Serial Study of Apparent Diffusion Coefficient and Anisotropy in Patients With Acute Stroke

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Background and Purpose—We sought to characterize the evolution of apparent diffusion coefficient (ADC) and apparent diffusion anisotropy (ADA) in acute stroke and to evaluate their roles in predicting stroke evolution and outcome.

Methods—We studied 26 stroke patients acutely (<24 hours), subacutely (3 to 5 days), and at outcome (3 months). Ratios of the ADC and ADA within a region of infarction and the normal contralateral region were evaluated and compared with the Canadian Neurological Scale, Barthel Index, and Rankin Scale.

Results—Heterogeneity in ADC and ADA evolution was observed not only between patients but also within individual lesions. Three patterns of ADA evolution were observed: (1) elevated ADA acutely and subacutely; (2) elevated ADA acutely and reduced ADA subacutely; and (3) reduced ADA acutely and subacutely. At outcome, reduced ADA with elevated ADC was observed generally. We identified 3 phases of diffusion abnormalities: (1) reduced ADC and elevated ADA; (2) reduced ADC and reduced ADA; and (3) elevated ADC and reduced ADA. The ADA ratios within 12 hours correlated with the acute Canadian Neurological Scale (r=0.46, P=0.06), subacute Canadian Neurological Scale (r=0.55, P=0.02), outcome Barthel Index (r=0.62, P=0.01), and Rankin Scale (r=−0.77, P<0.0005) scores.

Conclusions—Combined ADC and ADA provide differential patterns of stroke evolution. Early ADA changes reflect cellular alterations in acute ischemia and may provide a potential marker to predict stroke outcome. (Stroke. 1999;30:2382-2390.)

Key Words: cerebral edema ▪ cerebral infarction ▪ magnetic resonance imaging, diffusion-weighted ▪ stroke, ischemic ▪ stroke outcome

Diffusion-weighted imaging (DWI) has become an important MRI method for the early diagnosis and characterization of ischemic stroke.1–10 Early reports1,2 showed that acute infarcts appear hyperintense on DWI because of a reduction in the apparent diffusion coefficient (ADC) of water within minutes after the onset of ischemia,3 reflecting early disruption of energy metabolism.

However, the mechanism behind the ADC reduction in acute ischemia is not fully understood. In biological tissue, the ADC of water molecules is much lower than its free water value because of physical restrictions from membranes, fibers, and macromolecules such as proteins.11 The amount of dissolved organic molecules may also alter the viscosity of water. In acute ischemia, disruption of energy metabolism with failure of ion pumps causes cell swelling and accumulation of intracellular sodium and water (cytotoxic edema).7,8 The net migration of water from extracellular space (ECS, where ADC is presumed to be high) into intracellular space (ICS, where ADC is presumed to be low) has been considered the dominant mechanism for the ADC reduction.1,6 Another postulated mechanism is that the ADC reduction is a result of decreased membrane permeability caused by collapse of transmembrane ion gradients.12 Furthermore, recent studies have provided compelling evidence that the observed ADC reduction is dominated by the water ADC reduction in the ICS because of a decrease in energy-dependent cytoplasmic circulation or an increase in water viscosity.13–15 On the other hand, the time course correlation of the ADC reduction with the decrease in ECS volume and the increase in ECS tortuosity suggests that cell swelling may also cause ADC reduction of water or other molecules in the ECS.15,16 Recent numerical modeling has suggested both cellular swelling and membrane permeability to be important factors influencing ADC in spinal cord white matter.17

The temporal evolution of diffusion abnormalities is also important in tracking stroke progression. Studies using animal models have revealed profound ADC changes at early acute stages.2–4 Moreover, there is an increase in the lesion...
volume over time as measured by decreased ADC values. In human stroke, while some studies report the persistence of a reduced ADC for at least 4 days after stroke onset, others have found heterogeneity of ADC within the infarct while part or all of the lesion displayed pseudonormal or high ADC values by 24 to 48 hours. This disparity may be related to different patient populations or stroke etiologies, different data acquisition and analysis techniques, and anisotropic diffusion effects. The diffusion of water molecules in biological tissue is anisotropic, particularly in tissue containing nerve fibers and white matter tracts, where ADC is high in the direction parallel to fiber tracts and low in perpendicular directions. Anisotropic diffusion can cause conspicuous hyperintensities on DWI that may be confused with acute ischemia and influence the accurate quantitation of ADC. Such effects can be minimized by calculating the trace ADC and isotropic DWI images from DWI measurements in 3 orthogonal directions. Recent studies have evaluated the time course of the trace ADC in human stroke, eliminating the influences of anisotropic diffusion.

