Evolution of Water Diffusion and Anisotropy in Hyperacute Stroke: Significant Correlation between Fractional Anisotropy and T2

Yelda Ozsunar*, P. Ellen Grant*, Thierry A. G. M. Huisman, Pamela W. Schaefer, Ona Wu, A. Gregory Sorensen, Walter J. Koroshetz, and R. Gilberto Gonzalez

BACKGROUND AND PURPOSE: **We hypothesized that, in acute cerebral ischemic stroke, anisotropic diffusion increases if T2 signal intensity is not substantially elevated and decreases once T2 hyperintensity becomes apparent. Our purpose was to correlate fractional anisotropy (FA) measurements with the clinical time of stroke onset, apparent diffusion coefficients (ADC), and T2 signal intensity.**

METHODS: **Tensor diffusion-weighted images (DWIs) of 25 patients were obtained within 12 hours of symptom onset. Trace DWIs, ADCs, FAs, and echo-planar T2-weighted images (T2WI) were generated. Stroke and contralateral normal volumes of interest (VOIs) were outlined on DWIs and projected onto the inherently coregistered ADC map, FA map, and echo-planar T2WI. Mean signal intensity of the ischemic and contralateral normal VOIs were compared for relatives change in ADC, FA, and signal intensity on T2WIs.**

RESULTS: **A significant negative correlation was observed between FA and T2 signal-intensity change ($r = -0.61$, $P = .00009$). A trend of correlation between FA signal intensity and time of onset were found ($r = -0.438$, $P = .025$). No significant correlation was found between ADC and FA values ($r = -0.302$, $P = .134$). The mean ADC reduction in the ipsilateral ischemic volume was 31% ± 11 compared with the contralateral normal side.**

CONCLUSION: **Change in FA is inversely correlated with T2 signal intensity and, to a lesser extent, the time of onset, but it is not well correlated with ADC values in the acute stage.**

Diffusion-weighted imaging (DWI) is a highly sensitive and specific diagnostic tool for the early identification and evaluation of ischemic stroke (1–5). Temporal changes of the apparent diffusion coefficient (ADC) in ischemic tissue have been described in both animal models and human stroke (6–13). In humans, ADC typically decreases within minutes to hours of symptom onset, with a maximal decrease at approximately 18 hours and pseudonormalization typically within 7–10 days (11–13). ADC decrease has also been correlated with T2 hyperintensity to predict irreversible tissue necrosis (2, 14–19); some authors argue that low ADC values and high T2 signal intensity appears to predict irreversible injury (18). However, no absolute ADC or T2 value threshold has been shown to predict irreversible infarction.

To investigate thresholds of irreversible infarction, some investigators have explored the use of diffusion tensor imaging (DTI) (10, 20–23). Water diffusion is significantly anisotropic in white matter compared with gray matter (24–26), and DTI is thought to depict the structural alignment and integrity of myelin fibers (27, 28). Both reduced (20) and normal-to-elevated (10, 22, 23) anisotropy have been reported in acute infarcts less than 24 hours after the onset of symptoms. Some have proposed that increased diffusion anisotropy indicates continued structural integrity and tissue salvageability (10, 20, 21) and that increased anisotropic diffusion occurs as a result of fluid shift from the extracellular space to the intracellular space without membrane rupture (10, 21). Decreased diffusion anisotropy may signify the loss of cellular integrity with irreversible cellular injury.

Received February 13, 2003; accepted after revision October 24.

Grant support from R01NS34626-07 (R.G.G.), R01CA83159-04 (R.G.G.), R01NS1285-02 (R.G.G.), K23 NS42758 (P.E.G.), P41RR14075 (P.E.G., A.G.S.), MIND Institute (P.E.G., A.G.S.), PHS R01NS038477 (O.W., A.G.S.).

From the Departments of Radiology (P.E.G., P.W.S., O.W., T.A.G.M.H., A.G.S., R.G.G.) and Neurology (W.J.K.), Massachusetts General Hospital and Harvard Medical School, Boston; the MGH-NMR Center, Charlestown, MA (P.E.G., O.W., T.A.G.M.H., A.G.S., R.G.G.); and the Department of Radiology, School of Medicine, Adnan Menderes University, Aydin, Turkey (Y.O.).

Presented in part at the annual meeting and scientific assembly of the Radiological Society of North America, 2001.

Address reprint requests to R. Gilberto Gonzalez, MD, PhD, Department of Radiology, Massachusetts General Hospital Gray 2, Rm B285 55 Fruit St, Boston, MA 02114-2696.

* First authors

We hypothesized that, in hyperacute infarcts (<12 hours from the time a patient was last witnessed to be in their usual state), anisotropic diffusion increases if T2 signal intensity is not substantially elevated and decreases once T2 hyperintensity becomes apparent. To test our hypothesis, we measured the FA of an ischemic tissue volume defined as DWI hyperintensity and compared the findings with T2 signal-intensity change. We also compared changes in FA with ADC and the age of infarct.

