T2′ Imaging Predicts Infarct Growth beyond the Acute Diffusion-weighted Imaging Lesion in Acute Stroke

Purpose:
To show that measurement of the transverse relaxation time that characterizes signal loss caused by local susceptibilities (T2′) is sensitive to an increased deoxyhemoglobin concentration in the brain, indicating tissue at risk for infarction.

Materials and Methods:
The study was approved by the local institutional review board; patients or their guardians provided informed consent. Magnetic resonance (MR) imaging was performed within 6 hours of symptom onset and again 1–11 days thereafter in 100 consecutive stroke patients, all of whom received intravenous thrombolytic therapy (mean age, 67 years). The MR imaging protocol included diffusion- and perfusion-weighted imaging for determination of apparent diffusion coefficient (ADC) and time to peak (TTP), along with quantitative T2 and T2′ imaging. T2′ maps were calculated and visually compared with ADC and TTP lesions by two independent observers.

Results:
A T2′>ADC mismatch was observed by reader 1 in 73 (73%) of 100 patients, and by reader 2 in 65 (65%) patients. Respective sensitivities of T2′>ADC and of TTP>ADC mismatches for later infarct growth were 0.87 and 0.98 for reader 1 and 0.78 and 0.98 for reader 2, with respective specificities of 0.42 and 0.04 for reader 1 and 0.46 and 0.04 for reader 2. The odds ratios for infarct growth in the presence of a T2′ > ADC mismatch were 4.59 (reader 1 \( P = .002 \)) and 3.10 (reader 2 \( P = .012 \)), while the odds ratios for TTP>ADC mismatch were 2.22 (reader 1 \( P = .606 \)) and 1.73 (reader 2 \( P > .999 \)).

Conclusion:
The presence of a T2′ > ADC mismatch is a more specific predictor of infarct growth than is TTP>ADC mismatch and hence may be of clinical value in patient selection for acute stroke therapies in the future.
The penumbra in acute stroke patients has been defined as brain tissue with loss of electric activity that retains the potential for recovery after timely recanalization of the occluded artery (1). Determination of the size of the ischemic penumbra may help predict potential response to therapy (2). It is widely accepted that extension of an acute stroke lesion as delineated in perfusion-weighted (PW) magnetic resonance (MR) imaging beyond the corresponding lesion boundary in diffusion-weighted (DW) imaging is indicative of tissue at risk of progressing to infarction (3–5).

This “mismatch concept” has been challenged recently (6,7) on the grounds that PW imaging lesions do not discriminate reliably between benign oligemia and true penumbra. Moreover, PW imaging lesions have been reported to overestimate the extent of infarction seen at follow-up (8,9). These shortcomings may partly be a consequence of a given degree of perfusion impairment that has a different effect on the tissue depending on the anatomic location, the patient’s age, and the time from stroke onset. Overcoming these shortcomings may require a modality that looks at the response to the perfusion deficit, rather than simply the extent of the deficit.

The penumbra is characterized by an increase in the oxygen extraction fraction (10,11). Positron emission tomography (PET) studies can help depict this aspect of the metabolic status of ischemic and penumbral brain tissue directly but are not routinely available for acute stroke use in many centers. The ability to display a similar parameter by using a routine stroke imaging modality such as MR imaging could allow the metabolic conditions in penumbral tissue to be introduced to widespread clinical routine application.

It is well recognized that blood oxygen level–dependent signal changes on T2*-weighted MR images arise owing to changes in the local concentration of deoxyhemoglobin (12). Consequently, hypointense lesions in T2*-weighted images indicate increased local deoxyhemoglobin concentration. Thus, T2* changes may therefore reflect alterations in oxygen extraction and provide an estimation of the penumbra (13–15). Correcting T2* estimates for spin-spin effects yields a relaxation measure T2’ (1/T2’ = 1/T2* – 1/T2) that is isolated from the influences of deoxyhemoglobin on T2* values (16,17). The use of this derived T2’ parameter may, in effect, allow the reader to compensate for the considerable alterations in T2 imaging, which may also result from acute ischemic stroke (18).

