

Quantitative T2 Values Predict Time From Symptom Onset in Acute Stroke Patients

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Background and Purpose—We hypothesize that in comparison to diffusion-weighted imaging, quantitative T2 values (qT2) are more directly related to water uptake in ischemic tissue, depending on time from symptom onset. We measured the increase of qT2 in the infarct core to quantify the correlation between time from symptom onset and change in qT2.

Methods—Thirty-six patients with acute ischemic stroke in the territory of the proximal middle cerebral artery underwent MRI including diffusion-weighted imaging, fluid-attenuated inversion recovery, and a triple-echo T2 sequence (calculation of T2 maps) within 6 hours after symptom onset. Regions of decreased apparent diffusion coefficient $<550 \times 10^{-9}$ mm²/sec were defined and superimposed onto the corresponding T2 map and the unaffected side in the horizontally flipped maps. Differences of T2/apparent diffusion coefficient values between affected and unaffected side were calculated (differences of T2/differences of apparent diffusion coefficient). Fluid-attenuated inversion recovery images were rated for lesion visibility.

Results—Differences of T2 showed a significant correlation with time from symptom onset ($R=0.580$; $P<0.001$). T2 values measured in patients with visible fluid-attenuated inversion recovery lesions were significantly higher than in those without visible hyperintensity ($P<0.001$). The accuracy of qT2 to predict a time from symptom onset <3 hours was 0.794, whereas the corresponding accuracy for visual assessment of fluid-attenuated inversion recovery images was 0.676.

Conclusions—T2 values demonstrated a strong correlation with time from onset, suggesting different pathophysiologic mechanisms than diffusion restriction. Whereas fluid-attenuated inversion recovery only provides binary information on lesion visibility, T2 values correlate well with time from symptom onset, and are free from operator bias, increasing reproducibility to determine time from symptom onset. (*Stroke*. 2009;40:00-00.)

Key Words: acute stroke ■ brain imaging ■ brain infarction ■ brain ischemia ■ cerebral infarct ■ imaging ■ magnetic resonance ■ neuroradiology

The intravenous application of tissue plasminogen activator in acute stroke patients is usually initiated within 3 hours after symptom onset because its efficacy is strongly time-dependent.¹ Nevertheless, it has been shown that even beyond the 6 hour time window, viable tissue may exist until at least 9 hours after symptom onset and patients can be treated successfully if selected on MRI-based criteria.^{1,2} The existence and extent of this tissue at risk for infarction is known to be time-variant and constantly changing.^{3,4}

Up-to-date therapy decisions are based on rigid time windows instead of tissue pathophysiology and individual reaction of brain parenchyma to acute ischemia. Nevertheless, time plays an important role even for compensatory mechanisms, and especially for the interpretation of tissue pathophysiology, which is, after all, also time-dependent.

The probability for irreversible infarction within given thresholds for diffusion and perfusion varies with time.^{5,6}

Therefore, reliable assessment of time from symptom onset is crucial for interpretation and analysis of imaging in acute ischemic stroke. However, time of symptom onset is unknown in 20% to 25% of the patients.⁷ Ischemic lesions become visible on fluid-attenuated inversion recovery (FLAIR) imaging within the first hours. However, the sensitivity of FLAIR imaging within the first 6 hours of stroke onset was also reported to be time-dependent, and its relation to time from symptom onset is not well-defined.^{8,9} In addition, visual interpretation of FLAIR images only provides binary information on lesion visibility and reveals an inter-observer variability.

Animal studies indicated that in comparison to T2-weighted images, more subtle T2 increases may be observed much earlier when using quantitative T2 (qT2) imaging.¹⁰ We hypothesize that qT2 values predict time from symptom

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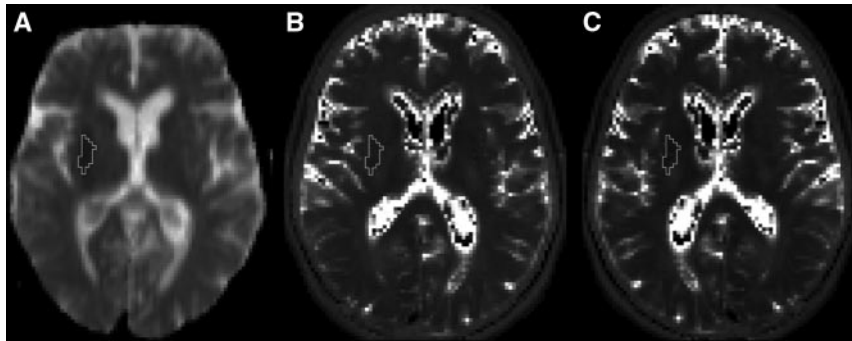


