Correlation of Apparent Diffusion Coefficient and Computed Tomography Density in Acute Ischemic Stroke

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Background and Purpose—Diffusion-weighted MR imaging is very sensitive for the detection of restricted molecular water diffusion in acute ischemic stroke. CT is sensitive to net water uptake in ischemic edema. We compared the decrease in the apparent diffusion coefficient (ADC) in diffusion-weighted MR imaging with CT density changes to study the correlation between diffusion restriction and water uptake in acute stroke patients.

Methods—Twenty-five patients with acute ischemic stroke of the anterior cerebral circulation underwent MR and CT imaging 1.3 to 5.4 hours after symptom onset. ADC and CT data were transferred into a common 3-dimensional space, and regions of decreased ADC (dADC) were superimposed onto the corresponding CT. Mean values of ADC and Hounsfield units (HU) were determined in comparison with the nonaffected hemisphere.

Results—Mean decrease in ADC (dADC) was $170 \pm 53 \times 10^{-6}$ mm$^2$/s and corresponded to a decrease (dCT) in CT density of $1.3 \pm 0.7$ HU. dCT showed a continuous linear decrease of 0.4 HU/h ($r=0.55$, $P<0.01$), whereas the decrease is ADC was almost complete after 1.5 hours. A correlation between the decrease in ADC and dCT was found ($r=0.41$, $P=0.04$).

Conclusions—The severity of diffusion restriction correlates with net water uptake in acute ischemic stroke. However, the underlying pathophysiology and different time courses indicate a common reason rather than a direct causality for both phenomena. The time delay and low value of CT density changes provide a reasonable explanation for the higher sensitivity of MR imaging in ischemic stroke. (Stroke. 2002;33:1786-1791.)

Key Words: brain edema ■ cerebral infarction ■ computed tomography ■ magnetic resonance imaging, diffusion-weighted ■ stroke, acute

Newer MRI protocols using perfusion- and diffusion-weighted imaging (DWI) in acute stroke have widened the spectrum of imaging modalities1 and offer insight into the pathophysiology of ischemic stroke at a very early phase,2 just when the salvage of tissue at risk of infarction by thrombolysis is thought to be beneficial to outcome3,4 but bears an inherent risk of deteriorating intracranial hemorrhage for a subgroup of patients.5,6 A reliable prediction of symptomatic hemorrhage is difficult within 3 to 6 hours after symptom onset. Patients presenting with early CT signs of ischemia in more than one third of the middle cerebral artery territory 21,22 are assumed to be at higher risk of hemorrhage. In a large patient collective, CT was found to be the only approved imaging modality for the prediction of hemorrhage after thrombolysis.5,9 Patients presenting with early CT signs of ischemia in more than one third of the middle cerebral artery territory within 6 hours after symptom onset are at high risk of symptomatic hemorrhage.9,10 These CT signs are subtle hypodensities of the affected brain parenchyma,11,12 which are the result of water increase caused by the early ischemic edema.13

Although some authors reported an apparently acceptable detectability of early CT signs,14,15 serious doubts have been expressed about reliable quantification within a broad application of this criterion and its prognostic value.16–18

Comparisons between DWI and CT in acute stroke patients revealed uniform results: DWI has a substantially higher sensitivity19,20 and more accurately detects the involvement of more than one third of the middle cerebral artery territory21,22 in patients eligible for thrombolytic treatment. In contrast to MRI,23–25 little is known about the quantification and time course of CT density changes within the first 6 hours after ischemia onset. The aim of the presented study was to quantify CT density values in brain regions with diffusion restriction in acute stroke patients and to seek a possible correlation between the apparent diffusion coefficient (ADC) of molecular water and CT density.

Subjects and Methods

Between May 2000 and March 2001, 59 patients with symptoms of acute ischemic stroke of the anterior cerebral circulation underwent CT and MRI as part of a standardized imaging protocol within 6 hours after symptom onset. Patients were screened for inclusion in a multicenter acute stroke MR imaging study (Kompetenznetzwerk
Schlaganfall study group B5) in search of radiological predictors of favorable outcome after thrombolytic stroke treatment. The local ethics committee approved the study, and informed consent was obtained. Of these patients, 25 met the following inclusion criteria: (1) sufficiently performed CT examination; (2) exclusion of intracranial hemorrhage; (3) successful completion of the MRI protocol, including DWI, proton density (PD)/T2 spin-echo and fluid-attenuated inversion recovery sequences, MR angiography, and perfusion-weighted imaging; and (4) intracranial vessel occlusion, proven by MR angiography or a territorial perfusion deficit in perfusion-weighted imaging. The main reason for exclusion was lack of CT data because the CT scan was done in referring hospitals before admittance to the local neuroradiological unit (n=16). Other reasons for exclusion were as follows: very small DWI lesions (<1 cm²; n=4), uncertain time point of symptom onset (n=3), old ischemic lesions contralateral or adjacent to the DWI lesion (n=3), considerable motion artifacts (n=2), lack of T2 data on follow-up (n=2), substantial white-matter signal intensity elevation resulting from cerebral microangiopathy (n=2), failure of the normalization procedure (n=1), and lack of vessel occlusion (n=1).