Methods

Patient Selection

We reviewed DTIs in all 95 patients in our stroke database with nonhemorrhagic acute ischemic stroke who were examined between August 1999, and May 2000. Only patients who also met the following inclusion criteria were included in the study: 1) MR imaging performed within 12 hours of symptom onset, with a known time of symptom onset; 2) infarct size of at least 18 mm in horizontal diameter and present on at least three contiguous, 6-mm-thick, axial sections to obtain a high accuracy of quantitative measurements and to avoid partial volume effects; 3) a unilateral embolic infarct; 4) no additional cerebral diseases and no MR imaging evidence of previous ischemic events or white matter disease; and 5) no notable asymmetric head tilting or motion artifacts that could cause difficulty in obtaining contralateral comparison and region-of-interest (ROI) measurements.

Imaging

Each patient underwent conventional MR imaging and DTI. MR examinations were performed with a 1.5-T MR machine (Signa Horizon LX; GE Medical Systems, Milwaukee, WI). DTIs were obtained by using single-shot echo-planar imaging with sampling of the entire diffusion tensor. Six high-*b*-value images corresponding to diffusion measurements in different gradient directions were acquired, followed by a single low-*b*-value image. Three signal-intensity averages were obtained to increase the signal-to-noise ratio of the images (20, 26). The low *b* value was 0 s/mm^2, and the high *b* value was 1000 s/mm^2. Axial images were acquired with the following parameters: TR/TE, 7500/75–100; field of view, 22 × 22 cm; matrix, 128 × 128 pixels; section thickness, 6 mm with a 1-mm intersection gap; and 22 axial sections. Because of the retrospective nature of this study, some patients underwent DWI with either the Stejskal-Tanner pulsed field gradient spin-echo sequence (29) or a balanced spin-echo sequence (30). The averaged DTI datasets were used to generate four image sets, including isotropic DWI, ADC, echo-planar T2-weighted (T2WI) and fractional anisotropy (FA) images. Echo-planar T2WI were acquired by averaging the signal intensities of three low-*b*-value images for each pixel. FA images were used to evaluate the degree of diffusion anisotropy. Although different techniques have been described to study anisotropic diffusion of water, the FA metric provides a superior contrast-to-noise ratio as a function of the signal-to-noise ratio (20, 21, 25). Details of the diffusion image-generation methods used in this study are similar to those described elsewhere (20).

Image Analysis

All selected studies were transferred to a personal computer for analysis with commercial software (Alice; Hayden Image Processing Group, Hayden, CO). The stroke volume of interest (VOI) was manually traced on the DWI map on a section-by-section basis so that the VOI included the entire hyperintense region. The same radiologist (Y.O.) drew all VOIs, which an experienced staff neuroradiologist (P.E.G.) checked. Subsequently, similar VOIs were obtained from the contralateral normal-appearing brain tissue, which was confirmed to be normal with follow-up CT or MR examinations and/or clinical follow-up. All selected VOIs were projected on coregistered ADC maps, FA maps, and echo-planar T2WIs, as demonstrated in Figure 1. The volume of each VOI was recorded, as was the mean signal intensity and standard deviation (SD) for ADC, FA, and echo-planar T2WI signal intensity. Mean signal intensities for each stroke VOI were divided by the signal intensity of the contralateral normal VOI to obtain relative values. With a cortical thickness of approximately 2.5 mm on MR images (31), we believed that the spatial resolution of our datasets (1.71 mm in plane × 6 mm in thickness) was insufficient to analyze cortex separate from the adjacent white matter.

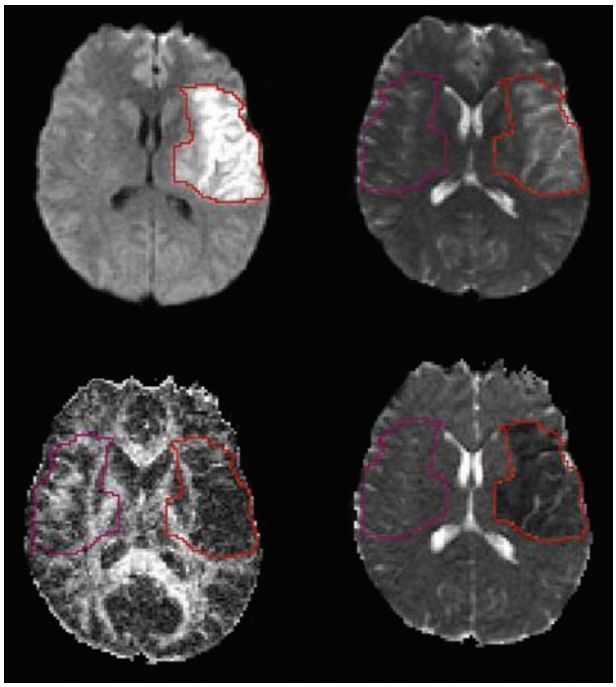

FIG 1. Tracing method for the VOIs. The infarct was outlined on isotropic DWI, section by section, by using a free-hand method. On each section, the ROI was flipped about the vertical axis and placed in the same location on contralateral normal side to obtain a mirror-image ROI. All section ROIs were combined to provide one stoke and one contralateral normal VOI for each patient. All VOIs were projected onto inherently coregistered echo-planar T2WIs, FA maps, and ADC maps. *Top left*, Isotropic DWI. *Top right*, Echo-planar T2WI. *Bottom left*, FA map. *Bottom right*, ADC map.