Computer-assisted segmentation analysis has further demonstrated ADC heterogeneity within the infarct and partial ADC elevation by 5 to 9 hours after ictus, although the average ADC in the lesion remained low.

Measurements of apparent diffusion anisotropy (ADA) may provide additional information about cellular changes in ischemic stroke. To our knowledge, no systematic study of the evolution of combined ADC and ADA in acute human stroke has been reported. In this study we evaluated the serial changes of ADC and ADA abnormalities in patients with acute ischemic stroke. We sought to improve our understanding of the mechanisms underlying the ADC and ADA changes in ischemia and to determine whether these data are useful in characterizing and predicting the evolution of acute ischemic stroke.

Subjects and Methods

Patients with sudden onset of focal neurological deficit consistent with hemispheric ischemic stroke were recruited from the Stroke Unit of the Royal Melbourne Hospital. Stroke onset was defined as the last time the patient was known to be without neurological deficit. Patients were excluded if they had cerebral hemorrhage, preexisting significant nonischemic neurological deficit (including dementia or extrapyramidal disease), or a history of prior stroke that would hinder interpretation of clinical and radiological data. Patients treated by putative neuroprotective or thrombolytic drugs were excluded. The study was performed with the approval of the ethics committee at our institution, and written informed consent was obtained from the patient or next of kin.

Clinical Assessment

The Canadian Neurological Scale (CNS), a validated neurological impairment score, was measured just before the acute and subacute MRI studies. Outcome clinical assessments were performed on the same day as the outcome MRI study and consisted of a repeated CNS and scores derived from the Barthel Index (BI) and the Rankin Scale (RS). The BI is a validated functional disability score, and the RS is a validated handicap scale. These clinical scales were used because they measure different aspects of recovery after stroke. All clinical assessments were performed by a neurologist or neurology resident trained in their administration and were administered without knowledge of the MRI results.

Imaging Parameters

All patients were scanned on a 1.5-T clinical whole-body scanner (Signa Horizon SR120, GE Medical Systems) with the use of an optimized protocol including a T1-weighted sagittal localizer, DWI sequence, contrast-enhanced perfusion imaging (CEPI) sequence, dual proton-density and T2-weighted fast-spin-echo sequence, spin-echo echo planar imaging (EPI) sequence, phase-contrast MR angiography (MRA), and finally a contrast-enhanced T1-weighted sequence. Similar slice locations were used to facilitate comparisons. The total “table time” for these sequences was approximately 20 minutes. Only the DWI results are reported in this study.

DWI scans were performed with a single-shot, spin-echo EPI sequence with the Stejskal-Tanner diffusion-encoding method. The DWI parameters were as follows: 40×20 cm field of view, 256×128 matrix size, 16 axial slices, 6-mm slice thickness, and 1-mm gap covering the whole brain. The first 19 patients were studied with a trace DWI sequence with 5 diffusion b values (0 to 1000 s/mm²) in each of 3 orthogonal directions and repetition time/echo time (TR/TE) of 6000/110 ms. The remaining 7 patients had diffusion tensor imaging (DTI) with 3 b values (0 to 1000 s/mm²) in each of 6 directions and TR/TE of 10 000/110 ms. Scanning time was 1 minute 18 seconds for the trace DWI and 2 minutes 10 seconds for the DTI.

