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MR Diffusion Imaging of Cerebral Infarction in Humans

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Purpose: MR diffusion imaging was performed to investigate changes in water diffusion in patients with cerebral infarction. **Methods:** Diffusion maps of the apparent diffusion coefficient (ADC) were created to show local water mobility in the brain tissue in 15 patients. These ADC maps were compared with conventional T2-weighted images. **Results:** Distinct subregions with different water diffusions were detected, even when the infarcted area appeared homogeneous on a T2-weighted image. The results also show that stroke lesions of the same age can have very different water diffusions. A trend towards an increasing diffusion coefficient in a lesion during the first several days following an acute event was observed in a group of patients imaged at multiple timepoints. **Conclusion:** The measurement of diffusion coefficients in vivo now offers an opportunity for greater understanding of the biophysical changes that occur during the evolution of infarction in humans.

Index terms: Brain, infarction; Magnetic resonance, diffusion weighted scanning

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The measurement of the proton self-diffusion coefficient by magnetic resonance (MR) is based on the loss of phase coherence as molecules diffuse along an applied magnetic field gradient (1–4). When measured in tissues, the apparent diffusion coefficient (ADC) reflects the local water mobility in vivo. In recent years, MR imaging has been combined with diffusion measurements to provide a two-dimensional mapping of the diffusion coefficient in vivo (5–8). The resulting map depicts the measured ADC at each spatial location. MR diffusion imaging has been used to study water mobility in the normal brain (7–9), directional dependency of water diffusion in the white matter (9–11), restricted diffusion in tissues (12–15), differentiation between cysts and epidermoid tumors (16), and patients with stroke and multiple sclerosis (7, 17).

Moseley et al, in their recent study of an acute stroke model in cats, demonstrated that lesions can be detected in diffusion-weighted images as early as 45 minutes after middle cerebral artery occlusion, whereas conventional T2-weighted images show no changes even 2–3 hours following the onset of stroke (18). In addition, the signal contrast between the lesion and the normal contralateral region is significantly higher in diffusion-weighted images than in T2-weighted images. These two results suggest that diffusion imaging may be more sensitive than conventional MR imaging in detecting early stages of stroke. Earlier detection of the lesion in diffusion-weighted images than in T2-weighted is also suggested in a study of acute stroke (19).

The purpose of this study was to determine the change in water mobility in humans with subacute and chronic stroke. We did diffusion imaging of stroke patients, generated ADC maps, and compared these with conventional T2-weighted images. In this paper, we report our results from a pilot study of 15 patients.

Methods

All of the 15 patients studied had well-described clinical stroke syndrome and had CT evidence of focal lesions

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consistent with ischemic infarct. Patients ranged from 22 to 70 years of age. The studies were approved by the Subcommittee on Human Research.

This stroke study was performed after optimizing the experimental parameters on a 0.6 T Technicare Teslacon MR whole body Imager (Solon, Ohio). In a previous paper (10), we reported the importance of the choice of the timing-gradient parameters and cardiac gating in diffusion imaging. In addition to technique optimization, diffusion imaging of 18 volunteers was performed to establish the ADC value of normal grey and white matter in the human brain.

In this stroke study, spin-echo T2-weighted, 2000/60,120/2 (TR/TE/excitations), axial multisection images were first acquired to localize the lesion and to provide diagnostic comparison (section thickness = 10 mm, matrix = 256 × 128, field of view = 20 cm). To assist stroke patients in minimizing head motion throughout imaging, each patient was fitted with a personal head holder with curable and expandable foam shaped to the individual's head contour (Smithers Hospital Supplies, Ohio). We found this to be important, since stroke patients often have difficulty keeping the head still and any external motion contributes to an increase in the measured ADC.

