Fluid-Attenuated Inversion Recovery and Diffusion- and Perfusion-Weighted MRI Abnormalities in 117 Consecutive Patients With Stroke Symptoms

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Background and Purpose—Diffusion-weighted MRI (DWI) is highly sensitive to early cerebral ischemia, but its dependence on lesion location, acuity, and etiology remains unknown. Furthermore, although a marked perfusion-weighted MRI (PWI)-DWI mismatch may exist in a subset of acute strokes, the frequency and distribution of these mismatches have never been methodically characterized in an unselected population. To address these 2 issues, we evaluated echo-planar imaging in 117 consecutive patients with signs and symptoms of acute stroke.

Methods—Clinical diagnoses were determined by chart review. Fluid-attenuated inversion recovery (FLAIR), DWI, and PWI sequences were scored for lesion acuity, neuroanatomy, and vascular territory. Lesion and PWI-DWI mismatch volumes were determined by image analysis.

Results—DWI was more sensitive than was FLAIR for the detection of stroke for all subtypes in all anatomic distributions and at all tested time intervals. Although DWI exhibited its greatest benefit over FLAIR during the first 6 hours, it was still superior to FLAIR even after 24 hours. PWI abnormalities were detected in 49% of patients with DWI abnormalities. In the majority of these cases, the PWI-DWI mismatch was substantially larger than the DWI lesion itself. Both the largest DWI lesion volumes and the largest mismatch volumes occurred in patients with carotid disease.

Conclusions—DWI nearly doubles the likelihood of detecting acute ischemic stroke lesions compared with FLAIR for all etiologies and in all anatomic locations. In the hyperacute period (0 to 6 hours), DWI more than triples the likelihood of acute-stroke detection over FLAIR. PWI reveals a measurable mismatch compared with DWI nearly 50% of the time; and in more than half of these patients, the ratio of the volume of the PWI lesion to the DWI lesion is several times larger than the core ischemic lesion itself. In the final analysis, approximately one fourth of all stroke patients present with a large volume of potentially salvageable tissue at risk for infarction. (Stroke. 2001;32:2774-2781.)

Key Words: cerebrovascular disorders, magnetic resonance imaging, diffusion-weighted, magnetic resonance imaging, perfusion-weighted

There are 2 main objectives in the evaluation of an acute cerebral ischemic event: (1) early identification of stroke anatomy and etiology and (2) early differentiation of brain tissue undergoing irreversible ischemic injury (the ischemic core) from brain tissue undergoing potentially reversible ischemic injury (the ischemic penumbra).

In the hyperacute stages of cerebral ischemia (within the first 6 hours), function of the energy-dependent Na⁺,K⁺-ATPase membrane pump begins to fail, ionic homeostasis becomes disrupted, and cytotoxic edema develops.1–3 CT and conventional MRI, including proton density–weighted and T2-weighted (T2W) MRI, are relatively insensitive to acute ischemia, inasmuch as they fail to identify regions of injury that have not yet undergone a net change in total water content.1–7 Diffusion-weighted MRI (DWI), on the other hand, is sensitive to shifts of water between extracellular and intracellular spaces and, thus, can detect regions of brain undergoing early injury within an hour of the onset of ischemia. Early ischemic brain injury detected by DWI has a high correlation with postmortem infarction, acute and chronic clinical severity, and clinical outcome1,3,5,6,8,9 and can approach a 100% detection rate for ischemic lesions in the hyperacute period.5 In the present study, we sought to test the hypothesis that DWI is more sensitive than fluid-attenuated inversion recovery (FLAIR) for detecting all stroke subtypes and anatomic localizations and for detecting lesions with differing acuities.

Stroke occurs when cerebral blood flow (CBF) is reduced below the threshold for irreversible cellular necrosis.10 The region of brain tissue undergoing irreversible cell death is
termed the “ischemic core.” The region of brain tissue surrounding the ischemic core is termed the “ischemic penumbra.” In this region, neurons are undergoing potentially reversible cellular changes that are due to a decrease in CBF, which is severe enough to abolish neural activity but sufficient to preserve the structural integrity of the cell, at least initially. The fate of the neurons, glia, and other supportive brain cells in the ischemic penumbra is variable and is dependent on both the degree and duration of ischemia. Histological cell death, which begins in the infarcted core, may expand out into the peri-infarct penumbral zone at rates that vary with the severity of the CBF deficit and collateral blood supply. Potentially viable brain tissue has been demonstrated to persist within the ischemic penumbra for up to 48 hours after stroke onset.