As with hyperacute ischemic lesions seen at computed tomography (CT), regions of abnormality in T2’ maps are clearly visible to the human eye (15) but hard to delineate or visualize by using thresholding techniques. Whereas dynamic susceptibility perfusion imaging displays nonspecific reductions in blood flow parameters in ischemic stroke patients, T2’ is thought to reflect the reaction of tissue metabolism in the presence of that perfusion deficit, leading to increased oxygen extraction fraction. Therefore, T2’ imaging may provide a more specific estimate of the clinically relevant impaired tissue metabolism than do mean transit time measures and thus, may more accurately predict tissue viability.

Therefore, the purpose of this study was to evaluate whether a T2’ lesion exceeding the dimensions of the corresponding apparent diffusion coefficient (ADC) lesion might provide a more specific predictor of infarct growth than does the traditional time-to-peak (TTP)>DW imaging mismatch.

**Advances in Knowledge**

- T2’ maps reflect transverse relaxation times that characterize signal loss attributable to local susceptibility effect and are therefore sensitive to changes in the local concentration of deoxyhemoglobin in brain tissue proportional to increased oxygen extraction fraction in the presence of a perfusion deficit.
- Whereas dynamic susceptibility perfusion imaging displays nonspecific reductions in blood flow parameters in ischemic stroke patients, T2’ imaging is thought to reflect the reaction of tissue metabolism in the presence of that perfusion deficit, leading to increased oxygen extraction fraction.
- T2’ imaging may provide a more specific estimate of the clinically relevant impaired tissue metabolism than do mean transit time measures and thus, more accurately predict tissue viability.
- Hypointense signal on T2’ images is visually detectable in a majority of acute stroke patients who qualify for intravenous thrombolysis.
- The presence of a T2’ > apparent diffusion coefficient (ADC) mismatch is a more specific predictor of infarct growth than is time-to-peak > ADC mismatch.

**Implication for Patient Care**

- Our data suggest that T2’ MR imaging may provide a rapid, clinically relevant measure of hypoxic metabolism, indicating tissue at risk in acute stroke patients.

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**Abbreviations:**
ADC = apparent diffusion coefficient
DW = diffusion weighted
PW = perfusion weighted
TE = echo time
TR = repetition time
TTP = time to peak

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Materials and Methods

Patients and Imaging

This study was approved by the local institutional review board, and the patients or their guardians provided informed consent. One hundred consecutive patients (57 men, 43 women) were selected from a prospectively acquired database. Inclusion criteria were acute cerebral ischemia in the anterior circulation, a complete MR imaging stroke protocol within 6 hours of symptom onset, and treatment with intravenous thrombolytic therapy. The decision to treat was made according to the European Stroke Initiative Recommendations for Stroke Management (19): all patients diagnosed within 3 hours of symptom onset were treated with intravenous thrombolytic therapy by using a tissue plasminogen activator (0.9 mg per kilogram of body weight; Actilyse, Boehringer-Ingelheim, Ingelheim, Germany) following acute stroke imaging, except where MR, as the primary imaging modality, showed signs of intracerebral hemorrhage or DW imaging lesions exceeding 50% of the middle cerebral artery territory (these patients were excluded from thrombolysis). For patients arriving 3–6 hours after onset of symptoms, the decision to perform intravenous thrombolyis was made individually on the basis of MR imaging findings and after informed consent. The decision of whether to treat included consideration of PW and DW imaging lesion volumes as assessed by the neuroradiologist on duty without further postprocessing. In general, patients with signs of intracerebral hemorrhage, large DW imaging lesions, and without a clear PW/DW imaging mismatch were excluded from thrombolysis.

The MR imaging protocol included fluid-attenuated inversion recovery imaging, DW imaging, PW imaging, multiecho T2 and T2* mapping sequences, and time-of-flight MR angiography. Time-of-flight MR angiography was determined by using three-dimensional fast imaging with a steady-state precession sequence with venous saturation, magnetization transfer saturation pulse, and tilted optimized nonsaturating excitation pulse.