Image Processing

Postprocessing of images was performed on a UNIX workstation with the use of customized software developed in IDL (Interactive Data Language, Research Systems Inc). Since the calculation of diffusion anisotropy is sensitive to image noise and artifacts, noise reduction and correction for image distortions were performed on all images. Raw images were filtered with a 9×9 gaussian kernel. The average background noise was subtracted to reduce the nonlinear influences on the DWI signal attenuation. The EPI sequence has first-order eddy current compensation to minimize image distortions. However, higher-order eddy current distortions due to the strong diffusion gradients may still cause artifacts, particularly on ADA quantification. Therefore, corrections for such distortions were applied with a modified approach based on the translation-shear-scaling model. Although the single-shot EPI sequence eliminated motion artifacts from each “snapshot” image, possible head movement during the DWI scanning time (1 to 2 minutes) would be captured, causing mismatch between images. Such mismatch may vary between images and slices and cannot be easily corrected with the use of standard rigid-body coregistration algorithms. Therefore, any data set with interimage mismatch was aligned by a dynamic visual-manual adjustment based on both ratio and difference maps, followed by an automated fine-tuning approach. All image corrections employed a cubic convolution interpolation method, which closely approximates the theoretically optimum sinc interpolation function to preserve image resolution. Motion and distortion artifacts were double-checked in animation mode between images of different b values in each direction and between images of the same b value at different directions. The DWI signal intensity attenuation curve was also dynamically checked, particularly in the region of interest (ROI). Any individual image with noticeable artifacts was excluded from the fitting process for calculation of the ADC map in each of the 3 (for trace DWI) or 6 directions (for DTI).

Both the trace DWI and the DTI allow the calculation of ADCs in each of 3 orthogonal directions, which then provide the average ADC (ADCₐ) noted as ADC hereafter and the orientation-dependent standard deviation index of ADA (ADAₑ). In addition, DTI allows the calculation of the full diffusion tensor and hence a more accurate orientation-independent anisotropy index, such as the fractional anisotropy (FAₑ). The trace DWI and DTI sequences were tested on a standard water phantom at room temperature. The calculated ADC value of free water was 2.2±0.1×10⁻³ mm²/s, with an ADAₑ value of 0.04±0.02 and a FAₑ value of 0.16±0.03. These non-zero ADAₑ values are mainly due to signal-to-noise ratio. Both ADAₑ indices range from 0 to 1, representing completely isotropic to extreme anisotropic diffusion.
Data Analysis

Heterogeneity of ADC within the lesion has been reported and further confirmed with computer-assisted segmentation analysis. Our experience confirmed this finding. The heterogeneous ADC and ADA distribution within the lesion can also be visualized by adjusting the image contrast level and window, particularly within large infarctions. Therefore, segmentation analysis of the lesion is necessary to properly study the evolution of ADC and ADA in different tissue areas. Automated segmentation analysis requires specialized computer software, which is not widely available. Furthermore, it would be difficult to automatically follow the same tissue area over serial studies because of the heterogeneous progression and edematous swelling of the lesion. Therefore, we used a segmentation approach based on anatomic location and tissue type similar to that used in animal model studies. Since different tissue structures have different ADA values, proper evaluation of ADA changes needs to be linked to specific tissue types. The ADA of the white matter is much greater than that of the gray matter, and the ADA map is very useful in delineating white matter. When one considers the image resolution and slice thickness of the DWI image, partial volume effects (PVE) were inevitable, particularly between the gray matter and the white matter or the cerebrospinal fluid (CSF) in cerebral gyral areas. Therefore, lesions were segmented and grouped as white matter (WM), cortical or deep gray matter (GM), and mixed gray/white matter (GWM) regions. The isotropic DWI (with b = 1000), T2-weighted image (which is DWI with b = 0), and ADC and ADA maps of serial studies were visualized simultaneously. A ROI was initially selected by free-hand tracing on the acute ADC map to outline the infarct with reduced ADC. The ROI was then projected on other images and further edited for reliable segmentation, guided by anatomic knowledge and histogram analysis. No serial measurement was performed for later expanded areas of infarction. Efforts were made to track each segmented tissue area with all 4 kinds of images, guided by anatomic knowledge, while edematous swelling was also considered. In a few cases in which asymmetric head angulation caused difficulties for comparison with the contralateral side on the same slice, multiple slices were analyzed. Additionally, it was not practical to reproduce the exact same slice locations over serial MRI studies for all patients, especially when head movements occurred during the scan, although a standard landmark was always used. Thus, some raw DWI data may be subject to PVE within half the slice thickness. However, efforts were made to minimize additional PVE during the data analysis. No segmentation was performed for small infarctions, which were evaluated separately from large lesions. The average ADC and ADA values within each segmented ROI were obtained with histogram analysis to eliminate contamination from individual noise. Care was also taken to avoid contamination from sulcal CSF. To attain a reliable measure of the evolution of the ADC and ADA changes between patients and over serial studies, ADC and ADA ratios were calculated by dividing the mean values in the lesion ROI by those in the corresponding contralateral ROI.