Perfusion-weighted MRI (PWI) allows the clinician to identify regions of brain tissue with diminished blood flow and, thus, at risk of infarction. Infarct volume often increases in the acute-stroke period. Therefore, identification of the ischemic penumbra as a target of salvageable brain tissue is an important goal in the imaging evaluation of acute stroke. We sought to define the frequency with which a penumbra can be demonstrated and to estimate the volume of salvageable brain tissue, as detected by DWI and PWI, in a consecutive series of patients who presented with acute ischemic stroke and to test the hypothesis that PWI-DWI mismatches occur in up to one half of all acute-stroke patients.

Subjects and Methods

Patients admitted to University Hospital with a diagnosis of acute ischemic stroke routinely undergo neuroimaging with a CT scan and an MRI “Brain Attack Protocol” within minutes of arrival at the Emergency Department. A series of 117 consecutive unselected patients that arrived at our emergency room between September 1, 1998, and June 1, 1999, with signs or symptoms suggestive of acute stroke were included. We defined the frequency with which a penumbra can be demonstrated and to estimate the volume of salvageable brain tissue, as detected by DWI and PWI, in a consecutive series of patients who presented with acute ischemic stroke and to test the hypothesis that PWI-DWI mismatches occur in up to one half of all acute-stroke patients.

The MRI protocol was acquired on a Marconi Edge 1.5-T MRI system (Marconi Medical Systems) located in the Stony Brook Magnetic Resonance Research Center. The protocol components included axial T2W fast spin-echo and FLAIR images, 3D time of flight intracranial MR angiography, and single-shot EPI diffusion-weighted images. For perfusion imaging, multiple blocks of single-shot EPI images were acquired (echo time 52 ms, repetition time 1400 ms, flip angle 90°, slice thickness 5 mm with 1-mm gap, field of view 24 cm, a 128×188 matrix, 12 slices, and 40 frames) after a bolus injection of 100 μmol/kg gadolinium contrast (Omniscan, Nycomed) delivered with the use of a Medrad Spectris magnetic

resonance–compatible injector (MedRad, Inc). Postcontrast axial T1-weighted spin-echo images were obtained after contrast injection. The EPI images obtained during the first pass of the bolus injection were processed on a pixel-by-pixel basis by fitting the signal-time data to a γ-variate function by nonlinear least squares analysis to yield relative time-to-peak and area under the curve (AUC) maps, which are related to mean transit time and cerebral blood volume, respectively, by using the software provided with the Edge system. The relative time-to-peak and AUC maps were defined with reference to a region of interest (ROI) that encompassed the parietal lobe of the clinically uninvolved hemisphere. Baseline points were chosen interactively for the reference ROI after visualization of the signal kinetics. At the same time, an end point for the γ-variate fit was chosen to avoid recirculation of contrast in the reference ROI. Unless otherwise specified, PWI images refer to the relative time-to-peak maps. MRI films were printed after adjustment to reduce the background signal, to span the largest possible portion of the gray scale, and to optimize the contrast of higher intensity regions.