Diffusion imaging was performed using a 0.6 T Technicare whole body imager with a receive-only head coil. To minimize the effects of cardiac pulsation, data was acquired during diastole by electrocardiogram triggering at three-quarters of the cardiac cycle after the R wave (scan time = 8.5 min for a RR interval of 1 sec, matrix = 128 × 64, section thickness = 10 mm, field of view = 20 cm). Diffusion-weighting was obtained by varying the duration of the x-read gradients (g = 0.4 G/cm) before and after the 180° pulse in a conventional spin-echo sequence, 1 RR interval/180/8 (TR/TE/excitation). The pulse sequence has been described in detail elsewhere (10). The b value is commonly used to describe the amount of diffusion sensitivity of the sequence (8). A baseline image with minimum diffusion-weighting was first acquired by using a small b value (b = 6 sec/mm^2). Then, a second diffusion-weighted image was acquired with extended diffusion gradients to obtain a larger b value (b = 400 sec/mm^2). The same TR and TE were used to produce the same amount of T1 and T2 weighting in the images so that the only difference in signal intensity between the images is due to diffusion.

The ADC map, which shows the diffusion coefficient measured at each pixel, is then generated based on the signal change between the two images acquired with different gradient strengths (7, 10). A minimum of two diffusion-weighted images are needed to calculate the ADC. Whereas the signal intensity in the diffusion-weighted image is still affected by T1 and T2 relaxation times, the ADC map is not. The ADC map directly represents water diffusion at each pixel in the image without the influence from T1 and T2 relaxation times. It is obtained by taking the logarithmic ratio of the signal intensity at each pixel according to the following equation:

$$ADC = \ln(S1/S2)/(b2 - b1)$$

where S1 and S2 are the signal intensity of the baseline and diffusion-weighted images, respectively, and b1 and b2 are the b values for the corresponding pulse sequences. Note that a simple subtraction image is not a direct indicator of water diffusion because it still contains T1, T2, and proton-density effects. The regions of interest were picked according to the lesion shown by the T2-weighted and diffusion-weighted image. The regions shown by the two images were compared to avoid inclusion of adjacent cerebral spinal fluid (CSF).

Results

Water diffusion causes a decrease in signal intensity in the diffusion-weighted image. In Figure 1A, a large region in the left putamen and insular area shows hyperintensity in the T2-weighted image. In the diffusion-weighted image (Fig. 1B), tissues with high ADC show the greatest loss in signal intensity compared to the baseline image. Typically, CSF appears dark due to the high ADC. Thus, CSF can be distinguished from the lesion. The diffusion-weighted image shows increased CSF space, consistent with encephalomalacia.

In the ADC map, tissues with high water mobility appear bright. The ADC map shows the calculated apparent diffusion coefficient at each pixel. Because T1 and T2 relaxation effects are canceled out when the logarithmic ratio of S1/S2 is taken, the ADC map is not influenced by T1 and T2 relaxation times. Figure 1C shows the ADC map. Note that tissues with high diffusion appear bright in the ADC map but dark in the diffusion-weighted image. There is indication that the insular area has increased ADC relative to normal brain tissue. This may reflect a true increase in water mobility or a partial volume effect with overlying CSF.

Our results also demonstrate that diffusion imaging can provide information not shown by conventional T2-weighted images. A comparison of the T2-weighted image (Fig. 2A) and the ADC map (Fig. 2B) shows that within an infarct with uniform hyper-intensity in a conventional T2-weighted image, diffusion imaging reveals subregions with varying amounts of water diffusion. Certain subregions have increased diffusion, whereas others have decreased diffusion relative to normal brain tissue. Table 1 shows the measured diffusion coefficient for all the patients studied. The average ADC of the infarcted regions is tabulated and the age of the stroke is provided. The standard deviation given in the table actually encompasses the heterogeneity of water diffusion