Linear regression analyses were performed between the ADC and ADA ratios and the clinical scores (CNS, BI, RS) with Pearson’s correlation coefficient (r) and significance level (P) of the F test. Results were considered statistically significant at levels of P<0.05.

Since the evolutions of ADC and ADA are heterogeneous and complicated, no statistical analysis was performed to test for ratio difference, but all data points are presented.

Results

Twenty-six patients (16 men, 10 women; mean age, 69±12 years; range, 42 to 92 years) were studied, with 9 small lesions (lacunar, striatocapsular, and small cortical infarctions) and 17 large lesions (major arterial territory infarctions). All 26 patients had acute studies, and 25 had subacute studies. One patient missed the subacute study but completed the outcome study. Twenty patients (including all 9 patients with small lesions) had outcome studies. Three patients refused, and 1 was unable to tolerate the outcome MRI scan, but all of them had the outcome clinical assessments. One patient died as a result of complications from stroke (assigned outcome BI=5 and RS=0), and 1 died of an unrelated cardiac event after the subacute study (outcome BI and RS not available). Time from stroke onset to the acute study was 11.5±7.2 hours (range, 2.5 to 23.5 hours), with 10 studies within 6 hours and 17 studies within 12 hours. Time to the subacute study was 3.7±1.2 days (range, 1.9 to 6.8 days). Time to the outcome study was 90±26 days (range, 35 to 154 days).

Trace DWI and DTI

A total of 71 MRI studies were performed with 51 trace DWI and 20 DTI scans. The mean ADC value in all normal ROIs was 0.85±0.14 (×10−3 mm2/s), which agrees well with other reports.

All 71 DWI scans provided ADA_{sd} maps, while 20 DTI scans provided additional ADA_{fr} maps. Since ADA_{sd} is orientation dependent, it underestimates the diffusion anisotropy of water in tissues depending on tissue types and fiber orientations relative to the 3 orthogonal diffusion-encoding directions. However, our experience indicated similar ADA_{sd} and ADA_{fr} changes in terms of elevation or reduction by comparing the ischemic lesion with the corresponding contralateral region. To further clarify this phenomenon, the mean values of both indices in the segmented infarcts and normal ROIs (including CSF) from the 20 DTI scans were plotted, as shown in Figure 1a. This illustrates the range of quantitative ADA values of different tissue types measured by both indices, in good agreement with other reports.

The non-zero ADA values in CSF agree well with those
measured in a water phantom. Figure 1a demonstrates the empirical relationship between ADA_{sd} and ADA_{fr}, described by a fitted curve: ADA_{fr} = 1 - e^{-4.2 \cdot ADA_{sd}}. A 2-dimensional histogram analysis of the associated ADA_{sd} and ADA_{fr} maps further supported such an approximate relationship. The ADA_{sd} values were converted into ADA_{sd}^* values, which are approximately equivalent to ADA_{fr} according to the above relationship. The ratios of ADA_{sd}^* in the lesion to that in the contralateral region were calculated and compared with the corresponding ADA_{fr} ratios, as shown in Figure 1b. A 1:1 relationship between the ADA_{fr} and the corrected ADA_{sd}^* ratios was found by linear regression analysis (slope = 1.00 ± 0.02, r = 0.94, P < 10^-12). This allowed us to extend the above correction to all the ADA_{sd} values measured by the trace DWI. The corrected ADA_{sd}^* ratios were included together with the ADA_{fr} ratios measured by the DTI to increase statistical power in subsequent analysis.

ADC and ADA Evolution in Small Infarctions
The time courses of the ADC and ADA ratios in 9 patients with small lesions are shown in Figure 2. All 9 acute lesions displayed reduced ADC; 8 had elevated ADA, while 1 WM lesion at 23.5 hours had low ADA ratio. Subacutely, the ADC ratios tended toward normal in 2 small cortical GM lesions and remained low in the others. The initially elevated ADA ratios persisted in 2 WM lesions, became reduced in 4 WM lesions, and approached normal in 3 small cortical GM lesions. At outcome, the ADC ratio became elevated in 8 patients, while 1 had persistent ADC reduction at 85 days. The ADA ratio became further reduced in all lesions. Overall, the ADC and ADC changes during infarct evolution were greater in WM than in GM lesions.