All films were viewed independently by a stroke neurologist with experience in reading EPI of acute ischemic stroke (G.C.N.) and a neuroradiologist (C.J.R. or P.E.R.). In all instances, the reader was blinded to both the patient name and the final etiologic diagnosis of the patient. Any discrepancy in interpretation was resolved through discussion between the 2 readers or, on 3 occasions, after consultation with the alternate neuroradiologist. FLAIR, DWI (together with a map of apparent diffusion coefficient [ADC]), and PWI images were analyzed systematically for all patients, supplemented by use of T2W images and perfusion AUC maps as needed. In all cases, DWI and ADC images were analyzed first, followed by FLAIR (with the DWI films still available) and then PWI (with DWI and FLAIR studies still available). The neuroanatomic distribution and neurovascular territories of all lesions were cataloged with reference to a standard atlas. A new infarct was defined as a DWI hyperintensity with a corresponding reduction in ADC. Old lesions were defined as lesions seen on FLAIR without corresponding DWI abnormality or as a DWI abnormality without a corresponding reduction in ADC ("T2 shine through"). Stroke etiology was classified on the basis of chart review and was sorted into the following categories: (1) carotid disease, ie, middle cerebral artery and/or anterior cerebral artery territory lesion with evidence of severe stenosis, occlusion, or occlusion of the internal carotid artery; (2) cardioembolus (includes lesions that may have originated from the aortic arch), ie, either multiple cerebral lesions in multiple vascular territories or acute lesions in a single-branch vascular distribution on neuroimaging with significant cardioembolic/aortoembolic risk factors (atrial fibrillation, patent foramen ovale, cardiomyopathy with thrombus visualized on cardiac imaging, and/or grade IV aortic arch disease); (3) single-vessel occlusion of undetermined etiology, ie, any nonpenetrating anterior vessel occlusion above the level of the internal carotid artery or involving the vertebral artery, posterior inferior cerebellar artery, anterior inferior cerebellar artery, or superior cerebellar artery (lesions were excluded from this category if there was a likely cardioembolic source on the basis of clinical criteria or if the patient was diagnosed with coagulopathy); (4) lacunar, ie, a lesion <1.5 cm involving the basal ganglia, internal capsule, thalamus, brain stem, or immediate periventricular white matter; (5) small-vessel disease, ie, nonlacunar infarct <1 cm in diameter involving the white matter but not the cortex, with either scattered punctate or confluent areas of ill-defined hyperintensities in the cerebral hemisphere, or a diffuse ill-defined hyperintensity in the brain stem; (6) watershed ischemia, ie, lesions involving parenchyma at the junction of 2 major vascular territories; and (7) coagulopathy, ie, presence of a demonstrated circulating anticoagulant or systemic cancer and no other significant vascular risk factors.

Lesion ROIs were selected for image analysis beginning with the visual analysis of the diffusion-weighted images. All image slices containing acute lesions were identified for future analysis. Multiple foci were considered a single lesion if there was overlap between the contiguous foci or if the lesions were all in a single vascular distribution even if there was no overlap. For example, a pair of DWI...
lesions in the frontal and parietal branches of the left middle cerebral artery in a patient with a single clinical event would be considered a single lesion. Similarly, the “string of pearls” of the watershed stroke was considered a single lesion rather than multiple lesions. FLAIR lesions were considered acute if the majority of the lesion was anatomically congruent to a DWI lesion. PWI lesions were selected visually from films of the time-to-peak map. PWI abnormalities were considered related to the DWI lesion if there was at least partial overlap between the regions on these 2 maps. For all cases with measurable PWI abnormalities, we operationally defined and calculated a PWI-DWI mismatch volume, related to the ischemic penumbra, as follows: PWI-DWI = PWI lesion volume − DWI lesion volume.

Image analysis was performed, after digitizing the film with a high-resolution digital camera and uniform back lighting, by use of a dedicated workstation (MCID). The lesion area of each slice was determined, after distance calibrations, by using semiautomatic edge detection based on film density boundary properties established with reference to contrasting densities selected by the investigator. All analyses were performed by a single person (E.K.). Reproducibility was established before analyzing this cohort by measuring 10 diffusion abnormalities of varying size 5 times each. The standard deviation of all measures was ±2% for all lesion sizes. Occasionally, it was necessary to draw a short segment of the boundary to prevent the edge-detection routine from crossing into adjacent regions that were not part of the ischemic lesion. Lesion volumes were calculated by multiplying the lesion area for each slice by the slice thickness (and gap) and then summing over all slices.