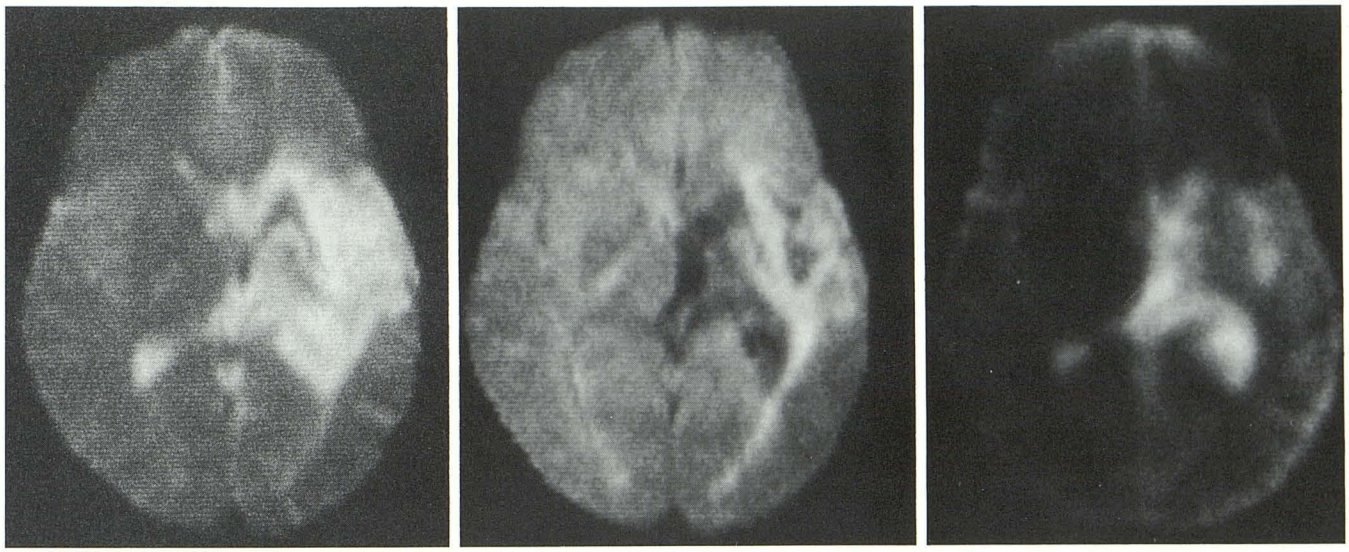

Fig. 1. A 22-year-old stroke patient with marked subcortical and cortical infarction was studied 4 years after the initial ischemic attack. The T2-weighted image (*A*) shows hyperintensity in a large region in the left putamen and insula area. In the diffusion-weighted image (*B*), tissues with high ADC have greater signal attenuation than tissues with low ADC. The large region with increased T2 is now resolved into subregions with high diffusion (that appear dark) and areas with lower diffusion (that appear bright). The lesion can be separated from the CSF in the ventricles, since the CSF now becomes dark due to diffusion-related signal attenuation. Within the lesion, there are two small areas that also show significant signal attenuation. In the calculated ADC map (*C*), bright areas now correspond to regions with high diffusion. It can be seen that CSF has a high ADC due to flow, while the lesion has increased ADC relative to normal brain tissue.