Statistical Analysis

Pearson correlation tests were performed to assess the correlation between the relative change in FA versus age of infarct, the relative change in FA versus the relative change in T2 signal intensity, and the percentage change in FA versus the relative change in ADC. These tests were also performed to assess correlations between relative change in ADC versus relative change in T2 signal intensity, as well as between both relative change in ADC and relative change in T2 signal intensity versus age of infarct. Statistical significance was tested by using a two-tailed Student *t* test for paired comparisons. A Wilcoxon matched-pairs signed-rank test was performed on the relative changes of the mean FA, T2 signal intensity, and ADC of ischemic tissue compared with those of contralateral normal-appearing tissue. Differences were considered statistically significant at $P < .05$.

Results in 26 patients with acute stroke

Territory	Volume (mm^3)	Interval from Onset to Imaging (hours)	Relative Change		
			FA	ADC	T2
R MCA	84	7	0.288	−0.27	0.036
L MCA	1969	4	0.281	−0.449	−0.069
L MCA	1254	6.5	0.25	−0.438	0.206
R ACA/MCA	10436	3.5	0.173	−0.251	−0.017
R MCA	2694	5	0.152	−0.365	0.174
R MCA	5682	8	0.139	−0.514	0.092
L ACA	1191	3.5	0.133	−0.323	0.099
R MCA	2217	3	0.107	−0.144	0.092
L MCA	3992	6	0.086	−0.453	0.181
L PCA	846	4.5	0.079	−0.322	0.094
R MCA	4831	1.3	0.057	−0.175	0.162
R MCA	195	6	0.056	−0.248	0.08
L MCA	6043	12	0.052	−0.55	0.099
L MCA	102	5	−0.001	−0.344	0.396
R ACA/MCA	233	9	−0.038	−0.17	0.103
R MCA	4567	9	−0.045	−0.38	0.388
L ACA/MCA	9046	3	−0.054	−0.228	0.16
R MCA	585	7	−0.066	−0.116	0.213
R MCA	1699	3.5	−0.068	−0.255	0.209
L MCA	6240	6	−0.081	−0.316	0.169
R MCA	152	3	−0.09	−0.331	0.555
L MCA	435	12	−0.116	−0.3	0.32
L MCA	3838	6	−0.134	−0.187	0.12
R MCA	883	11	−0.149	−0.423	0.449
R MCA	452	12	−0.204	−0.226	0.697
L MCA	718	11	−0.241	−0.307	0.341

Note.—FA, ADC, and T2 values were obtained from initial MR examinations and the relative values were used to express changes in FA, ADC and T2 signal. ACA indicates anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.

Results

Twenty-six of 95 patients met all the inclusion criteria. They included 13 men and 13 women with a mean age of 65.2 ± 19.7 years (range 10 – 93 years). Eleven patients underwent follow-up MR examinations within 3–13 days, 13 patients underwent follow-up CT examinations, and all patients had clinical follow-up results that confirmed infarction. The mean infarct volume was 2707 ± 2882 mm^3 (range, 84–10,436 mm^3), and the mean number of ROI measurement sections for each infarct was 7.0 ± 2.6 (range, 3–12 (Table). Three stroke patterns were identified: 1) cortex and underlying white matter (19 patients), 2) deep gray nuclei greater than white matter (five patients), and 3) predominantly white matter (two patients). Data from all three groups were combined for analysis because of the small numbers of patients with patterns 2 and 3.

Relative FA change showed a significant inverse linear correlation with relative T2 signal-intensity change, with a slope of −0.564 (r = −0.691, P = .00009) (Fig 2). Although the mean FA averaged over all infarcts (0.333 ± 0.071) was not significantly different from that in the contralateral normal brain (0.327 ± 0.057, P = .493), all nine patients with a <10% increase in T2 signal intensity had increased FA compared with FA in a similar contralateral, normal region; the mean relative FA increase was 15%