**CT Protocol**
Cranial CT scanning (Somatom plus 4, Siemens Medical) was performed in sequential data acquisition mode without gantry tilt but with the patient’s head positioned in plane with the orbitomeatal line. The posterior fossa was scanned with a slice thickness of 2 mm, gap of 1 mm, and tube current of 600 mA. Continuous 6-mm slices with a tube current of 480 mA were acquired supraclinoidally. The field of view (FOV) was 210×210 mm, and matrix size was 512×512.

**MRI Protocol**
All MRI studies were performed with a 1.5-T scanner equipped with a 20-mT/m gradient system (Siemens Medical). Diffusion-weighted data resulted from a spin-echo, echo-planar-imaging DWI sequence with a repetition time of 4800 ms, an echo time of 105.2 ms, and a flip angle of 90°. Twenty slices with a slice thickness of 6 mm, an interslice gap of 10%, an FOV of 240×240 mm, and a matrix of 256×256 pixels were acquired. Three different b values (0, 500, and 1000 s/mm²) were applied, and ADC maps were calculated by the Stejskal-Tanner equation (MRVision Software): \( ADC = -\ln(SI_{b00} / SI_{b}) / b \), and \( ADC = -\ln(SI_{b000} / SI_{b0}) / b_{1000} \), where SI is signal intensity.

**Data Analysis**
ADC and CT data sets were transferred into a 3-dimensional (3D) image format (Analyze, BIR, Mayo Foundation) without interslice gaps, and spatial normalization was done by use of SPM99 (Wellcome Department of Cognitive Neuroscience). This software performs a 3D transformation of the data sets into a standardized space similar to the atlas by Talairach and Tournoux.26 In case of CT data, voxel intensities of the skull were adjusted to the preexisting transmission template, which was used to calculate the 3D transmission parameters. Hounsfield units (HU) of the original data could be recalcualted by known scaling factors. The normalization procedure resulted in continuous 3D data sets of 23 slices with a voxel size of 1×1×6 mm.

With researchers blind to clinical data, the regions of interest (ROIs) of ADC reduction were manually surrounded. These ROIs were transferred to corresponding slices in the CT data set, and volume and mean ADC and CT density were measured. For comparison, each ROI was mirrored onto the contralateral hemisphere. Statistical analysis was done by use of SPSS 10.0 (SPSS Inc).

**Results**
The data of 25 patients (8 female, 17 male; mean age, 60±13 years) were analyzed. At admittance, all patients presented with symptoms of acute stroke, and the mean National Institutes of Health Stroke Scale score was 12±6 (Table 1). Mean time interval between symptom onset and imaging was 2.5 hours (range, 1.3 to 5.4 hours) for CT and 2.8 hours (range, 1.4 to 4.8 hours) for MRI, resulting in a mean delay between CT and MRI of ~14 minutes. Mean volume of ADC lesions was 43.3±49 cm³ (range, 1.5 to 214.9 cm³). Detailed data are given in Table 1.

The spatial normalization procedure provided acceptable 3D data sets of both ADC and CT in all 25 cases. Minor distortions occurred in CT data sets in apical brain regions because of the missing scull in the uppermost source images, but the geometry within the axial image plain was preserved. After normalization, differences in FOV, slice thickness, image matrix, and patients’ head orientation between CT and MRI were compensated for, and manually delineated ROIs of ADC decrease (dADC) could be directly transferred to the corresponding CT image (Figure 1).