Diffusion and perfusion scans on all patients entered into the present study were performed by using uniform imaging acquisition parameters and instrument data processing software, which was installed on our Marconi Edge 1.5-T MRI on September 1, 1998. On June 1, 1999, this software (and some hardware) was upgraded. Thus, sample size was determined by the number of patients imaged by our MRI during this time interval rather than a priori power calculations. However, the power of detecting a difference in the FLAIR and DWI detection rates for subgroups was calculated by using an overall DWI detection rate of 94.9%, an overall FLAIR detection rate of 44.3%, and a desired significance level of P < 0.05 for a 1-tailed test. On the basis of these assumptions, only 7 cases were needed to confer a power of 0.80; 10 cases, to confer a power of 0.90; and 13 cases, to confer a power of 0.95. Thus, with the exception of small-vessel disease and watershed ischemia, all etiologies of stroke were tested with a power of at least 0.80 (Table 2). Results were presented either as frequencies of detection rates or as the mean ± SE of lesion volumes, DWI and PWI lesion volumes were transformed for use as independent variables in MANOVA (but not for MANOVA or linear regression) into lesion groups that were (1) <5 mL, (2) 5 to 24.9 mL, (3) 25 to 49.9 mL, and (4) ≥50 mL. The independent variable of time also was transformed for χ² analyses into 4 categories: (1) 0 to 5.9 hours, (2) 6 to 11.9 hours, (3) 12 to 23.9 hours, and (4) ≥24 hours. The influences of etiology and neuroanatomy on the frequency of detectable FLAIR and PWI lesions and on PWI-DWI mismatch volumes were analyzed by using Pearson χ² and the likelihood ratio χ². The effects of time and DWI lesion volumes, after transformation, were analyzed by using the Mantel-Haenszel χ² test for linear association. Comparisons of lesion volumes by etiology and neuroanatomy were performed by MANOVA. The relationships of lesion volumes with each other and with time were studied by linear least squares regression analysis using the actual measured values without transformation. All statistical analyses were performed with the use of SPSS-PC+ (SPSS, Inc.).

**Results**

A total of 117 patients with acute-stroke symptoms were evaluated with DWI. One patient underwent multiple MRIs during 2 separate episodes of ischemic symptoms, for a total of 118 cases (see Table 1). Seventy-nine (63.9%) of these 118 cases met at least 1 of the 2 criteria for acute stroke; 75 of these 79 cases revealed an acute ischemic lesion on DWI, imparting a 94.9% sensitivity to DWI for the detection of acute stroke in our series (consistent with other studies). One patient (to be discussed later) had an isolated PWI abnormality without a DWI abnormality. The remaining 3 cases met our clinical criteria for acute stroke (signs and/or symptoms of acute cerebral ischemia that persisted for >24 hours), but no abnormality was detected on DWI or PWI. Etiologically, these cases were classified as small-vessel disease, with symptoms consistent with a lesion of the caudal brain stem (an area particularly difficult to visualize on DWI). From the total of 75 cases with a detectable DWI abnormality, the case that represented a recurrent ischemic event was excluded from further analysis. Of the remaining 74 unique cases with DWI abnormalities, complete data, including an accurate time of stroke onset and a complete set of images for volumetric analysis (FLAIR, DWI, and PWI), were available for 67 patients who formed the bases for all subsequent analyses. Thirty-nine of the 118 cases presenting to our emergency room for evaluation of cerebral ischemia were ultimately given a diagnosis other than ischemic stroke: 26 patients (22%) were diagnosed with transient ischemic attack; 2 patients (1.7%) each were diagnosed with seizure and complicated migraine; and 1 patient (0.8%) each was diagnosed with aneurysm, dementia, encephalopathy, intracerebral hemorrhage, sensory neuropathy, carbon monoxide poisoning, HIV-related lymphoma, hyperperfusion syndrome, and syncope.

The frequency of patients with each etiologic stroke subtype is shown in Table 2, along with the sensitivity of FLAIR compared with DWI for detection of these lesions. There were 31 cases with a FLAIR abnormality among the 67 cases with DWI lesions, for an overall detection rate of
The overall detection rate of FLAIR is 44.3%. If the 3 patients with clinical stroke without DWI/PWI abnormality are taken into account, the overall detection rate of FLAIR increases to 44.3%. We found that DWI was more sensitive than FLAIR for the acute detection of all stroke subtypes, inasmuch as FLAIR uniformly failed to identify an acute lesion approximately one half of the time for all stroke subtypes, inasmuch as FLAIR uniformly failed to identify an acute lesion approximately one half of the time for all stroke subtypes. Watershed is a notable exception, as FLAIR sensitivity was limited to a value of either 0% or 100%. There was no statistically significant difference in the detection rate of acute stroke by FLAIR imaging among the different disease states (P=0.52, by Pearson χ²).