In both the pretreatment and follow-up studies, a single-shot, spin-echo, echo-planar imaging sequence was used for DW imaging, and images were collected with b = 0 and 1000 sec/mm², from which the ADC was determined. For PW imaging, a gradient-echo echo-planar imaging sequence was employed, and the changes in relaxation rate (ΔR2*, where R2* = 1/T2*) were calculated as ΔR2*(t) = −ln[S(t)/S0]/TE, where S(t) is the signal intensity at the time after injection of the contrast agent, S0 is the signal intensity without contrast agent, and TE is the echo time. TTP maps were generated by finding the time to the maximum difference of S(t) from S0 for each voxel.

For T2 determination, a fast spin-echo sequence with 13 echoes per shot was used to acquire images by using the following parameters: repetition time (TR) msec, 4550; TEs, 12, 84, and 156 msec; total acquisition time, 74 seconds; number of sections, 24; section thickness, 5 mm; section spacing, 0 mm; field of view, 240 mm; matrix, 74 × 128; and refocusing flip angle, 150°. Single-shot gradient-echo echo-planar images with TR, 3240 msec; TEs, 20, 52, and 88 msec; and flip angle, 90° were similarly used for T2* mapping and were obtained during a total acquisition time of 19 seconds. Average total acquisition time for all MR imaging sequences was 10 minutes. Follow-up imaging was obtained by using CT in 14 patients and MR in 86 patients and was performed 1–11 days (mean, 4 days) after the initial examination.

Calculation of T2* Images

T2 and T2* maps were made by using fast spin-echo and echo-planar imaging acquisitions, respectively, with TEs of 12, 84, and 156 msec for T2 and TEs of 20, 52, and 88 msec for T2* and a pixel-wise fit of the image intensities to an exponential decay function yielding the time constants T2 and T2*, respectively.

T2, T2*, and T2* maps were obtained with the MR system by using an extended image reconstruction algorithm. T2* and T2 maps were first calculated separately by fitting the single exponential terms S(t) = S0 e−t/T2 and S(t) = S0 e−t/T2* to the signal decay curves of the respective multiecho T2- and T2*-weighted data (SI[t]). The T2* map was then obtained as the T2* corrected for spin-spin (T2) effects (16) by applying the relationship 1/T2* = 1/T2 − 1/T2 to each voxel (Fig 1) (17). The imaging sequences and reconstruction required for T2* mapping was easily incorporated in the routine MR imaging stroke protocol with an extra acquisition time of 1 min 33 sec.

Data Analysis

The reading strategy was chosen to resemble the acute situation where clini-
cal information and other MR imaging data are available for a summary evaluation. This involved initial independent comparisons of the T2’ and TTP lesion volumes with the initial ADC lesion volume by two independent observers (S.S., T.F.) (Fig 2). At the first reading, the T2’ and TTP lesion volumes were compared with the initial ADC lesion volume by both observers independently. In reading, the observers were blinded to the final lesion size in follow-up images. At the second reading, the original ADC lesion volumes and final lesion sizes seen in follow-up fluid-attenuated inversion recovery–CT images (days 1–11) were compared to determine lesion growth. In the absence of a follow-up fluid-attenuated inversion recovery scan (n = 14), the final infarct size was assessed on the follow-up CT images by using visual evaluation. As a uniform basis for comparison, the initial perfusion deficit (TTP lesion) was assessed with identical viewing window and level attenuations (3000 and 500 HU, respectively) for all subjects. Any visually identified difference in lesion sizes was considered as mismatch.