Figure 1. Example of images analysis showing an ADC image (A) and the corresponding T2 map (B) and horizontally flipped T2 map (C), with corresponding ROI on each image.

onset. We measured the increase of T2 relaxation time in the infarct core of acute stroke patients to investigate the correlation between time from symptom onset and change in qT2 values. In addition, we studied the relationship of FLAIR lesion visibility to qT2 values. To our knowledge, this is the first study to investigate changes of qT2 values measured in the infarct core in hyperacute stroke lesions in stroke patients.

Materials and Methods

Patients and Inclusion Criteria

Thirty-six consecutive patients (18 males and 18 females) were selected from a prospective database. Inclusion criteria were a clearly known time from symptom onset, an acute cerebral ischemia in the territory of the proximal middle cerebral artery (MCA), and M1 occlusion detected in time-of-flight angiography. All patients underwent MRI within 6 hours after symptom onset (mean, 185 minutes; minimum, 60 minutes; maximum, 345 minutes). The mean patient age was 68 ± 10 years (mean \pm SD), and ages ranged from 44 to 89 years. The study was approved by the local institutional review board, and patients or their guardians provided informed consent.

MRI Sequences

The MRI protocol included diffusion-weighted imaging for determination of apparent diffusion coefficient (ADC), FLAIR, time-of-flight MR angiography, and a multi-echo T2 mapping sequence. Time of flight MRA was obtained by a 3-dimensional fast imaging with steady state precession (FISP) sequence with venous saturation, magnetization transfer saturation pulse, and TONE-up pulse. For diffusion-weighted imaging (DWI), a single-shot, spin-echo, echoplanar-imaging isotropic DWI sequence (echo time=105.2 ms, repetition time=4800 ms, field of view=240 mm, matrix 256×256 , 20 slices, 6-mm slice thickness, 10% gap) was used and images were collected with $b=0$ and $b=1000$, from which the ADC was determined. FLAIR sequence parameters were echo time=108 ms, repetition time=8140 ms, and inversion time=2500 ms (field of view=230 mm, matrix 256×184 , 24 slices, and 5-mm slice thickness, 30% gap). For T2 determination, a fast spin-echo sequence with 15 echoes per shot was used to acquire images at 3 different echo times of 12, 84, and 156 ms within a total acquisition time of 74 seconds (number of slices=24; slice thickness=5 mm; slice spacing=0 mm; field of view=240 mm; matrix= 74×128 ; repetition time=4550 ms; refocusing flip angle= 150°).

Calculation of T2 Images

T2 maps were based on a fast spin-echo imaging acquisition, with 3 different echo times (12 ms, 84 ms, and 156 ms for T2) and a pixel-wise fit of the image intensities to an exponential decay function yielding the time constant T2. T2 maps were calculated by fitting the single exponential term $SI(t) = SI_0 e^{-t/T2}$ to the signal decay curve of the multi-echo T2 data $[SI(t)]$. Voxel sizes of the obtained parameter maps were $3.2 \times 1.9 \times 6.5$ mm³.

Region of Interest Definition

All acquired images were normalized to a standardized 3-dimensional space to assure an optimal 3-dimensional comparability between the modalities. For this purpose, a coregistration of the ADC map to the corresponding T2-weighted image (third echo, echo time=156 ms) using the standard coregistration options of SPM5 software package (Version SPM5; Wellcome Department of Neuroimaging Neuroscience) was followed by a normalization of the T2-weighted image to the SPM-implemented T2 template. The transformation parameters were consecutively applied to the coregistered ADC and T2 maps. We used the standard normalization options of SPM and set the voxel size at 2×2 mm horizontally and 6 mm vertically.

In addition, horizontally flipped images of normalized ADC maps and T2 images were created by using Image J software; the midline of the normalized images is chosen automatically by the program (ImageJ 1.4 Rasband W; National Institutes of Health).

Regions of decreased ADC below a threshold of 550×10^{-9} mm²/s were defined using imageJ software and superimposed onto the corresponding T2 map and also onto the unaffected side in the horizontally flipped T2 and ADC maps (Figure 1). Because the normalization process does not produce entirely symmetrical brains, after flipping the region of interest (ROI) to the unaffected hemisphere, they were adjusted manually if necessary to obtain optimal comparability.