As expected, FLAIR sensitivity was significantly associated with the interval of time elapsed between the onset of stroke symptoms and MRI acquisition (P=0.025, by Mantel-Haenszel) (see Table 3). DWI exhibited its greatest impact over FLAIR for the detection of acute stroke in the shortest intervals, although it was still superior to FLAIR imaging even after 24 hours. In the hyperacute period after stroke (0 to 6 hours), FLAIR was able to detect only 29% of the acute ischemic strokes that were identified by DWI. As the time after the acute stroke increased, so did the ability of FLAIR to detect acute strokes. In the 6- to 12-hour period after stroke, FLAIR was able to detect 35% of acute strokes; and in the 12- to 24-hour period after stroke, FLAIR detected 50% of acute strokes. Even after 24 hours, however, FLAIR was unable to identify a significant portion of acute ischemic strokes and, in our cohort, missed 31% of acute ischemic strokes that were detected by DWI. An illustration of the inability of FLAIR (or T2 and proton-density images) to detect an acute stroke even after 24 hours is shown in Figure 1. There was an insignificant trend toward improved detection by FLAIR with increasing DWI lesion volume (P=0.097, by Mantel-Haenszel χ²).

As illustrated by Table 4, the frequency of FLAIR lesion detection was not correlated with neuroanatomy; thus, DWI was more sensitive than FLAIR for the detection of acute stroke in all neuroanatomic distributions. Thus, overall, DWI demonstrates an advantage over FLAIR imaging that is manifest throughout the full spectrum of diseases, neuroanatomic locations, and time frames.

Figure 2 demonstrates the relationship of the size of the 31 FLAIR lesion volumes compared with their corresponding DWI lesion volumes. The best-fit linear regression line passed close to the origin and had a slope of 0.84±0.06 (R=0.94, P<0.0001). There was no association of FLAIR lesion volume with etiology or neuroanatomy or correlation with time or PWI lesion volume.

A total of 33 PWI lesion volumes were found (49.3% of DWI lesions), 18 of which also showed FLAIR abnormalities. The presence of a PWI lesion did not correlate with DWI lesion volume (P=0.086). Nor was etiology, neuroanatomy, or time associated with the presence of a PWI lesion (even though PWI lesions involved strokes in a lobar territory in 22 [67%] of 33 instances). The major determinant of PWI lesion volume was clearly disease etiology (Table 2; P=0.005, by MANOVA). The largest volumes were found in carotid disease; smaller, but substantial, lesions were found in single-vessel disease and cardioemboli; and the smallest PWI abnormalities were found in lacunar disease. There were no...
other associations with neuroanatomy or correlations with FLAIR lesion volume, DWI lesion volume, or time.

A PWI-DWI mismatch was observed in 28 of the 33 cases with PWI abnormalities. That is, in 5 of the 33 cases, the PWI abnormality was equal to or smaller than the DWI lesion volume. These cases are easily identified in Figure 3 because they are below the line of identity, which indicates where PWI and DWI lesion volumes are equal. These cases include 3 patients with lacunes and 2 with single-vessel occlusion. In the rest of the cases, the PWI lesion volume is larger than the DWI lesion volume. This graph also indicates that for the majority of cases in which a PWI lesion exists, the ratio of the volume of the PWI lesion to the volume of the DWI lesion is very large; ie, the ischemic penumbra is often several times larger than the core ischemic lesion itself. In 16 of 33 cases with a PWI lesion (48.5%), the ratio of the PWI lesion volume to the DWI lesion volume was >3. These 16 cases represent 23.4% (16 of 67) of all cases with DWI abnormalities. There was no association between the likelihood of detecting a PWI-DWI mismatch with etiology, neuroanatomy, time, or DWI lesion volume. Not surprisingly, there was a strong correlation of mismatch volume with the PWI lesion volume ($r=0.98$, $P<0.0001$) and a strong association with the disease etiology ($P<0.001$, by MANOVA). There was no association of mismatch volume with neuroanatomy or correlation with time, FLAIR, or DWI lesion volume.

**Discussion**

Our data illustrate the value of DWI and PWI in achieving the 2 primary objectives in the evaluation of an acute cerebral ischemic event: (1) early identification of stroke, its anatomy, and its etiology and (2) early identification of brain tissue that is undergoing potentially reversible ischemic injury.