ADC and ADA Evolution in Large Infarctions
A total of 69 segmented lesion ROIs were sampled in serial studies of 17 patients. The time courses of the ADC and ADA ratios in all the segmented ROIs are shown in Figure 3. General patterns of ADC and ADA evolution are similar to those in the small lesions of the same tissue types, except that no acutely elevated ADA was observed in the deep GM. The evolution of ADC and ADA ratios in the GWM tissues is also similar to that of small WM lesions. However, earlier ADC pseudonormalization or elevation by 24 to 48 hours can be seen in both WM and GM lesions. Figure 4 demonstrates the serial ADC and ADA maps of a patient with initially reduced ADC and elevated ADA in the WM-dominated lesion. These evolved to elevated ADC and reduced ADA by 42 hours after stroke onset. Heterogeneous ADC distribution within the lesion can be seen. In addition, the initial lesion expanded by 42 hours, with a peripheral rim of reduced ADC and elevated ADA resembling the initial diffusion abnormalities of the infarct core. At 93 days, both the infarct core and the rim displayed different levels of ADC elevation and ADA reduction (Figure 4). Such expanded infarct areas were not included in the serial analysis. Figure 5 demonstrates differences in both ADC and ADA evolutions within the same lesion, in which the initial infarct had relatively homogeneous ADC reduction and ADA elevation but displayed significant heterogeneities between the WM and peripheral GWM areas at 5 days. Although there are some differences between the ADA_{fr} and ADA_{sd} maps, similar features of ADA changes in the lesion can be seen compared with the contralateral side. This patient’s head was tilted to the left at the subacute stage, reflecting the actual clinical situation. However, no severe head movement occurred during the DWI sequence, and any interimage mismatch was eliminated.

For most of the small and segmented large lesions, 3 patterns of ADA evolution were observed generally: (1) elevated ADA acutely and subacutely; (2) elevated ADA acutely and reduced ADA subacutely; and (3) reduced ADA acutely and subacutely. At outcome, elevated ADC with reduced ADA was observed generally. The exceptional cases, including 1 WM lesion (Figure 3, solid squares in top row) and 3 small cortical GM lesions (Figure 2, bottom row), had both ADC and ADA ratios slightly different from normal by outcome studies. Figure 6 demonstrates the serial ADC and ADA maps, isotropic DWI, and
T2-weighted image in the WM lesion case. Despite the usual progression of the peripheral GWM lesion area (white arrowhead in Figure 6, solid diamonds in middle row of Figure 3), the acute WM lesion (white arrow) progressed gradually, approaching normal ADC and ADA and slight T2-weighted image hyperintensity (black arrow) by outcome. This is the only case in this study in which the control ADC and ADA values were sampled from surrounding nonlesional tissues to avoid an old lesion on the contralateral side (double black arrows), which might have led to less reliable ratios. The absolute ADC values were 0.56, 0.73, and 0.87 ($10^{-3}$ mm$^2$/s) in the WM lesion and 0.71, 0.78, and 1.21 ($10^{-3}$ mm$^2$/s) in the peripheral GWM lesion area at 4.5 hours, 51 hours, and 85 days, respectively. The absolute ADC value was 0.86±0.05 ($10^{-3}$ mm$^2$/s) in the normal tissues of this patient, which confirmed the slow ADC recovery in the WM lesion area. Examination of the MRA and CEPI results in this patient indicated early reperfusion. However, the slight T2 hyperintensity in this WM area at outcome suggests some permanent pathological changes.

**Relationship Between ADC and ADA**
The combined ADC and ADA ratios in all lesions over serial studies are shown in Figure 7. Three phases of diffusion abnormalities are distinguishable: (1) elevated ADA and reduced ADC; (2) reduced ADA and reduced ADC; and (3) reduced ADA and elevated ADC. Most infarctions displayed a transition from phases 1 to phase 2 between the acute and subacute stages, then to phase 3 by outcome. However, phase 3 had occurred by the subacute stage in some WM and GM regions of large lesions, while phase 2 persisted from the subacute to outcome stages in 1 small WM lesion. It is noted that the 3 small cortical GM lesions (solid circle in Figure 7)
and the slowly evolving WM lesion (Figure 6, solid square in Figure 7) tended to transform from phase 1 via the normal ADC and ADA cross point into phase 3. For all small and large lesions, there is a correlation between ADC and ADA ratios for transition from phase 1 to phase 2 ($r = 0.41$, $P = 0.0005$) and from phase 2 to phase 3 ($r = -0.52$, $P < 0.00005$). However, the overall transition between all 3 phases is nonlinear, presumably reflecting different pathological processes during infarct evolution.