Relative side differences of T2 values and ADC values (difT2 and difADC) were calculated by comparison of the lesion ROI with the mirrored ROI of the contralateral side. These differences were consecutively analyzed by statistical testing.

FLAIR Reading

In addition, corresponding FLAIR images were rated for lesion visibility by 2 experienced neuroradiologists (S.S. and B.H.). In a first reading, FLAIR images were rated separately by each observer. Any visually identified lesion in FLAIR correspondent to the location of the ADC lesion was considered as visible.

For the rating of FLAIR images for lesion visibility, the dichotomized choices were visible or not visible. In reading, the corresponding acute DWI and ADC images were available for comparison. We considered this information to be crucial because some patients presented hyperintense lesions in FLAIR attributable to microangiopathy not corresponding to the acute stroke lesion detected in ADC images. In case of differing results, a consensus rating with a third experienced neuroradiologist (T.R.) was accomplished.

For testing the predictive value of FLAIR lesions for time from symptom onset, the patient collective was divided into 2 groups: a first group with a time window <3 hours, and a second group with a time window ≥ 3 hours.

Statistics

Statistical analysis was conducted using R software (R version 2.7.0; The R Foundation for Statistical Computing). Mean absolute values and SD for T2 and ADC values were calculated. The correlations between time from symptom onset and ADC and difT2 were determined. In addition, the sensitivity and specificity of FLAIR values in predicting time from symptom onset was assessed. Also,

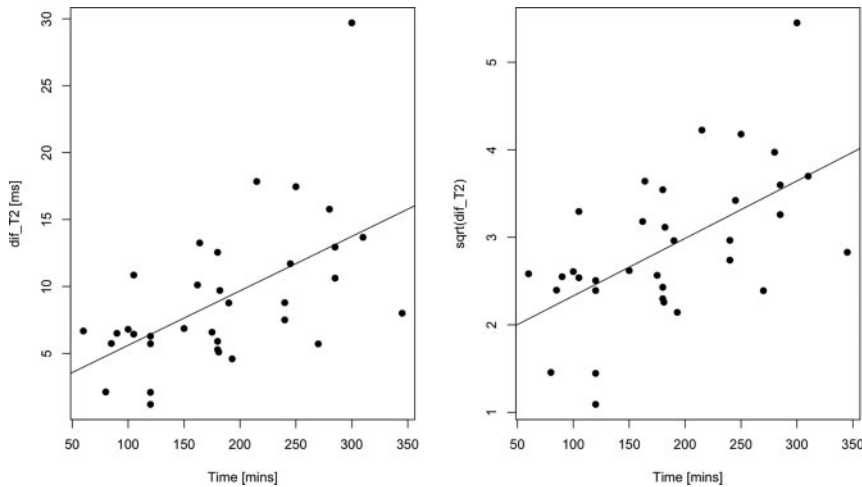


Figure 2. The left graph shows the correlation between T2 values (dif_T2 =difference between affected and unaffected side) and time from symptom onset. This plot indicated a quadratic relation between dif_T2 and time, and the variance also tended to increase with time. To reduce this dependence between T2 and time, ie, to ensure variance homogeneity and to obtain a linear relation, we transformed T2 values using the square root of dif_T2 [$\text{sqrt}(\text{dif_T2})$], shown on the right.

the accuracy for visual assessment of FLAIR lesions and dif_T2 values to predict a time from symptom onset <3 hours was computed. Finally, the predictive performance was compared between dif_T2 and ADC in terms of the area under the receiver operating characteristic curve, measuring the probability of correct ranking.

Results

The mean patient age was 68 ± 10 years (mean \pm SD), and ages ranged from 44 to 89 years. In 18 patients the right hemisphere was affected and in 18 patients the left hemisphere was affected. No FLAIR lesion was visible in 13 (36.1%) patients, whereas a visible FLAIR lesion was found in 23 (63.9%) patients. Patients with visible FLAIR lesions showed significantly higher dif_T2 values than patients without a visible lesion in FLAIR images (mean, 10.80 ms vs 4.29 ms; $P < 0.001$).

