electron, forming coincident photons travelling in opposite directions that are measured by the detectors. Thus, a measure of glucose metabolism is obtained that, with the use of an operational equation, yields quantitative metabolic measures.

Glucose metabolism and perfusion or blood flow is not dissociated in the presence of Alzheimer disease. This coupling allows us to use alternate techniques such as single-photon emission tomography (SPECT) or perfusion MR scanning to measure CBV or rCBV, and indirectly, cerebral metabolism.

Results of PET measures have shown decrements of up to 30% to 35% in glucose metabolism in moderate AD versus those of healthy age-matched control subjects. The most pronounced deficits involve the hippocampi and the temporal and the parietal lobes. The perfusion results in the present study seem to be comparable, showing rCBV decrements as high as 47% for the left hippocampal region. Sensitivity and specificity measures derived from PET for the diagnosis of AD are in the 80% range. In the current study, Bozzao et al achieved sensitivity measures as high as 91% in the identification of moderately impaired patients with a presumed diagnosis of AD. These results are very encouraging and suggest that perfusion MR may be at least as sensitive as PET in the diagnosis of AD and in the identification of subjects who are likely to develop AD at 3- to 5-year follow-up. This is particularly important, because Food and Drug Administration–approved treatments are available that may retard, arrest, or delay symptoms of AD.

What, then, are the shortcomings, if any, to using perfusion scanning routinely in dementia if not more widely to help identify patients at risk?

Perfusion MR allows us to measure rCBV, but are these measures truly comparable to PET measures? MR perfusion measures and SPECT are not quantitative. For this reason, various strategies have been devised to compensate for the subjective nature of the results. The authors' strategy of using the cerebellum as a reference measure is made on the basis of SPECT research in the literature. There are, however, pitfalls with this strategy. For example, Klinger et al (1988) found that PET determined cerebellar metabolic rates were elevated in subjects with periventricular white matter disease and Ishii et al (1997) reported that in advanced Alzheimer disease cerebral as well as cerebellar glucose metabolism measures are decreased. Thus, we can approximate quantitative measures by using fMR, but there is a potentially limiting error built into the method.

There is an important weakness in brain behavior research studies that derive measures of brain (volumes, perfusion data, proton spectroscopy) and either correlate them with behavior measures such as the Mini Mental Status Examination or use them to identify pathologic abnormality. When we attempt to answer the question ''is this subject a member of the AD group or the control group?'', we obtain impressive results. Unfortunately, this type of question, posed in a research setting, is markedly different from the questions posed in the day-to-day reading of a stack of films. In the latter setting, many potentially dementing diseases, including Parkinson disease and vascular dementia, are considered.

In addition to PET and SPECT studies, structural MR studies such as volumetric assessments of the temporal lobes by means of thin-section cuts, and CT studies before that, have also shown strong correlations between hippocampal atrophy and cognitive measures and excellent accuracy in discriminating between AD and normal subjects. Recent proton MR spectroscopy reports have shown correlations between metabolite measures and cognitive deficits. A simple clinical measure, such as delayed paragraph recall, can predict subsequent decline in approximately 80% of subjects. One

might ask why we should pursue yet another complex technique to accomplish similar results.

It would appear that we are not quite ready to diagnose AD in a routine clinical setting, but we can identify patients who may have or are at risk to develop the disease. What may be very useful at this stage is to attempt to sort out the relative contribution of the multiple studies at our disposal. It would be particularly interesting to determine whether the structural measures, such as hippocampal volume, are independent of perfusion deficits, and whether the perfusion measures provide additional diagnostic information independent of the hippocampal atrophy. The authors did in fact apply an atrophy correction for the whole-brain perfusion measures, but a regional atrophy correction would be particularly interesting because of the well-known sensitivity of hippocampal atrophy to AD.

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CT Perfusion Flow Assessment: "Up and Coming" or "Off and Running"?