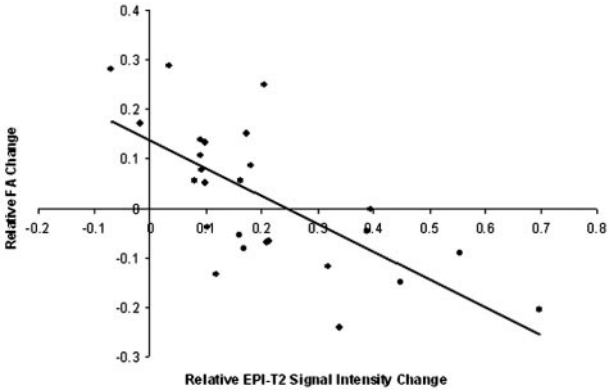

FIG 2. Graph demonstrates a highly significant inverse linear correlation between FA and T2 signal intensity (r = −0.691, P = .00009). Note that all patients with a relative increase in T2 signal intensity of < 0.10 also have increased relative FA values.

(Fig 3). This finding was statistically significant, as shown by the two-sided Wilcoxon matched-pairs signed-rank test (n = 9, P = .004). Seven patients with a 10–20% increase in T2 signal intensity in the lesion had variable FA changes. Among them, three had elevated FA, and four had decreased FA compared with FA on the contralateral normal side; the overall mean relative decrease was 0.1% and not statistically significant. All but one of 10 patients with a relative increase in T2 signal intensity of 20% or more had a decreased relative FA; the overall mean relative FA decrease was 7% (Fig 4) and not statistically significant.

A significant inverse linear correlation was also found between relative FA change and the time from symptom onset, with a slope of −0.020 (r = −0.438, P = .025). For all patients, the mean time between the onset of symptoms and initial MR examination was 6.5 ± 3.2 hours (range, 1.25–12 hours). The mean time between symptom onset and MR examination in patients who had elevated relative FA values was 5.4 ± 2.7 hours (range, 1.25–12 hours); and the time interval for those who had reduced relative FA values was 7.5 ± 3.4 hours (range, 3.5–12 hours). However, differences for the two groups were not significant.

Relative FA change was not significantly correlated with relative ADC change for whole group of patients (r = −0.302, P = .134) or the subgroups based on T2 signal-intensity change. There was no correlation between relative ADC change and relative T2 change (r = 0.009, P = .966). There was also no significant correlation between relative ADC change and time from symptom onset (r = −0.291, P = .150). However, a significant linear correlation between relative T2 change and time from symptom onset was observed, with a slope of 0.023 (r = 0.409, P = .038).

The mean ADC value for all infarcts (669 ± 139 × 10^{-6} mm^2/s) was significantly decreased compared with the mean for the corresponding normal, contralateral brain (975 ± 141 × 10^{-6} mm^2/s, P = 8.8 × 10^{-6}). The mean T2 signal intensity over all infarcts (770 ±164) was significantly increased compared with contralateral normal brain (644 ± 137, P = 1.4 ×

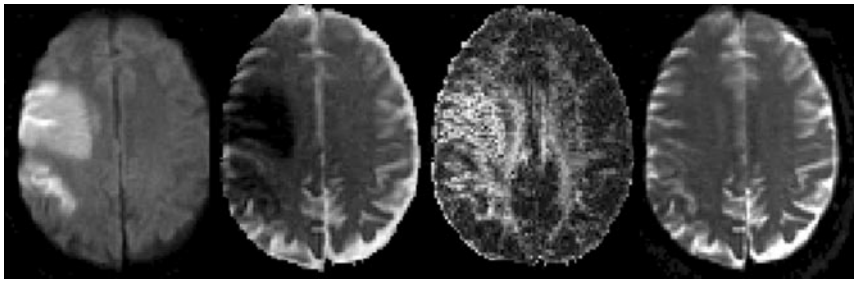

FIG 3. Images in a 59-year-old man who underwent an MR examination 8 hours after the onset of symptoms. An acute infarction in the right middle cerebral artery distribution was observed; this was due to thromboembolism. The FA map demonstrates increased signal intensity, whereas the echo-planar T2WI shows no hyperintensity. This is an example of how increased FA was associated with minimal T2 change. *Far left*, Isotropic DWI. *Middle left*, ADC map. *Middle right*, FA map. *Far right*, echo-planar T2WI.

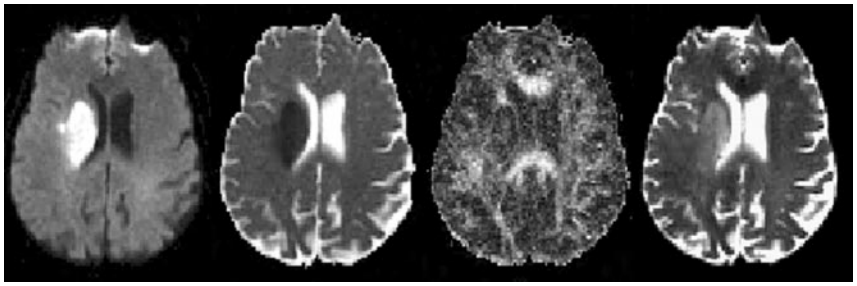

FIG 4. Images in a 71-year-old woman who presented with slurred speech and left-sided weakness and who was imaged 11 hours after the onset of these symptoms. DWI demonstrates an acute infarction involving the right MCA territory. Decreased FA (*far left*) and increased T2 signal intensity (*far right*) was observed in the right corona radiata. This is an example of how decreased FA was associated with increased T2 signal intensity. *Far left*, Isotropic DWI. *Middle left*, ADC map. *Middle right*, FA map *Far right*, Echo-planar T2WI.