We found a significant correlation between dif_T2 and time from symptom onset ($R = 0.497$; $P = 0.002$). A plot of time vs dif_T2 , however, indicates an increase in variation with time from onset, as well as a slight quadratic trend. To reduce variance heterogeneity and to linearize the relation, we transformed T2 values using the square root of dif_T2 (Figure 2). For any further analysis, we only included patients with increased T2 values in the affected hemisphere in comparison to normal values measured on the unaffected side (2 patients were excluded for this analysis). This transformation resulted in a higher correlation between the square root of dif_T2 ($\text{sqrt}(\text{dif_T2})$) and time from symptom onset ($R = 0.580$; $P < 0.001$). Analogously, we found a significant correlation between ADC values measured in the thresholded ROI in the affected hemisphere and time from symptom onset ($R = -0.469$; $P < 0.004$).

There was no significant correlation between dif_ADC and time from symptom onset ($R = 0.301$; $P = 0.074$). Mean absolute values and SD for T2 values measured in the affected and unaffected hemisphere were 113.80 ± 11.67 ms (mean \pm SD) and 105.10 ± 9.79 ms, respectively. Differences of T2 values between affected and unaffected side were calculated (dif_T2). Mean and SD for dif_T2 were 8.45 ± 5.95 ms (mean \pm SD). We also found a significant correlation between $\text{sqrt}(\text{dif_T2})$ values and corresponding ADC values measured in the affected hemisphere ($R = -0.581$; $P < 0.001$).

The sensitivity and specificity of FLAIR for predicting time from symptom onset <3 hours was 0.824 (95% CI, 0.566–0.962) and 0.526 (95% CI, 0.289–0.756), respectively. The accuracy for visual assessment of FLAIR lesions to predict a time from symptom onset <3 hours was 0.676. In comparison, the maximum accuracy of square root of T2 to predict a time from symptom onset <3 hours was 0.794 (corresponding cut-off value for dif_T2 was 7.5 ms). The area under the curve for dif_T2 of 0.757 indicates that overall performance in predicting time from symptom onset is excellent compared to ADC with an area under the curve of 0.635.

Discussion

In our study we found T2 values measured in the infarct core to be strongly correlated with time from symptom onset. The accuracy of T2 values to predict a time from symptom onset <3 hours was 0.794. In comparison, the accuracy for visual assessment of FLAIR lesions to predict a time from symptom onset <3 hours was 0.676.

The decrease of the ADC indicates tissue with restricted diffusion in acute ischemic stroke. Early recanalization of the occluded artery may reverse ADC decrease and preserve tissue from final infarction. Hence, the ADC does not necessarily define the irreversibly damaged ischemic core.^{5,11,12} After experimental MCA occlusion, immediate brain tissue net water uptake is associated with a decrease in x-ray attenuation, and ischemic edema in an acute stroke can be monitored by CT.¹³

These changes display the infarct core with high specificity in early stages.¹⁴ In analogy, hyperintensities in FLAIR and T2 images are interpreted as reflecting brain edema.¹⁵

CT density is known to correlate linearly with the specific gravity of tissues,^{16,17} ie, with net water changes in ischemic brain tissue, thus describing the course of water uptake after ischemia.^{13,18} Kucinski et al¹⁹ reported a continuous linear decrease in CT density during the observation period of 6 hours in stroke patients. In line with this finding, T2 values in brain tissue were observed to be correlated with water increase in an experimental study²⁰ rendering T2 lesions equivalent of the CT signs of infarction. The time course of water uptake studied by MRI relaxation time measurements^{10,20} in the ischemic brain has been shown to yield a 2%

water increase within the first 4 hours and showed a highly linear relationship between MR-estimated brain water content.^{21,22} Hoehn-Berlage et al¹⁰ observed a continuous increase of T2 values with time in the ischemic territory after MCA occlusion in rats. Our results based on actual stroke patients are in line with these experimental predictions. We found a significant correlation between increased T2 values measured in the infarct core and time from symptom onset. Therefore, T2 values might be helpful to determine lesion age if time from symptom onset is unknown.

In the acute phase of brain ischemia, DWI is theoretically the best examination to demonstrate restricted water motion related to the cytotoxic edema,^{23,24} whereas conventional MRI including FLAIR and T2-weighted sequences are mainly sensitive to vasogenic edema observed in the subacute phase of stroke.²⁵ Theoretically, an acute infarct should give high signal, reflecting prolonged T2 relaxation attributable to increased water on conventional T2-weighted images. Nevertheless, it is often difficult to visually detect these sometimes subtle changes in signal intensity. In this study, we found a significant difference in T2 values between patients with visible and patients without visible FLAIR lesions. Lesion visibility therefore might be dependent on the amount of T2 increase, depending on the severity of edema or amount of water uptake. A T2 threshold on the general visibility of a FLAIR lesion cannot be derived from the data because the ROI does not cover the entire lesion.