Until recently, options for cerebral blood flow measurements were restricted to positron emission tomography (PET) or xenon CT (Xe-CT) that applied freely diffusible tracers for perfusion assessment and tracer kinetic modeling. Because both techniques suffer from a somewhat limited availability, the introduction of perfusion CT for quantitative flow assessment has been received with immediate, strong enthusiasm from the neuroradiologic community. CT perfusion can be performed noninvasively on a standard CT scanner in a very short time and, potentially, in an emergency setting. Resulting quantitative information on cerebral blood flow could have tremendous implications for the management not only of acute stroke patients, but also of patients with chronic steno-occlusive vascular disease.

It is of utmost importance to validate the CT perfusion technique before using the resulting flow estimates for treatment decisions. Importantly, both the methodologies of data acquisition and kinetic analyses differ from established alternatives like PET or Xe-CT. Dynamic contrast-enhanced CT perfusion reflects a different physiology by using an *intravascular* tracer to assess perfusion rather than a *freely diffusible* tracer. Validation studies in animals already have been published (1).

Wintermark et al (2) present an important validation study of CT perfusion in humans. The authors address one important validation parameter, the *accuracy* of CT perfusion, comparing this technique with Xe-CT. Their major conclusion is that perfusion CT in regions excluding major vessels reveals flow values that are in agreement with the reference standard, Xe-CT. This is indeed a very important statement. However, a full, rigorous validation of perfusion CT requires more studies.

A careful consideration in validation studies is the definition of the study population. Wintermark et al present an inhomogeneous selection of underlying diseases. This leaves some questions unanswered: How does the technique perform in complicated physiological scenarios not found in this group of patients, eg, in a unilateral carotid occlusion with various amounts of collateral flow? Following this, what is the best way to use the CT perfusion technique? Flow quantification requires a vascular input function: which vessel (ipsi- or contralateral, more proximal or distal) should be used to calculate flow values in a hemisphere? And does the size of the vascular region of interest (ROI) matter? This is important not only for asymmetrical, but also for symmetrical flow. Are the flow maps affected by the vascular input (eg, anterior cerebral vs middle cerebral vs carotid artery), and if yes, which one is "more correct"? How much does the clinical history of a patient matter in the selection of a vascular ROI? These questions need to be addressed in a rigorously planned trial with defined inclusion and exclusion criteria.

Although these considerations still address the *accuracy* of CT perfusion, a second parameter for study validation has not been targeted: the *reproducibility*. CT perfusion analysis software is commercially available and will soon be widely distributed. The software providers emphasize that the technique is very easy to use. But does an untrained technologist really differ from an experienced researcher? Conversely, and importantly, how does an untrained researcher do compared with an experienced technologist? How much operator training is required to yield reliable flow values? How much can the process be automated? How does the same technologist (or radiologist) perform on different days? Clinicians have to be assured that the numbers are reliable regardless of the time and operator, before they can use them for treatment decisions.

To address these additional considerations is straightforward and in part underway in ongoing studies. Even when all the remaining questions are answered and the optimal use of the CT perfusion technique is defined, a last and yet unresolved technical limitation of the CT perfusion technique is, as indicated by the authors, its limited anatomic coverage. Even with multislice CT scanner technology such as that used by the au-

thors, the anatomic coverage is limited to approximately 2 cm. In particular, in an acute stroke patient with a normal non-contrast CT scan, the ischemic area might be underestimated or even missed. This limitation has to be overcome with different imaging approaches (3) and/or CT scanner technology advances.

In summary, Wintermark et al take an important step toward the validation of a new, noninvasive technique for cerebral flow measurements. They demonstrate its potential value and accuracy compared with Xe-CT under optimal conditions with experienced readers. They also highlight pitfalls, such as the error introduced by inadvertent inclusion of vascular structures in analysis ROI. Thus, more work needs to be done regarding standardization and evaluation of sources or error, and more questions need to be answered, both of technical and practical value, before the CT perfusion technique can be unequivocally recommended to the radiology community for reliable flow quantifications.

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