Before the present study, DWI had already been proven to yield a superior detection rate over conventional MRI for the identification of acute stroke. However, none of the prior studies addressed the question of whether the gain in sensitivity achieved by DWI for detection of acute stroke applied across all stroke etiologies and anatomic locations. The present study demonstrates that DWI is more accurate

**TABLE 4. Detection Rates and Lesion Volumes by Neuroanatomy**

<table>
<thead>
<tr>
<th>Location</th>
<th>Patients, N</th>
<th>DWI Volumes, mL</th>
<th>FLAIR Lesions, n (%)</th>
<th>FLAIR Volumes, mL</th>
<th>PWI Lesions, n (%)</th>
<th>Perfusion Volumes, mL</th>
<th>Penumbra (PWI-DWI), mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobar</td>
<td>24</td>
<td>8.2±2.7</td>
<td>11 (46)</td>
<td>8.0±3.2</td>
<td>12 (50)</td>
<td>54.2±20.8</td>
<td>40.0±19.8</td>
</tr>
<tr>
<td>Lobar + basal ganglia</td>
<td>4</td>
<td>7.2±2.7</td>
<td>3 (75)</td>
<td>2.1±0.6</td>
<td>3 (75)</td>
<td>193.8±114.0</td>
<td>184.4±113.1</td>
</tr>
<tr>
<td>Lobar + centrum semiovale</td>
<td>3</td>
<td>22.5±6.9</td>
<td>2 (67)</td>
<td>10.7±1.0</td>
<td>3 (100)</td>
<td>120.2±7.9</td>
<td>109.5±13.1</td>
</tr>
<tr>
<td>Lobar + basal ganglia + centrum</td>
<td>9</td>
<td>31.6±20.8</td>
<td>4 (40)</td>
<td>7.3±2.6</td>
<td>4 (44)</td>
<td>86.8±46.6</td>
<td>69.2±47.7</td>
</tr>
<tr>
<td>semiovale</td>
<td>10</td>
<td>0.6±0.1</td>
<td>3 (30)</td>
<td>0.3±0.2</td>
<td>4 (40)</td>
<td>1.0±0.2</td>
<td>0.5±0.2</td>
</tr>
<tr>
<td>Basal ganglia + centrum semiovale</td>
<td>4</td>
<td>5.0±2.0</td>
<td>3 (75)</td>
<td>3.9±0.3</td>
<td>3 (75)</td>
<td>13.5±9.2</td>
<td>10.2±10.7</td>
</tr>
<tr>
<td>Basal ganglia + brain stem + cerebellum</td>
<td>1</td>
<td>2.35</td>
<td>1 (100)</td>
<td>1.15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Centrum semiovale</td>
<td>4</td>
<td>3.3±1.2</td>
<td>1 (25)</td>
<td>1.1</td>
<td>2 (50)</td>
<td>26.3±20.7</td>
<td>23.4±21.7</td>
</tr>
<tr>
<td>Brain stem</td>
<td>5</td>
<td>0.6±0.2</td>
<td>2 (40)</td>
<td>0.3±0.2</td>
<td>2 (40)</td>
<td>0.5±0.0</td>
<td>0.2±0.1</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>2</td>
<td>33.1±20.5</td>
<td>1 (50)</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain stem + cerebellum</td>
<td>1</td>
<td>0.5</td>
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</table>
than FLAIR in the detection of acute stroke secondary to all etiologies and in all anatomic localizations. Although the present study did not compare sensitivity between DWI and T2W MRI for the detection of acute cerebral ischemia, a similar gain in sensitivity would be expected to be achieved by DWI over T2W MRI, inasmuch as FLAIR has been demonstrated to be more sensitive than T2W MRI in the detection of acute cerebral ischemia. Although clinical experience suggests that T2W MRI or proton density imaging may be superior to FLAIR for definition of brain stem infarcts, that has never been rigorously tested. Because, as in other studies, brain stem and cerebellar infarcts accounted for only 11.9% of lesions, any additional information about FLAIR sensitivity to posterior fossa lesions available from the present study is limited.