Measurements of voxel intensities in control ROIs revealed a mean ADC of 803±36×10⁻⁶ mm²/s in normal brain tissue. The mean dADC found in ischemic lesions was 170±53×10⁻⁶ mm²/s (Table 2), corresponding to a decrease in CT density of 1.3±0.7 HU. Although some dispersion between individual dADC and dCT values is apparent, a significant linear correlation between dADC and dCT was found (r=0.61, P<0.01) (Figure 2). An even better correlation (r=0.72, P<0.01) between dADC and dCT was disclosed by a partial correlation analysis, with the time interval between CT and MRI as the intervening variable. Thus, a substantial amount of dispersion within the data can be explained by different time delays between CT and MRI in individual patients.

Within the observation period, dADC was not time dependent: Mean ADC values at early time points 1.5 hours after ictus did not differ from the ADC at later stages (Figure 3). On the contrary, dCT was initially low but progressed linearly over time. This resulted in a significant correlation between dCT and the time point of CT imaging of ~0.4-HU decrease per hour (dCT=0.36×h+0.40, r=0.55, P<0.01). The small increase in ADC values in control ROIs within the first hours after stroke was not significant (r=0.36, P=0.08). But ADC values in normal brain tissue of our patients increased significantly within 24 hours from 805±31 to 830±33×10⁻⁶ mm²/s in the 15 cases for which follow-up DWI was available (P=0.01).

**Discussion**
The most important finding in the present study is the correlation between dADC and dCT within the first 6 hours after stroke. dCT is known to correlate linearly with the specific gravity of tissues, and, with net water changes in ischemic brain tissue, thus describing the course of water uptake after ischemia.29 On the other hand, dADC in acute ischemia correlates with the reduction in extracellular space caused by a shift of extracellular water into intracellular compartments with consecutive restriction of molecular water diffusion.30,31 This water shift results from ion pump failure caused by a severe decrease in oxygen and nutritive metabolite supply. Considering these mechanisms of dADC, a direct causality between diffusion restriction (dADC) and net water uptake (dCT) in ischemia is not obvious but has been found in animal models of acute ischemia32 and hyponatremic cytotoxic brain edema in previous studies.

The different time courses of dADC and dCT underline an uncertain direct causality between diffusion restriction and water uptake: ~1.5 hours after onset of symptoms, dADC

\[ \text{ADC} = -\ln \left( \frac{SI_{b00}}{SI_b} \right) / b \]
was almost complete and showed no substantial further decrease. This is consistent with experimental results in animals showing a sudden ADC drop within minutes after induction of ischemia23,24 (Figure 4). On the other hand, our study showed a continuous linear decrease in CT density during the observation period, indicating a delay between cytotoxic cell swelling and a substantial net water uptake. This is in accordance with the time course of water uptake studied by direct13,34 and/or MRI relaxation time measurements 25,35 in the ischemic brain, which has been shown to yield a 2% water increase within the first 4 hours. 13,34 Instead of a direct causality between ADC and dCT decrease, we propose a common underlying reason for both phenomena: the severity of regional cerebral blood flow reduction. The water increase may be a consequence of an evolving osmotic gradient between the intravascular and extracellular compartment evoked by the water shift into the intracellular space,36 which again results from the impairment of energy metabolism of the cell as a result of ischemia. Thus, the early ischemic edema is supposed to be a passive “net water uptake” delayed to the steep, initially occurring dADC (Figure 4). It should occur before the blood-brain barrier breaks down (the classic vasogenic edema36).

Another reason for the superiority of DWI in uncovering early ischemic lesions is the substantially lower contrast of early ischemic changes in CT. It has been postulated by in vitro studies that an increase of 1% water would decrease CT density by \( \frac{2.6}{1000} \) HU.37 In their study, Unger et al37 determined the correlation between water content and dCT in the range of 76% to 91% water content, which is higher than the normal water content of human brain tissue. Actually, the water content of brain is 71% in white matter and 84% in gray matter. 28,38 Unger et al37 also implicitly assumed that the density decrease per percent change in water content is constant over the measured range. But in reality, dCT values significantly depend on the a priori water content. A theoretical estimation of what would happen if an increase of 1% water occurs in our patients or in the gelatin gel37 reveals a crucial difference: Assuming a mean water content of 77.5% (corresponding to a 1:1 composition of gray and white

### Table 1. Demographic Data, Clinical Assessment, Occlusion Type, and Imaging Characteristics

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<th>Sex</th>
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<th>Decrease in ADC, 10⁻³ mm²/s</th>
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NIHSS indicates National Institutes of Health Stroke Scale; CTO, carotid T occlusion (intracranial occlusion of the internal carotid artery (ICA) bifurcation); ICA&MCA, ICA occlusion with secondary embolism in the middle cerebral artery; MCA&ACA, combined peripheral MCA and anterior cerebral artery occlusion; MCA trif, MCA trifurcation (M1/2); and MCA trunk, proximal MCA trunk occlusion (M1). Decreases in ADC and HU were determined from the differences between control and lesion ROIs.
matter41) and a mean of 34 HU in normal brain tissue as in our control ROIs, the change in CT value is about 1.5 HU per percent water increase, more closely matching the found value of 1.3 HU. This is substantially different from the 2.6 HU published by Unger et al.37 and explains why the CT density decrease in early ischemia is smaller than believed until now.