Correlation With Clinical Score
For large infarctions with multiple segmented ROIs, the average ADC and ADA ratios weighted by the segmented tissue volume were calculated to represent an average diffusion abnormality of the entire lesion slice. Correlation analyses were performed between the patient's clinical scores (CNS, BI, RS) and the average ADC and ADA ratios for the time intervals of <12 hours, 12 to 24 hours, 2 to 10 days (subacute stage), and >35 days (outcome). Correlations were found between ADA ratios within 12 hours of stroke onset and the acute CNS ($r = 0.46$, $P = 0.06$), subacute CNS ($r = -0.55$, $P = 0.02$), outcome BI ($r = 0.62$, $P = 0.01$), and RS ($r = -0.77$, $P < 0.0005$) scores. Additional analysis confirmed there was no significant correlation between the ADA ratios and the entire acute DWI lesion volume or outcome T2 lesion volume. This suggests that the correlations between the ADA ratio and clinical scores are not biased by the lesion size. Furthermore, there was no significant correlation between clinical scores and ADA ratios at later stages or ADC ratios at any stage. This suggests that early ADA changes may provide an important marker in predicting stroke outcome.

Discussion
In this study of patients with acute ischemic stroke, we have found different patterns of ADC and ADA evolution over time and different phases of combined ADC and ADA abnormalities. In addition, we have observed differences in both ADC and ADA evolution not only between patients but also within individual lesions. Furthermore, we have found that ADA ratios within 12 hours of stroke onset correlate significantly with acute, subacute, and outcome clinical scores.
The combined ADC and ADA information may provide insight into cellular changes during ischemia evolution. In acute ischemia, early disruption of energy metabolism leads to failure of transmembrane ion pumps and cell swelling (cytotoxic edema). As infarction evolves, vasogenic edema may develop as a result of the blood-brain barrier breakdown, causing excessive water accumulation and tissue swelling. However, both cytotoxic and vasogenic edema may present simultaneously in ischemic lesions, and early vasogenic edema may not always cause ECS swelling. Thus, it is helpful to regard the progression of an ischemic lesion with specific compartment-related swelling.

Different ADC models could be applied in attempt to explain the combined ADC and ADA changes. In the ECS model, the ADC of water is presumed to be high in the ECS and low in the ICS, with the ADC reduction in acute ischemia explained by the net shift of water from the ECS into the ICS, as a result of cell swelling in cytotoxic edema. In addition, the shrinkage of the ECS with increased ECS tortuosity may cause increased restriction of extracellular water movement, leading to elevated ADA. While this may qualitatively explain the reduced ADC with elevated ADA in phase 1, excessive water accumulation and ECS swelling in vasogenic edema would lead to reduced ADA accompanied by elevated ADC (phase 3). However, reduced ADC and reduced ADA (phase 2) were observed in many cases with T2-weighted image hyperintensities and extensive tissue distortions, suggesting excessive water accumulation and ECS swelling due to vasogenic edema. Thus, phase 2 could not be easily explained by this model.

In other models, the ADC reduction in acute ischemia may be dominated by decreased ADC in the ICS due to decreased membrane permeability or cytoplasmic circulation or increased viscosity of water. In these ICS models, the ADC of water in the ICS and ECS may be similar. To explain our results of combined ADC and ADA changes, we postulate that elevated ADA may reflect enhanced restriction of intracellular water movement, due to decreased membrane permeability, or enhanced ICS weighting, due to water shift from the ECS into ICS caused by cell swelling. However, cell swelling may cause reduced restriction of ICS water movement and hence a reduction of the elevated ADA. The level of ADA elevation may reflect the degree of cellular swelling and membrane degradation and hence the severity of the ischemic injury. Additional ECS swelling and possible membrane fragmentation may lead to further ADA reduction below normal. Therefore, a decline in ADA most probably reflects the process of cell swelling, extracellular edema, and cell lysis. The reduced ADA in phase 2 may be characterized by the development of ECS swelling and membrane degradation, while the reduced ADC can be explained by the ICS models. In contrast, persistently elevated ADA (phase 1) may suggest lack of ECS swelling and preserved membrane integrity, although vasogenic edema may be present at the early ischemic stage. The elevated ADC and reduced ADA (phase 3) most probably reflects cell lysis toward necrosis with the destruction of membrane integrity. Recently, reduced ADA and elevated ADC have been found in chronic white matter lesions of ischemic leukoaraiosis, which is consistent with axonal loss and gliosis.