10^{-5}). The mean ADC for infarcts remained significantly decreased and the mean T2 signal intensity remained significantly increased compared with contralateral normal brain when they were split into three grouped according to T2 changes of $<10\%$, 10%–20%, and $>20\%$.

Discussion

In this study of 26 patients imaged within 12 hours after the onset of stroke symptoms, we found a significantly negative correlation between relative FA and T2 signal-intensity change. Additionally, FA was significantly elevated in ischemic lesions with a $<10\%$ increase in T2 signal intensity. We also identified a significant negative correlation between FA and time from stroke onset and a significant positive correlation between T2 signal-intensity change and time from stroke onset. In this hyperacute phase, ADC appeared to be completely independent of T2, and no significant correlations were found between ADC change and either FA or time from stroke onset. These observations suggest that FA changes occur in the hyperacute phase of acute infarcts when there is no significant change in ADC and that FA measurements may provide important information, complementary to ADC values that may be useful in the management of hyperacute stroke.

The negative correlation between FA and time from stroke onset is consistent with results showing early increases in anisotropy that decreased over time. In that study, Yang et al (10) described three different, temporally related phases in the relationship between anisotropy, ADC, and stage of the infarct. The first phase was characterized by an increase in anisotropy and a reduction in ADC; the second, by a reduction in anisotropy and a reduction in ADC; and the third, by a reduction in anisotropy and an elevation in ADC. In large lesions, the transition from the first phase to the second phase could occur within the first 24 hours. Our findings are consistent with this description; infarcts with elevated FA had a mean time from symptom onset of 5.4 hours compared with 7.5 hours for those with decreased FA. We extend these previous observations by finding a significant inverse correlation between FA and T2 signal-intensity change in the hyperacute phase. In the first 12 hours, this correlation was stronger than that between FA and time from symptom onset.

The complete lack of correlation between ADC and T2 in the first 12 hours is consistent with previously published data showing that, within the first 6 hours, decreased ADC is sensitive and specific for the diagnosis of acute stroke, whereas increased T2 signal intensity is not (32). The trend toward an inverse correlation between FA and ADC is also consistent with results of prior studies (10, 33). The lack of statistical significance in our study probably occurred because our analysis was limited to the <12-hour time period, whereas these other studies followed the evolution of FA for many days, with typically only one time point of <12 hours.

The observation of a relationship between FA and T2 suggests a new understanding of the biophysical basis of the observed changes in water diffusion during hyperacute ischemia. The changes in the FA of water are not well understood; indeed, uncertainty also persists as to the mechanisms underlying the overall decrease of water diffusion in acute stroke. Several potential mechanisms have been proposed to explain the decreased ADC in acute stroke: 1) shift of water from the extracellular space to the intracellular space resulting in a) increased tortuousity in the shrunken extracellular space and b) restriction of movement in the shrunken extracellular space; 2) reduced water permeability across the membranes due to ionic pump failure, and/or 3) increased viscosity in the intracellular space due to macromolecular

structural protein breakdown or 4) reduced energy-dependent transport mechanisms inside the cell.

Each of these mechanisms has also been invoked to explain the increased anisotropy water diffusion that is observed early during ischemia (10, 20–23, 25). However, the striking temporal differences between the changes in ADC and FA suggest some divergence in the underlying mechanisms that may be exploited for clinical purposes. In particular, FA measures may be sensitive to biophysical changes that are not detected by using the ADC.

We speculate that the high correlation between a decrease in FA and an increase in T2 signal intensity suggests a biophysical relationship between the two measurements. Increased T2 signal intensity may be due to several causes, generally an increase in T2 signal intensity implies prolongation of T2 relaxation. Factors that influence the T2 relaxation time include the temperature, viscosity, and water content of the tissues being measured. Temperature effects are unlikely to be responsible for the changes in the T2 relaxation observed in ischemia because a substantial temperature increase is required. A decrease in the viscosity of the microenvironment might explain prolongation of T2. However, current understanding of the diffusion of water in ischemic stroke suggests increased viscosity in ischemic tissue (34–37). Therefore, the most likely explanation is an increase in water content. This is consistent with the source of T2 prolongation associated with most neuropathologies including most neoplasms, infections, inflammatory processes, and gliosis.