When DWI is combined with PWI, information regarding ischemic regions of the brain that are potentially salvageable becomes available to the clinician. From our cohort of 67 acute-stroke patients with DWI lesions, 33 patients (49%) had a cerebral perfusion deficit; 16 (48%) of these 33 patients had an ischemic penumbra that could be categorized as “large” (ratio of PWI volume to DWI volume >3). Our data reveal that the largest penumbra volumes occur in patients with carotid artery disease, followed by patients with cardioembolic disease and single-vessel occlusion. Our definition of the ischemic penumbra as the difference between PWI lesion volume and DWI lesion volume is only an approximation of the actual penumbra. Strictly speaking, the penumbra is that region of tissue with reduced CBF sufficient to impair ionic homeostasis but insufficient to produce immediate infarction. It can be defined physiologically in this manner or approximated by species-specific thresholds established by measurement of CBF. Our definition is based on neither of these but assumes that the volume of infarcted core can be approximated by the DWI lesion volume and that all of the identifiable PWI lesion is below the threshold for cellular dysfunction. The former is almost certainly not true because some part of the diffusion abnormality is likely to be reversible, so the volume of the penumbra may be underestimated. Nevertheless, the simple difference between the 2 volumes is easily measured and likely to be a reasonable approximation to more rigorously defined penumbra volumes.

It is interesting to note that linear regression of FLAIR and DWI lesion volumes reveals a slope of 0.84 ± 0.06. That is, FLAIR lesions are ≈ 84% of the corresponding DWI volumes during the acute phase. This is similar to results of studies comparing acute DWI lesion volumes with follow-up FLAIR or T2 lesion volumes obtained 3 months later. Our results suggest that this difference in FLAIR and DWI lesions does not evolve over time but is already present in the acute-stroke period and then remains stable thereafter.

The distribution of stroke subtypes in our population of patients appears to be typical of stroke populations in general. The Trial of ORG 10172 in Acute Stroke Treatment (TOAST trial) enrolled 1281 patients with a distribution of recognized stroke subtypes as follows: large-artery atherosclerosis (27%), cardioembolism (31%), small-vessel occlusion (36%), and other causes (3%). In comparison, our population of stroke patients included the following: carotid disease (14.9%), single-vessel occlusion (16.4%) (carotid disease and single-vessel occlusion taken together as large-artery atherosclerosis would total 31.3%), cardioembolism (25.4%), coagulopathy (10.4%), lacunar disease (23.9%), small-vessel disease (7.5%) (lacunar disease and small-vessel disease taken together as small-artery disease would total 31.4%), and watershed (1.5%). It is possible that some of the single-vessel occlusions may actually represent undetermined cardioembolic stroke, underestimating the true percentage in that category. Thus, our results with these unsellected patients should be applicable to most stroke populations.

Seven cases from our original data collection with DWI abnormalities were excluded from final analysis because they did not have a complete data set. These cases were eliminated either because the exact time of stroke onset was unknown or because FLAIR and/or PWI sequences were not available. Among this group, there were 3 cases of cardioembolism, 3 cases of single-vessel disease, and 1 case of watershed ischemia. Including these 7 cases in the various analyses produced no statistically significant changes in our results.

There was 1 patient with clinically symptomatic cerebral ischemia and a PWI abnormality who never developed a lesion on DWI or FLAIR. This was an 83-year-old white female with a medical history significant for hypertension, mitral regurgitation, and severe pulmonary hypertension who presented with an acute onset of confusion, global aphasia, right-sided homonymous hemianopia, neglect, hemisensory loss, and leg weakness. Her initial National Institutes of Health Stroke Scale (NIHSS) score was 11. Her DWI obtained 5 hours after symptom onset revealed no acute ischemic lesion, but PWI revealed a relative delay in time to peak in a 67-mL wedge-shaped region in the left parieto-occipital lobes. The patient was treated with intravenous heparin and enrolled in a clinical neuroprotective agent trial (Citicholine Protocol No. IP302-018, Interneuron Pharmaceuticals). Over the next few days, the patient experienced a dramatic clinical improvement (NIHSS 1). Subsequent MRI
study did not demarcate a lesion on T2W or FLAIR sequences. This case illustrates that even large PWI abnormalities are potentially reversible and that a detectable lesion in PWI, without a correlative DWI lesion, may be manifested clinically.