As in the clinical setting, quantitative volumetric analysis was not performed, and analyses were performed on the basis of dichotomous forced-choice comparisons. The TTP>ADC mismatch, which is routinely used for evaluation of perfusion deficits in many centers (5), was determined by comparison of the initial ADC and TTP lesion volumes. The presence of a T2’>ADC mismatch was determined in a similar manner. For the comparisons of ADC lesion sizes with those in TTP and T2’ images, the choices were mismatch and no mismatch. “No mismatch” indicated that the ADC lesions were equal in size or exceeded the corresponding TTP or T2’ lesion. For comparison of initial ADC lesions with final lesion sizes on follow-up images, the dichotomized choices were lesion growth and no lesion growth. The image quality of the T2’ images was graded “good,” “reasonable,” or “poor” by each observer. The interobserver agreement (κ) for T2’>ADC was calculated. We considered κ < 0 as poor, κ = 0.0–0.20 as slight, κ = 0.21–0.40 as fair, κ = 0.41–0.60 as moderate, κ = 0.61–0.70 as substantial, and κ = 0.71–1.00 as very good agreement (20).

In addition, the acute MR imaging and angiography of day 1 were independently rated, if available, for recanalization by both readers. Recanalization was defined on MR angiographic images of day 1 when there was recanalization with remaining mild stenosis or normal arterial caliber. In the case of differing results, a consensus rating was accomplished.

**Statistical Analysis**

Statistical analysis was performed by using software (SPSS, version 13.0; SPSS, Chicago, III).

The Fisher exact test was used to assess the relationship between the time since symptom onset and the presence of T2’ lesion, T2’>ADC mismatch, and TTP>ADC mismatch. The relationship between presence of a T2’<ADC mismatch and the presence of a

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**Figure 2**

A–E, First patient with lesion growth in follow-up fluid-attenuated inversion recovery imaging (E) shows clear T2’>ADC (D>A) mismatch in acute situation. F–J, Second patient without lesion growth in follow-up fluid-attenuated inversion recovery imaging (J) shows no T2’ lesion (I, no T2’>ADC mismatch). Both patients initially had TTP>ADC mismatch (A<C and F<H).
TTP>ADC mismatch and the site of vessel occlusion were similarly analyzed by using the Fisher exact test.

The sensitivity, specificity, positive predictive value, negative predictive value, and odds ratio for infarct growth in the presence of a T2'>ADC mismatch and the presence of a TTP>ADC mismatch were determined separately for each reader. For all tests, P values of less than .05 were considered to indicate a significant difference.

### Results

The mean patient age was 67 years ± 13 (standard deviation); range, 34–93 years. The interval between symptom onset and MR imaging was 2.47 hours ± 0.77. All patients were imaged within 6 hours after symptom onset but the exact time of symptom onset was not available in nine (9%) of 100 patients.

No ADC lesion was visible in two (2%) of 100 patients and no T2' lesion was visible in five (5%). A TTP lesion was visible in 100 (100%). The image quality of the T2' images was rated good in 52 (52%) patients and reasonable in 48 (48%), while observer 2 rated 83 (83%) cases as good and 17 (17%) as reasonable.

Both observers identified a TTP>ADC mismatch in 97 (97%) of 100 patients. In the three remaining patients, the TTP lesion was rated by reader 1 as equal in size to the ADC lesion, while reader 2 considered one to be equal to the ADC lesion and two to be smaller.

The T2' lesion was rated as smaller than the ADC lesion in 15 (15%) of 100 patients by reader 1 and in 33 (33%) patients by reader 2, while the lesions were considered equal in size for 12 (12%) and two (2%) patients by the respective readers. A T2'>ADC mismatch was observed in 73 (73%) patients by reader 1 and 62 (65%) patients by reader 2 (κ = 0.53 for interobserver agreement). There was no time-dependent difference in the presence of T2' lesions. In addition, time-dependent (≤3 hours vs >3 hours) differences were not found for presence of T2'>ADC mismatch (Fisher test, P = .330) or for the presence of TTP>ADC mismatch (Fisher test, P = .590).

In the evaluation of MR angiography data, no apparent vessel occlusion was observed in three (3%) of 100 patients, occlusion of the carotid bifurcation or of the combined middle cerebral artery and anterior cerebral artery occlusion was seen in 10 (10%) patients, occlusion of the middle cerebral artery trunk was seen in 49 (49%) patients, and occlusion of a middle cerebral artery branch in 38 (38%) patients. In our sample, the relationship of T2' lesion volume to the ADC lesion was not dependent on the vessel occlusion site (Fisher test, P = .796).