The earliest well-documented T2 effect in ischemia is a decrease in this relaxation time. Using animal models, high field strength, and high temporal resolution, Grohn and collaborators (38, 39) have convincingly demonstrated that this observation is due to a blood oxygen level–dependent (BOLD) effect directly related to decreased perfusion. Grohn et al suggest that a reduction in T2 might indicate a period of ischemia in which tissue injury is fully reversible (38, 39). We observed decreased T2 in two patients (Table, rows 2 and 4). Both of them had considerably increased FAs compared with values on the contralateral normal side.

If increasing water content is responsible for the T2 prolongation observed in acute stroke, it might also explain the evolution of FA from increased to decreased anisotropy. Of the various other mechanisms proposed to explain the observed changes in FA, none are consistent with both persistently depressed ADC and a relatively rapid change in tissue water content resulting in decreased FA and increased T2 signal intensity. In explaining the observations, it is crucial to define the space in which the increased water resides. During ischemia, there is an initial increase in the intracellular water content (cytotoxic edema of early necrosis) followed by increase of water in the extracellular compartment primarily as a result of vasogenic edema (40).

A speculative but reasonable hypothesis to explain our observation is the following. In the earliest stages of severe ischemia, there is cytotoxic edema with resultant shift of water in the extracellular space to the intracellular space. In this scenario, the mechanisms responsible for the initial decrease in ADC also result in an increase in FA. With progression of the ischemic insult, extracellular water begins to accumulate, increasing the extracellular volume and, as a result, decreasing the observed FA while increasing the observed T2 signal intensity. If the FA measured by MR imaging results from an averaging of two or more populations of differentially anisotropic water pools, an expanded version of our hypothesis would be needed to explain our observations. In the simplest case, intracellular water would retain a high anisotropic character while the extracellular water would be or become less anisotropic. As a result, the initial shift of fluid from the extracellular to intracellular space would increase FA due to an increased proportion in the more anisotropic intracellular compartment and an increase in the FA of extracellular apparent diffusion. With increasing extracellular fluid, the fraction of extracellular water would increase relative to intracellular water, decreasing the relative amount of water in the more anisotropic intracellular compartment while increasing the amount of fluid and decreasing the mean FA value in the extracellular space. Thus, the overall result would be a decrease in the observed FA. An increase in ischemic tissue water is known to increase temporally after the onset of ischemia and has been invoked to explain the prolongation of T2 as seen in ischemic stroke, both clinically and in animal models (40–42). This mechanism would explain persistence of the reduced ADC, the increasing T2 signal intensity, and the initial increase followed by a decrease in the FA, as well as the correlation between FA and T2. Other factors that may contribute to decreased FA over time include loss of axonal transport, loss of cellular integrity (especially of the myelin sheath), and decreases in interstitial fluid flow. This hypothesis could be tested in humans if proton density, a measure of water content, were quantified, something we hope to do in future studies. Our speculations are qualified by the reality that only a fraction of the true water content is visible with nuclear MR studies, and therefore, the increase in water that might be present could actually be only a shift in the visibility of the water rather than the actual amount of water in a given voxel.

Regardless of the precise biophysical mechanisms responsible for the observed changes in FA in acute stroke, measurements of this physical quantity may be useful in more precisely characterizing the stage of ischemia. The combination of FA with T2 signal intensity and ADC measurements may provide a means for developing a biophysically based staging procedure. The most interesting potential use of this combined biophysical information is in differentiating tissue that is irreversibly injured from potentially viable tissue. If successfully implemented, such a technique would have high utility in the management of acute stroke, allowing for treatment based on the more meaningful physiologic stage of each individual in-

farct instead of treatment based on the notoriously inaccurate apparent age of the infarct derived from the clinical history.

This study has certain limitations. Most importantly, the patients were highly selected and restricted to those with relatively large infarcts. Therefore, our observations might not be relevant to small embolic or lacunar infarcts. In addition, we focused on the earliest stages of ischemia (<12 hours) and therefore did not evaluate the relationship between FA and T2 beyond this period. A better understanding of the mechanisms responsible for the observations described here would be best explored by using experimental models. Because of the spatial resolution and low number of patients with isolated infarcts in the deep gray nuclei, we were not able to assess differences in gray matter and white matter.

Another limitation was that the DTI sequence did not compensate for all possible sources of error, including eddy-current effects. As a result, the signal-to-noise ratio and accuracy of our results could have been improved with additional postprocessing. However, given the quality of the FA images (as can be observed in Figs 3 and 4) the inclusion of only large areas of infarction and the use of FA ratios instead of absolute FA values minimized the effects of these errors and gave us valid results to within the errors reported.

Conclusion

We observed a significant correlation between the evolution of FA and T2 signal intensity in ischemic brain tissue in patients imaged within 12 hours of the onset of stroke symptoms. One possible explanation for these observations is an initial decrease followed by a progressive increase in the extracellular water content of ischemic brain tissue. Measurements of the diffusion anisotropy of water may thus provide a means to more precisely characterize the biophysical status of ischemic brain tissue and become an important tool in the management of acute stroke.