Our results suggest a water increase of ≈0.9%, corresponding with −1.3 HU at 2.5 hours after symptom onset, a value somewhat below that estimated in animal studies.13,32,35 An explanation for this difference may be the definition of the abnormal CT regions by derivation from ADC lesions. The manual delineation of CT hypodensities would have led to much smaller ROIs with an assumed larger decrease in HU and a consequently larger increase in water42 because the visible CT lesion was always smaller than the corresponding ADC lesion. Additionally, regions surrounding the ischemic core may be characterized by an increase in cerebral blood volume caused by recruitment of collateral blood flow. This could maintain density values at normal levels if the increase in water content is compensated for by an increase in cerebral blood volume, because blood has a higher density than brain tissue.39 A DWI sequence with a shorter echo time would have led to larger measurement of ADC lesions as a result of a superior contrast of diffusion restriction. This could result in reduced mean values of both dADC and dCT, possibly strengthening their linear correlation.

Without knowledge of the ADC lesion, we would not have been able to define a CT lesion in 7 of our 25 patients. Obviously, a CT density difference of 1.3 HU cannot be precisely delineated because image noise, even in our high-quality images, ranges between 2.0 and 3.5 HU in homogenous brain regions. This is especially true with smaller lesions, because density resolution is directly correlated with object size.43 In summary, our findings are suitable to explain the substantially lower sensitivity of CT in early ischemia compared with DWI.19–22 Nevertheless, if CT lesions are clearly visible, they might represent the most severely affected brain parenchyma,44 and their extension could have a substantial prognostic value within the 6-hour window.5,9,15 But within the first 3 hours after stroke onset, the prognostic value might be low because of the pathophysiological reasons discussed earlier that sufficiently explain the recent findings of the National Institute of Neurological Disorders and Stroke (NINDS) study.18 Compared with DWI, CT seems to repre-

<table>
<thead>
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<th>Table 2. Mean Values of ADC and dCT in ROIs of 25 Patients</th>
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<td>Mean ± SD</td>
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<td>ADC lesion, 10⁻⁶ mm²/s</td>
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<td>ADC control, 10⁻⁶ mm²/s</td>
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<td>dADC, 10⁻⁶ mm²/s</td>
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<td>CT density, control, HU</td>
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<td>dCT, HU</td>
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</table>

dADC is indicated by the difference between the ADC of control and lesion; dCT is defined equivalently.

Figure 2. Differences in ADC between control and lesion vs dCT in each patient.

Figure 3. Values of ADC (A) and CT (B) vs time interval (t) from symptom onset to image acquisition.
sent only the tip of the iceberg, probably with the most severely diminished blood flow, a hypothesis that remains to be confirmed in future studies.

Our study has some limitations. First, the procedure used to normalize CT and MRI data resulted in minor spatial differences between both modalities in basal and apical cortical regions, which could be partly responsible for dispersion in our data. A CT template for the normalization procedure could further improve future studies. Second, we did not test the reversal of our correlation, starting with the delineation of the CT lesion and then determining corresponding ADC values. However, this approach would be erroneous because it is impossible to precisely delineate the CT lesions objectively at early time points. Third, the evaluation of time courses of \( d_{CT} \) and \( d_{ADC} \) 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, including the increased risk of excessive radiation exposure. Problems surrounding the somewhat-inaccurate determination of the time point of symptom onset also could not be ruled out. But this may not substantially affect the correlation of \( d_{ADC} \) with \( d_{CT} \) because the time interval between CT and MR imaging is precisely known.

In conclusion, the present study shows a correlation between ADC and CT density decrease in acute stroke patients. We assume a time-dependent decrease in CT density, which correlates with a net water increase. The delayed occurrence of CT hypodensity and the relatively small quantity could explain the lower sensitivity of CT compared with DWI for detection of early ischemic changes in imaging studies.

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