In patients with acute stroke observed in this study, the duration of the initial ADC reduction ranged from <48 hours to 85 days. The observed differences in ADC and ADA evolution support that ADC heterogeneity within the lesion reflects different temporal rates of stroke progression. The feature of a lesion with elevated ADC in the infarct core and a rim of reduced ADC at a later stage (Figure 4) has been reported in animal model studies with histopathological correlates of later development of infarction in the rim. In this study, the elevated ADA in the rim supports later development of ischemic infarction rather than edema. At outcome, the ADC in the rim is only slightly elevated in comparison with the infarct core, which may suggest different pathological processes. Furthermore, the outcome ADC elevation of the rim is similar to that of the small cortical GM lesions (Figure 2, bottom row). Although the measurement of ADC in small lesions or the rim area of larger lesions may be influenced by PVE, the slow recovery of the ADC and ADA in the WM lesion case (Figure 6) is less likely due to PVE. This may be a human case of reversible focal ischemic injury or ischemic-induced spreading depression found in animal models. On the other hand, the slow evolution of ADC and ADA in these cases (in situations of better collateral flow or early reperfusion) may relate to other processes such as apoptosis, in which selective delayed cell death is likely to occur in areas of milder ischemic injury for days after the initial insult.

The correlation of ADA changes within 12 hours with the acute, subacute, and outcome clinical scores supports that early ADA changes reflect severity of the ischemic injury and predict stroke outcome. In contrast, the lack of correlation between clinical scores and ADA changes at later stages suggests that other processes, such as ECS swelling in vasogenic edema and cell lysis with membrane fragmentation, may have developed and contributed to a heterogeneous evolution. Furthermore, no significant correlation between ADC and clinical scores was found, suggesting that ADC alone does not have sufficient predictive power in terms of histopathological and clinical outcome in patients with acute ischemic stroke. This contrasts with a study in which ADC measured within 60 hours of stroke onset correlated with stroke outcome at 4 months. Such disparity may relate to...
different sampling methods. The other study reported systematically higher ADC values by measuring the entire lesion slice, including the peripheral area. This may become particularly important for small lesions, in which a measured higher ADC value may be coupled with more PVE and hence better outcome biased by the small lesion size. Second, it ignored the heterogeneity of ADC within the lesion, which may relate to different pathophysiological properties, particularly between the infarct core and periphery. Different processes within the lesion may already have developed within 60 hours of stroke onset. Nevertheless, whether there is an ADC threshold in predicting tissue viability and stroke outcome requires further understanding of the mechanisms underlying the ADC changes in acute ischemia. However, ADA may be the better diffusion property to track stroke progression.

Recently, elevated ADA in the acute “ischemic penumbra” delineated by DWI and CEPI has been observed and related to tissue salvage. This may reflect possible membrane changes related to autoregulation of local blood flow in acute ischemia. It is possible that the ADA changes in ischemia may be influenced by early reperfusion. This is beyond the scope of the present study. Further studies to correlate the ADA changes with perfusion parameters and MRA results may help to elucidate the underlying pathophysiology in acute ischemia.

It should be noted that the empirical relationship between $\text{ADA}_0$ and $\text{ADA}_{ax}$ was not expected theoretically. For an individual cell or fiber structure, the $\text{ADA}_0$ value is variable, depending on specific orientation of the cell relative to the diffusion-encoding directions. For a macroscopic ROI containing a large amount of differently orientated cells, it is possible that the average effect may reduce the orientation-dependent influence. In addition, the use of relative ratios comparing the same tissue types in the same subject may further minimize this influence and contribute to the observed correlation between $\text{ADA}_0$ and $\text{ADA}_{ax}$ ratios. However, the empirical relationship observed in this study may not always be valid and should not be generalized. This may be subject to further evaluation with more available DTI data.

ADA, as another diffusion property of water molecules provided by DWI, is readily available to provide additional insight into the cellular changes in acute ischemia. Combined ADC and ADA data are valuable in characterizing stroke evolution and predicting clinical outcome. These data may also help to monitor cellular changes of acute ischemia in response to putative drug treatments.

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