Acknowledgment

As this was a clinical research project, we are indebted to the rest of the clinical neuroradiology staff and the neurology stroke team for their support.

References

1. Jones SC, Perez-Trepichio AD, Xue M, Furlan AJ, Awad IA. **Magnetic resonance diffusion-weighted imaging: sensitivity and apparent diffusion constant in stroke.** *Acta Neurochir Suppl (Wien)* 1994;60:207–210
2. van Everdingen KJ, van der Grond J, Kappelle LJ, Ramos LM, Mali WP. **Diffusion-weighted magnetic resonance imaging in acute stroke.** *Stroke* 1998;29:1783–1790
3. LovbladKO, Laubach HJ, Baird AE, et al. **Clinical experience with diffusion-weighted MR in patients with acute stroke.** *AJNR Am J Neuroradiol* 1998;19:1061–1066
4. Gonzalez RG, Schaefer PW, Buonanno FS, et al. **Diffusion-weighted MR imaging: diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset.** *Radiology* 1999;210:155–162
5. Ricci PE, Burdette JH, Elster AD, Reboussin DM. **A comparison of fast spin-echo, fluid-attenuated inversion-recovery, and diffusion-weighted MR imaging in the first 10 days after cerebral infarction.** *AJNR Am J Neuroradiol* 1999;20:1535–1542
6. Moseley ME, Kucharczyk J, Mintorovitch J, et al. **Diffusion-weighted MR imaging of acute stroke: correlation with T2-weighted and magnetic susceptibility-enhanced MR imaging in cats.** *AJNR Am J Neuroradiol* 1990;11:423–429
7. Hoehn-Berlage M, Norris DG, Kohno K, Mies G, Leibfritz D, Hossmann KA. **Evolution of regional changes in apparent diffusion coefficient during focal ischemia of rat brain: the relationship of quantitative diffusion NMR imaging to reduction in cerebral blood flow and metabolic disturbances.** *J Cereb Blood Flow Metab* 1995; 15:1002–1011
8. Warach S, Boska M, Welch KM. **Pitfalls and potential of clinical diffusion-weighted MR imaging in acute stroke.** *Stroke* 1997;28: 481–502
9. Baird AE, Warach S. **Magnetic resonance imaging of acute stroke.** *J Cereb Blood Flow Metab* 1998;18:583–609
10. Yang Q, Tress BM, Barber PA, et al. **Serial study of apparent diffusion coefficient and anisotropy in patients with acute stroke.** *Stroke* 1999;30:2382–2390
11. Schlaug G, Siewert B, Benfield A, Edelman RR, Warach S. **Time course of the apparent diffusion coefficient (ADC) abnormality in human stroke.** *Neurology* 1997;49:113–119
12. Lansberg MG, Thijs VN, O'Brien MW, et al. **Evolution of apparent diffusion coefficient, diffusion-weighted, and T2-weighted signal intensity of acute stroke.** *AJNR Am J Neuroradiol* 2001;22:637–644
13. Copen WA, Schwamm LH, Gonzalez RG, et al. **Ischemic stroke: effects of etiology and patient age on the time course of the core apparent diffusion coefficient.** *Radiology* 2001;221:27–34
14. Mintorovitch J, Moseley ME, Chileuitt L, Shimizu H, Cohen Y, Weinstein PR. **Comparison of diffusion- and T2-weighted MRI for the early detection of cerebral ischemia and reperfusion in rats.** *Magn Reson Med* 1991;18:39–50
15. van Bruggen N, Cullen BM, King MD. **T2- and diffusion-weighted magnetic resonance imaging of a focal ischemic lesion in rat brain.** *Stroke* 1992;23:576–582
16. Pierpaoli C, Righini A, Linfante I, Tao-Cheng JH, Alger JR, Di Chiro G. **Histopathologic correlates of abnormal water diffusion in cerebral ischemia: diffusion-weighted MR imaging and light and electron microscopic study.** *Radiology* 1993;189:439–448
17. Loubinoux I, Volk A, Borredon J, et al. **Spreading of vasogenic edema and cytotoxic edema assessed by quantitative diffusion and T2 magnetic resonance imaging.** *Stroke* 1997;28:419–427
18. Welch KM, Windham J, Knight RA, et al. **A model to predict the histopathology of human stroke using diffusion and T2-weighted magnetic resonance imaging.** *Stroke* 1995;26:1983–1989
19. Darby DG, Barber PA, Gerraty RP, et al. **Pathophysiological topography of acute ischemia by combined diffusion-weighted and perfusion MRI.** *Stroke* 1999;30:2043–2052
20. Sorensen AG, Wu O, Copen WA, et al. **Human acute cerebral ischemia: detection of changes in water diffusion anisotropy by using MR imaging.** *Radiology* 1999;212:785–792
21. Zelaya F, Flood N, Chalk JB, et al. **An evaluation of the time dependence of the anisotropy of the water diffusion tensor in acute human ischemia.** *Magn Reson Imaging* 1999;17:331–348
22. Kajima T, Azuma K, Itoh K, et al. **Diffusion anisotropy of cerebral ischaemia.** *Acta Neurochir Suppl (Wien)* 1994;60:216–219
23. Armitage PA, Bastin ME, Marshall I, Wardlaw JM, Cannon J. **Diffusion anisotropy measurements in ischaemic stroke of the human brain.** *MAGMA* 1998;6:28–36
24. Le Bihan D, Turner R, Douek P. **Is water diffusion restricted in human brain white matter? An echo-planar NMR imaging study.** *Neuroreport* 1993;4:887–890
25. Pierpaoli C, Basser PJ. **Toward a quantitative assessment of diffusion anisotropy.** *Magn Reson Med* 1996;36:893–906
26. Basser PJ. **Inferring microstructural features and the physiological state of tissues from diffusion-weighted images.** *NMR Biomed* 1995; 8:333–344
27. Douek P, Turner R, Pekar J, Patronas N, Le Bihan D. **MR color mapping of myelin fiber orientation.** *J Comput Assist Tomogr* 1991; 15:923–929
28. Coremans J, Luypaert R, Verhelle F, Stadnik T, Osteaux M. **A method for myelin fiber orientation mapping using diffusion-weighted MR images.** *Magn Reson Imaging* 1994;12:443–454
29. Stejskal EO, Tanner JE. **Spin diffusion measurements: spin echoes in the presence of a time-dependent field gradient.** *J Chem Phys* 1965;42:288–292