The sensitivity, specificity, positive predictive value, negative predictive value, and the odds ratio for infarct growth are displayed in the Table for each reader separately.

Follow-up MR angiography was available in 59 (59%) of 100 patients and showed recanalization in 36 (61%) patients. In this subgroup of patients with recanalization the positive predictive value for lesion growth in the presence of a T2'>ADC mismatch was lower (0.42 for reader 1, 0.44 for reader 2) than in patients without recanalization (0.13 for reader 1, 0.57 for reader 2). The sensitivity for lesion growth in the presence of a T2'>ADC mismatch in patients with recanalization was 0.92 for both readers. In patients with a T2'>ADC lesion, the respective negative predictive values for readers 1 and 2 were 0.36 and 0.32, and 0.66 and 0.68 without recanalization.

### Discussion

MR imaging has emerged as the primary modality for acute stroke imaging in many major stroke centers worldwide (21–24). A key factor in this emergence has been the ability of DW and PW imaging to help determine the regions of ischemic brain tissue at risk of developing subsequent infarction since viable tissue may exist until at least 9 hours after symptom onset and patients can be treated successfully if selected on MR imaging-based criteria (25,26).

Specifically, the TTP>ADC mismatch between PW and DW imaging, which is thought to estimate the tissue at risk for infarction (27), has been successful in patient selection and has, in fact, been demonstrated for time windows longer than the 3 hours after the event currently advised for intravenous thrombolytic treatment (5,25,26,28). The identification of patients who may benefit from therapy is especially important for the expansion of the time window for treatment beyond 3 hours (29). However, there is growing evi-
dence that the TTP > ADC mismatch concept only weakly approximates the real penumbra and that the concept appears to be an oversimplification of the metabolic and electrophysiologic processes involved. As a result, the PW imaging lesion overestimates the real penumbra and cannot reliably discriminate between benign oligemia and penumbra (8,9). Our results reinforce this observation, as the TTP > ADC mismatch was not predictive for infarct growth.

In contrast to the infarct core, the penumbra is characterized by less severe perfusion impairment, which may lead to electrical failure but sustain energy metabolism and consequently the potential for recovery (11,30,31). In a routine stroke MR imaging protocol, perfusion imaging displays the cause of tissue damage in ischemic stroke. T2* imaging on the other hand, is thought to reflect the response of tissue metabolism to that perfusion deficit with increased local deoxyhemoglobin levels used as an indicator of increased oxygen extraction fraction (32). The presumed physiologic basis for T2* imaging is the modulation of paramagnetic deoxyhemoglobin in the cerebral capillaries and veins as by decreased or increased oxygen ejection fraction in penumbral brain tissue (33). Thus, hypointense lesions in T2* images may represent increased deoxyhemoglobin as an indicator of increased oxygen ejection fraction, which might increase with ongoing perfusion impairment. PET has been the method of choice for obtaining in vivo measurements of oxygen ejection fraction (32) but it is not widely available for use in acute stroke. T2* imaging provides a similar metabolic parameter by means of the more widespread noninvasive modality of MR imaging (15). The number of patients included in a previously reported feasibility study of T2* imaging was insufficient to assess its reliability in predicting lesion growth (34). Our study is the first to examine T2* images in a larger number of stroke patients.

Our method of visual lesion rating closely replicates the reporting conditions in the acute setting. The findings support the hypothesis that a T2’ > ADC mismatch represents a useful additional criterion for the prediction of lesion growth. The specificity of a T2’ > ADC mismatch for predicting final lesion size among patients treated with intravenous thrombolysis was considerably higher (0.42 for reader 1, 0.46 for reader 2) in comparison with the highly unspecific TTP > ADC mismatch (0.04 for both observers). This greater specificity is achieved at the cost of a slight reduction in sensitivity; the sensitivity of the T2’ > ADC mismatch as a predictor of lesion growth (0.87 for reader 1, 0.78 for reader 2) was somewhat inferior to that of TTP > ADC mismatch (0.98 for both observers).