The clinical relevance of acute-stroke identification, neuroanatomy, and etiology is diverse and varied. First, the diagnosis of ischemic stroke based on clinical presentation may be incorrect in >10% of the cases, and the addition of CT scanning to the clinical examination does not significantly decrease the percentage of misdiagnosed cases. During the hyperacute period of stroke, which is the period of time that thrombolytic and/or neuroprotective agents may be administered with maximal efficacy and minimal risk, our data confirm that in the absence of DWI, decisions to administer therapeutic agents will be based primarily on clinical information in >70% of the patients. Delineation of the involved neuroanatomic structures by DWI also allows clinicians to assess acute lesion volume, which is correlated with the acute and chronic NIHSS scores as well as with chronic lesion volume. This information may be useful to the clinician, patient, and/or family of the stroke victim, who are weighing the risks and benefits of acute interventional stroke therapy. Early identification of the stroke subtype and involved vascular territory by DWI and MR angiography may be of great value in choosing whether to administer thrombolytic agents intravenously or intra-arterially and may also be of value in selecting an antiplatelet agent versus a heparinoid. Estimation of the volume of the penumbra from PWI and DWI data provides additional information of potential value in stroke management, inasmuch as it has already been demonstrated by positron emission tomography that the volume of the penumbra that escapes infarction is highly correlated with neurological recovery. If cerebral blood flow is not restored in penumbral brain tissue, there is a gradual expansion of the infarct core into the penumbra, which diminishes in volume over time.

Our data indicate that roughly one half of all acute-stroke patients have an ischemic penumbra and that roughly one half of these penumbra are large. It is this tissue, present in one quarter of all stroke patients on presentation, that is the target for most interventional treatments. DWI and PWI sequences provide physicians with the ability to select patients who are most vulnerable to neurologic deterioration and who have a significant potential for improvement with thrombolytics and/or neuroprotective agents. For the subset of acute-stroke patients with a large volume of cerebral tissue with diminished blood flow (nearly one quarter in our series), PWI may help identify the region of brain with the highest risk of infarction.

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References

It has been 10 years since diffusion- and perfusion-weighted MRI techniques (DWI and PWI, respectively) were first applied to the hyperacute stroke patient. Over that period of time, the technology has evolved from conventional imaging acquisition methods limited to a single scan slice, which was possible only in patients able to keep motionless, to ultrafast echo-planar imaging of the entire brain on virtually every stroke patient who may safely be scanned.

MRI has advantages that make it particularly appealing as a method of choice for acute stroke imaging. Several brain imaging techniques can measure abnormalities in tissue hemodynamics and vascular pathology. Not only can MRI measure ischemia, but, by means of DWI, it is the only method that can depict ischemic tissue injury within minutes after onset of symptoms. Combined PWI and DWI thus depicts both the altered hemodynamics that is the primary pathology of ischemic stroke as well as the resultant tissue injury from cerebral blood flow reduced below a threshold needed for the maintenance of cell metabolism. The technology is continuing to evolve. With the current state of technology, subtle changes in DWI or PWI for very early lesions or lesions smaller than the spatial resolution of the scanning methods may be missed. False-negative scans are thus possible, but for clinically definite stroke with fixed disabling deficits, the acute sensitivity of these methods approaches 100% and in all studies to date has been superior to CT, T2-weighted MRI, and fluid-attenuated inversion recovery (FLAIR) MRI.

Several themes have emerged in work using these methods: (1) defining the limits of diagnostic accuracy of PWI and DWI in acute stroke; (2) assessing their clinical utility and impact on patient management; (3) studying ischemic pathophysiology of human stroke, which has unique features not predictable from many animal models; (4) predicting the clinical and tissue outcome from the acute scan; and (5) using DWI and PWI as a tool in the development and application of therapeutic interventions in stroke. Work such as the present study of Perkins and colleagues illustrates an additional topic of increasing interest: the sensitivities and associations of DWI and PWI abnormalities attributable to different stroke characteristics such as time from onset, anatomic localization, and stroke etiology.

The traditional teachings on cerebral localization of function are derived from a handful of postmortem observations and accepted neurological principles. In recent years, a refinement of these concepts has come from the study of chronic infarct localization on CT or T2-weighted MRI corresponding to the clinical features of chronic deficits. The breakthrough with DWI and PWI, by permitting the definition of ischemic pathology in the hours immediately after onset of deficits, has opened the door for a reevaluation of the principles of cerebral localization in acute stroke. The near future may see redefinition of the causes and localization of stroke syndromes on the basis of early MR imaging. The importance of accurate history and physical examination will never be obsolete, but the era in which clinical reasoning based solely on bedside assessment as the ultimate standard of diagnosis and localization has passed.

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