30. Reese TG, Weisskoff RM, Wedeen VJ. **Diffusion NMR facilitated by a refocused eddy-current EPI pulse sequence.** In: *Proceedings of the ISMRM, Sixth Scientific Meeting.* Sydney: ISMRM; 1998:663
31. Fischl B, Dale AM, **Measuring the thickness of the human cerebral cortex from magnetic resonance images.** *Proc Natl Acad Sci U S A* 2000;97:11050–11055
32. Gonzalez RG, Schaefer PW, Buonanno FS. **Diffusion-weighted MR imaging: diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset.** *Radiology* 1999;210:155–162
33. Sorensen AG, Wu O, Copen WA. **Human acute cerebral ischemia: detection of changes in water diffusion anisotropy by using MR imaging.** *Radiology* 1999;212:785–792
34. Harada M, Uno M, Hong F, Hisaoka S, Nishitani H, Matsuda T. **Diffusion-weighted in vivo localized proton MR spectroscopy of human cerebral ischemia and tumor.** *NMR Biomed* 2002;15:69–74
35. Wick M, Nagatomo Y, Prielmeier F, Frahm J **Alteration of intracellular metabolite diffusion in rat brain in vivo during ischemia and reperfusion.** *Stroke* 1995;26:1930–1933, discussion 1934
36. van der Toorn A, Dijkhuizen RM, Tulleken CA, Nicolay K. **Diffusion of metabolites in normal and ischemic rat brain measured by localized 1H MRS.** *Magn Reson Med* 1996;36:914–922
37. Duong TQ, Ackerman JJ, Ying HS, Neil JJ. **Evaluation of extra- and intracellular apparent diffusion in normal and globally ischemic rat brain via 19F NMR.** *Magn Reson Med* 1998;40:1–13
38. Grohn OH, Kettunen MI, Penttonen M, Oja JM, van Zijl PC, Kauppinen RA. **Graded reduction of cerebral blood flow in rat as detected by the nuclear magnetic resonance relaxation time T2: a theoretical and experimental approach.** *J Cereb Blood Flow Metab* 2000;20:316–326
39. Grohn OH, Lukkarinen JA, Oja JM, et al. **Noninvasive detection of cerebral hypoperfusion and reversible ischemia from reductions in themagnetic resonance imaging relaxation time, T2.** *J Cereb Blood Flow Metab* 1998;18:911–920
40. Kim HJ, Lee CH, Lee SH, et al. **Early development of vasogenic edema in experimental cerebral fat embolism in cats: correlation with mri and electron microscopic findings.** *Invest Radiol* 2001;36: 460–469
41. Neumann-Haefelin T, Kastrup A, de Crespigny A. **Serial MRI after transient focal cerebral ischemia in rats: dynamics of tissue injury, blood-brain barrier damage, and edema formation**. *Stroke* 2000;31: 1965–1972, discussion 1972–1973
42. Brant-Zawadzki M, Weinstein P, Bartkowski H, Moseley M. **MR imaging and spectroscopy in clinical and experimental cerebral ischemia.** *AJR Am J Roentgenol* 1987;148:579–588