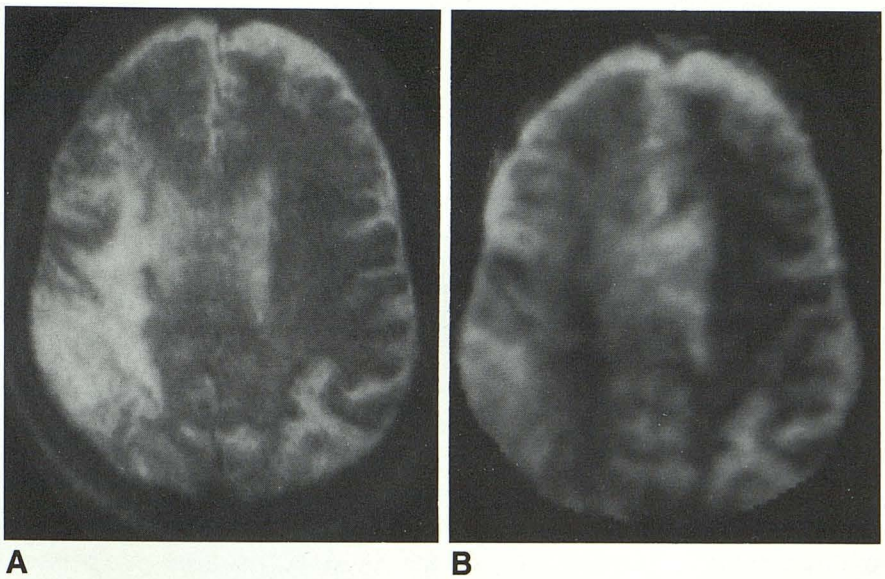

Fig. 2. A 70-year-old patient with embolic infarction of the right middle cerebral artery was studied at 8 weeks after the ischemic attack. A comparison of the T2-weighted image (*A*) and the ADC map (*B*) shows that, within an infarct with uniform hyper-intensity in a conventional T2-weighted image, diffusion imaging reveals subregions with varying amounts of water diffusion. Certain subregions have increased diffusion, while others have decreased diffusion relative to normal brain tissue.

within the lesion, because a region with elevated T2 can contain subregions with different ADC values.

For comparison, we found from our previous study of normal volunteers that in the normal brain, CSF has the highest diffusion coefficient ($D = 3.5 \times 10^{-5} \pm 0.7 \times 10^{-5}$ cm^2/sec), followed by gray matter ($D = 1.0 \times 10^{-5} \pm 0.3 \times 10^{-5}$ cm^2/sec) and then white matter ($D = 0.7 \times 10^{-5} \pm 0.2 \times 10^{-5}$ cm^2/sec) (10). Note that the standard deviations provided here include the natural variability of ADC among the 18 normal volunteers. Furthermore, the large standard deviation observed in CSF is likely due to its pulsatile motion.

Across the patient group, lesions of the same age were observed to have widely varying diffusion coefficients. Given this variation, we found

no statistically significant correlation between measured ADC and the age of the infarct among different patients. This is not surprising because ADC reflects the translational motion of water and this depends on the extent of tissue damage and the amount of edema that results. Within the small subset of patients imaged at multiple time points, however, we noted a trend towards an increasing diffusion coefficient for individual patients (patients 1–3) during the first several days following the acute event.

Discussion

Cerebral infarction exhibits a wide spectrum of etiologies and a complex evolution. Although MR imaging has proven useful for the evaluation of stroke in both research and clinical settings, its ability to characterize different physiologic events in tissues is still limited. In particular, relaxation time measurements in conventional studies cannot differentiate infarcted regions from ischemic regions that will become infarcted, or from ischemic regions that are likely to recover when blood flow is restored. These different regions cannot be distinguished from one another based solely on relaxation times because ischemic, edematous, and infarcted tissue all have elevated T1 and T2 relaxation times. Moreover, there is significant overlap in relaxation times found in different pathologies. This causes difficulties in tissue characterization. The overlap in T1 and T2 is difficult to resolve because the relaxation times are functions of complex molecular motions, including spin tumbling, rotations, and spin exchanges.

In a previous study by Moseley et al (18), decreased ADC was observed prior to changes in T1 and T2 relaxation times during the first 6 hours following experimental middle cerebral artery occlusion. Several hypotheses have been suggested to account for these changes, including temperature changes, diminished blood vessel pulsation, exchange of interstitial with intracellular water, decreased bulk intracellular transport, and blood deoxygenation (20) (personal communication from ME Moseley). The exact mechanism is still not known.

We observed an increase in ADC in most patients with subacute and chronic stroke (see Table 1), which is different from Moseley's observations of acute stroke in an animal model. Furthermore, in the group of subacute stroke patients with repeated diffusion measurements over time (starting from 10 hours on), we observed an increase in ADC as time progressed (see Table 1). This elevation in ADC can be explained by increasing vasogenic edema, which is known to develop hours or days after an ischemic insult (21). In patients with remote infarcts (patients 14 and 15), the elevated ADC values very likely reflect gliosis and CSF secondary to encephalomalacia.