Thrombolytic therapy is known to increase vessel recanalization rates and to lower the propensity for lesion growth (35). Thus, the positive predictive value of the TTP > ADC mismatch for lesion expansion can be expected to be lower in our study than in studies without thrombolytic therapy.

We relied on hypointensities in a T2* imaging method that is fast and easily applied in clinical routine while limiting postprocessing of acquired image data. However, we are not able to fully disentangle the processes contributing to the appearance of T2* hypointensities. An and Lin (17) showed that local deoxyhemoglobin concentration in brain tissue is dependent not only on the oxygen ejection fraction but also on the cerebral blood flow. Thus, T2* imaging should be assessed in combination with PW imaging results. Nevertheless, T2* imaging provides additional information since it reflects the metabolic reaction to the presence of a perfusion deficit.

As one might expect, the presence of a T2’ > ADC lesion had a lower positive predictive value for lesion growth when combined with later recanalization than without. Accordingly, the negative predictive value and sensitivity were higher in patients with recanalization than in those without. These findings support the view that the hypointense T2’ lesions represent meaningful information on the extent of the penumbra (15). Despite their evident prognostic value, the underlying pathophysiologic mechanism of T2’ lesions remains to be further elucidated.

In contrast, the relation between T2’ and ADC lesion volume was not dependent on site of vessel occlusion, as one might expect. We suspect that the number of patients in each occlusion type might still be too low to show significant differences.

The T2* measurement was easily incorporated in a routine MR imaging stroke protocol (extra acquisition time, 1 hour 33 minutes). Automatic generation of quantitative T2* images from the triple echo T2 and T2* sequences by using an extended image reconstruction algorithm is implemented in our routine protocol. While scientific papers usually report on threshold levels for perfusion imaging (36,37), the majority of stroke centers and major stroke studies (23) rely on visual inspection (“eyeballing”) of perfusion abnormalities for clinical decisions. Therefore, our approach of visual comparison of lesion volumes instead of thresholding and volumetric analyses is likely to be representative of typical practice. Interobserver reliability in visual assessment of the T2* images was reasonable and was comparable or superior to the levels previously reported for ischemic signs in CT of acute stroke (38). As with hyperacute ischemic lesions in CT, the regions with abnormalities in T2* imaging are clearly visible to the human eye but hard to delineate manually or visualize by thresholding techniques, since T2* values in brain tissue show large variability (39). Therefore, in our opinion, it is not possible to delineate T2* lesions by using threshold levels. In addition, one purpose of our study was to prove feasibility of this method and investigate the clinical application of the T2* images. This requires a quick visual interpretation of the images.

The main limitation of our study was that the TTP > ADC mismatch was an inclusion criterion for treatment within 3–6 hours and therefore led to 97% of the patients meeting this criteria. This homogeneous population avoided bias from different treatment regimens allowing comparison of T2’ > ADC with TTP > ADC mismatch as an alternative
variable for prediction of lesion growth in this patient group. This selection criterion limits our ability to comment on the role of $T2' > ADC$ in understanding the natural history of untreated patients. However, owing to the accepted effectiveness of intravenous thrombolytic treatment, such an investigation of untreated patients is likely to be impossible outside of the placebo group from a randomized trial, as the untreated patients from clinical routine under current best practice now represent a biased patient group with heterogeneous reasons for exclusion from therapy. As a further weakness of the present study, we note that the use of gray-scale perfusion maps for lesion volume assessment on raw PW imaging maps has been shown to be subject to high interreader variability (40).

We have shown that $T2'$ lesions exceeding the dimensions of the corresponding ADC lesion were a more specific predictor of infarct growth among patients undergoing treatment with intravenous thrombolysis than was the traditional $TTP>DW$ imaging mismatch. Our data suggest that $T2'$ MR imaging may provide a rapid, clinically relevant measure of metabolism, indicating tissue at risk in acute stroke patients.

In the future, this information might be most beneficial for patients in whom the decision of whether to treat with thrombolysis is difficult, for example, in a patient arriving more than 3 hours or with known elevated risk of bleeding complications.

References