A number of studies evaluated the value of FLAIR and T2-weighted images in the setting of acute stroke and also their predictive value for determining lesion age. But only a few studies have assessed the sensitivity of FLAIR sequences vs T2-weighted imaging or DWI for the detection of brain ischemia within the first 12 hours after symptom onset.^{8,26–28} Nevertheless, in line with our own observations, previous data suggest that FLAIR and T2-weighted imaging may show hyperintensities also in hyperacute cerebral infarction.¹⁵ Increased signal intensities in T2-weighted MRI are reported to appear ≈ 2 to 4 hours after cerebral ischemia and are thought to reflect irreversible tissue damage.^{15,29} In macaque monkeys subjected to MCA occlusion, increased T2 signal intensity was reported to be seen as early as 2 hours after MCA occlusion.³⁰ In another study,³¹ the evolution of acute cerebral ischemia was documented by MRI in 13 mongrel cats with occlusion of the MCA. The animals were imaged at intervals from 30 minutes to 10 days after production of the lesion. In this study, the earliest lesion was seen at 30 minutes as an area of high signal intensity on T2-weighted images. In addition, Gauvrit et al⁹ found that the sensitivity of FLAIR was significantly correlated with time interval between stroke onset and MRI acquisition. At the hyperacute period of stroke (0–6 hours), FLAIR allowed the detection of only 29% of acute ischemic strokes identified on DWI. In line with these studies, in our study FLAIR lesions could be detected as early as 90 minutes (mean, 203 minutes) after symptom onset.

To our knowledge, this is the first study to evaluate lesion age using T2 values. Establishing a method to reliably predict lesion age has practical clinical implications because it influences the interpretation of imaging when symptom onset is unclear. Moreover, new multivariate prediction methods

and thresholds for diffusion and perfusion are time-dependent.^{5,6,32} We found a higher accuracy for diffT2 values >7.5 ms to predict lesion age in comparison to binary lesion visibility in FLAIR. A reason for this observation could be that FLAIR lesions only become visible beyond a certain threshold of water uptake reflected by an increase of T2 values because visible FLAIR lesions presented significantly higher T2 values than not visible FLAIR lesions.

One limitation of this study is that the evaluation of time courses of ADC and T2 values is based on values from single time points and not on serial imaging data. Obtaining serial data in humans is difficult in the first few hours after acute stroke because of ethical implications.

In addition, limitations of the quantitative T2 values need to be addressed. In theory, the more echoes, and thus more points, for calculation of the signal intensity decay curve would be beneficial for the derivation of T2 than from triple-echo sequences. In clinical routine, though, multi-echo MR images with more echoes also require a longer repetition time. This leads to a longer MR acquisition time and higher sensitivity to artifacts from patient movement, which is most relevant in patients with acute stroke. Problems surrounding the somewhat-inaccurate determination of the time point of symptom onset also could not be ruled out. In addition, statistical testing was conducted using relative T2 and ADC values (difference to contralateral). In our opinion, this is a reasonable approach because all included patients showed ADC lesions comprising gray and white matter attributable to proximal MCA occlusion. Therefore ROI were transferred to the flipped images to take into account these regional differences.

Another limitation of this study is that for FLAIR rating, the DWI was available. Nevertheless, the DWI may act as a prompt to aid identification of more subtle enhancement on FLAIR that may otherwise have been missed. This could have an effect on sensitivity and specificity of FLAIR to predict time from symptom onset.

Summary

The application of qT2 values is feasible in routine use. The qT2 values within the region with most severe ADC decreases demonstrated a high correlation with time from onset, suggesting different pathophysiologic mechanism than ADC decrease. T2 values might be helpful to predict lesion age to support the interpretation of imaging in patients with unknown time from symptom onset. Like ischemic CT signs, distinct T2 increase could therefore serve as an indicator of severe ischemia and irreversibly damaged brain tissue, which should be subject of further evaluation. This method is likely more robust than ADC DWI or FLAIR, and could therefore be helpful to obtain a better “tissue time window”; in addition, this imaging approach may improve patient selection and subsequent efficacy of tissue plasminogen activator.

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Disclosures

None.

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