Diffusion, unlike T1 and T2 relaxation times, reflects only translational motion. Therefore, it may be more specific in tissue characterization.

TABLE 1: Tabulated values for the average diffusion coefficient measured in the lesion for the 15 stroke patients studied

Patient	Age of stroke	ADC (10^{-5} cm^2 sec^{-1})
1	10 hr	1.0 ± 0.2
	4 days	1.8 ± 0.2
	7 wk	2.4 ± 0.4
2	13 hr	1.8 ± 0.2
	3 days	2.3 ± 0.2
	4 days	2.3 ± 0.2
3	18 hr	0.8 ± 0.2
	4 days	1.0 ± 0.2
4	2 wk	1.0 ± 0.1
	11 wk	1.0 ± 0.1
5	30 hr	1.0 ± 0.2
6	4 days	1.1 ± 0.2
7	6 days	1.1 ± 0.2
8	7 days	1.9 ± 0.1
9	4 wk	0.9 ± 0.2
10	4 wk	0.6 ± 0.1
11	6 wk	1.1 ± 0.2
12	8 wk	1.5 ± 0.3
13	9 wk	1.8 ± 0.2
14	2 yr	3.0 ± 0.2
15	4 yr	2.2 ± 0.2

Note.—Tabulated values for the average ADC measured in the lesion for the 15 stroke patients studied. Given also is the time between the ischemic attack and when the diffusion study was performed. Four of the patients studied had repeated examinations over time. The earliest stroke patient studied was 10 hours after the ischemic attack. In three of the four patients who had repeated examinations, there was a trend in increasing ADC with time. The standard deviation reported here includes the variation of ADC due to heterogeneity of diffusion within the lesion.

This point is illustrated by our data that diffusion imaging can reveal subregions with increased and decreased water mobility within an infarct that appears to be uniformly bright on T2-weighted images. This shows that the change in water diffusion does not necessarily parallel the change in T2 relaxation time. Thus, tissue that shows an increase in T2 relaxation time does not necessarily show an increase in water mobility. This demonstrates that the biophysical process responsible for changes in T2 relaxation time differs from that responsible for changes in the diffusion coefficient. Diffusion imaging may thus improve tissue specificity and enable the differentiation between various types of tissue damage that are not distinguishable by their relaxation times alone.

Our data shows that different lesions of the same age can exhibit very different ADC. The evolution of measured ADC over time after the onset of stroke does not follow a strict time course, but may be dependent on the etiology, the nature, and the extent of tissue damage.

Even without the complicated biophysical changes involved in cerebral infarction, the ADC can be affected by a number of experimental parameters, as demonstrated previously (10). Therefore, it is important to optimize the diffusion imaging technique and apply the same protocol to all patients, so that the results can be directly compared. We have taken extra precaution in preparing for the clinical study, including: 1) minimizing head motion by fitting the patient with a personal head-holder made to fit the individual's head contour; 2) optimizing the pulse sequence in phantoms and in normal volunteers; and 3) acquiring data during diastole by electrocardiogram triggering to minimize CSF pulsation. All these precautions are important since diffusion imaging sequences are made extra sensitive to small motions. Thus, technique imperfections and bulk motion, such as CSF pulsation or head motion, can all contribute to an inflated diffusion coefficient. Furthermore, care should be taken in choosing the region of interest because partial voluming, especially with CSF, can affect the ADC measured. This problem can be minimized by using thinner sections or by using a CSF-suppressed diffusion imaging technique (22).

With care, in vivo diffusion imaging is reproducible and can provide accurate information about the local water mobility in living tissue. Recent advances in high speed imaging (23, 24) should allow ADC maps to be generated more quickly in a clinical setting. Further studies are underway to assess the biophysical mechanism behind the observed changes and the biologic and clinical significance of these early observations.

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