Severe ADC Decreases Do Not Predict Irreversible Tissue Damage In Humans

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Background and Purpose—A mismatch between diffusion- and perfusion-weighted MRI is thought to define tissue at risk of infarction. This concept is based on the assumption that diffusion slowing of and decreases in the apparent diffusion coefficient (ADC) serve as indicator of tissue proceeding to infarction. We tested this hypothesis.

Methods—MRI (diffusion weighted, perfusion weighted, MRA, T2 weighted) was performed in 15 patients with acute stroke within 2.9±0.8 hours (mean±SD) of onset and on days 1 and 7. After intraindividual realignment of the ADC maps, the development of ADC range volumes and ADC values was determined.

Results—An increase (354%, group A1) in the total ADC-based lesion volume below a threshold of <80% occurred in 4 patients on day 1, persisting on day 7 with a pronounced increase of ADC range volumes with low ADC values. An increase in total ADC-based lesion volume (201%, group A2) followed by a secondary drop to day 7 was found in 7 patients. A significant reduction in total ADC-based lesion volume (14%, group B) was found in 4 patients. ADC-based lesion volume increase was associated with persistent vessel occlusion in group A, whereas recanalization in group B resulted in ADC volume decrease. ADC normalization was observed independently from the degree of the initial ADC decrease on days 1 and 7 in group B.

Conclusions—In line with results from animal experiments, ADC decreases do not reliably indicate tissue infarction Even severely decreased ADC values may normalize in human stroke, and it seems likely that ADC normalization depends on the duration and severity of ischemia rather than the absolute value. (Stroke. 2002;33:79-86.)

Key Words: diffusion ■ magnetic resonance imaging ■ signal processing, computer assisted ■ stroke

Diffusion- and perfusion-weighted MRI (DWI and PWI) enables rapid detection of the ischemic deficit in acute stroke.1,2 DWI is sensitive to the self-diffusion of water protons. In ischemia, the failure of ATP-dependent ion pumps results in ischemic cell depolarization and a water shift from extracellular to intracellular space. As a result of this decrease in extracellular water, diffusion is restricted in the extracellular space, resulting in signal increases in DWI, whereas the apparent diffusion coefficient (ADC), a quantitative measure of water diffusion, decreases.1,3 Studies of peri-infarct depolarization and spreading depression, as well as transient hypoglycemia, have shown that ADC decreases as low as 60% of normal may completely reverse.4–6

In experimental ischemia3,7,8 and human stroke,9,10 severely decreased ADC values are found within the ischemic core after acute focal ischemia with a gradient of lower ADC values toward the center of the lesion. In a rat model of permanent focal ischemia, the core of the ischemic lesion with the lowest ADC values continuously spreads to adjacent areas, recruiting tissue with moderately reduced values.8 Severely decreased ADC values in the ischemic core are correlated with ATP depletion and dense hypoperfusion, whereas moderate ADC decreases at the periphery were correlated with a lactate increase and tissue acidosis, indicative of penumbral tissue.3 Thus, it was hypothesized that a severe ADC decrease might serve as an indicator of tissue viability.11,12

The definition of irreversibly damaged tissue by severe ADC decreases seems attractive and could be valuable in the selection of patients for therapeutic interventions such as thrombolysis.11,13 However, ADC is a moving target, and pseudonormalization, defined as ADC normalization in the advent of a signal-intensive lesion in T2-weighted MRI, occurs somewhere between days 1 and 10.14–17 In animal experiments, early ADC normalization and transient ADC normalization with secondary ADC decrease have been described, depending on the duration and severity of ischemia.18–21 With increasing numbers of short-term DWI studies in acute stroke patients, normalization of initially decreased ADC values is reported in patients with spontaneous22,23 or therapeutic reperfusion.24
Little is known about the distribution and temporal development of ADC changes in humans and about the fate of the tissue with respect to the severity of the ADC decrease. We therefore addressed the distribution of ADC values within acute ischemic lesions over time to test the hypothesis that the proportion of severely decreased ADC values extends toward the periphery of the lesion. Moreover, we addressed the question of whether ADC normalization depends on the severity of the initial ADC decrease.

**Patients and Methods**

**Patients**

We enrolled 15 consecutive patients (1 woman, 14 men; age, 56.3 ± 8.0 years [mean ± SD]) with sudden onset of ischemic stroke within the last 6 hours. Initial MRI was performed 2.9 ± 0.8 hours (range, 2.0 to 4.8 hours) after the onset of symptoms. Follow-up examinations were done on days 1 and 7. The National Institute of Health Stroke Scale (NIHSS) score was assessed by a stroke neurologist at each imaging time point. Informed consent was obtained from all patients. The study was approved by the local ethics committee. Patients with global aphasia and neurological diseases other than ischemic stroke were excluded from the study.

**Imaging Methods**

MRI studies were performed on a 1.5-T clinical whole-body scanner (Magnemot Symphony, Siemens) with a standard head coil. The measurements included an axial DWI sequence, a PWI sequence, and an MR angiography (MRA). The table time was <20 minutes. DWI and PWI studies were run in corresponding slice positions (commissura anterior/posterior) to accomplish tissue parameter correlation between imaging modalities and within imaging time points. The single-shot, spin-echo, echoplanar-imaging anisotropic DWI sequence was acquired with a repetition time (TR) of 4800 ms and an echo time (TE) of 105.2 ms, 20 slices with a slice thickness of 6 mm, an interslice gap of 10%, a field of view (FOV) of 240 mm, a matrix of 256 × 256 pixels, and a flip angle of 90°. The resulting voxel dimensions were 0.9375 × 0.9375 × 6.6 mm, including interslice gap. Gradients with 3 different b values (0, 500, and 1000 s/mm²) in the x, y, and z axes were used. PWI was performed with a gradient-echo echoplanar imaging sequence, a TR of 1500 ms, a TE of 45.3 ms, 11 slices, slice thickness of 6 mm, interslice gap of 10%, an FOV of 240 mm, and a matrix of 128 × 128 pixels, with resulting voxel dimensions of 1.875 × 1.875 × 6.6 mm. The slice position was obtained from the DWI scan and placed in the center of the DWI lesion area. Contrast agent (25 mL gadolinium-DTPA 0.5 mmol/L, Magnevist, Schering, or equivalent compositions from other manufacturers) was applied by a power injector at 5 mL/s via a flexible cannula (1.2 to 1.4 mm Ø) into an antecubital vein. The bolus injection started 3 seconds after the first scan and was continuously followed by an infusion of 20 mL isotonic saline at a flow rate of 5 mL/s. Time-of-flight MRA was obtained by a 3-dimensional FISP sequence with a tracking saturation pulse, magnetization transfer saturation and TONE-up pulse, a TR of 29 ms, a TE of 6 ms, a flip angle of 20°, 3 slabs of 32-mm slab thickness, 32 partitions, a slice thickness of 1.0 mm, an FOV of 150 × 200 mm, and a matrix of 144 × 256 pixels.

**Postprocessing**

Postprocessing of the DWI and PWI data was performed offline with custom-written software (MRVision) and SPM 99 (Wellcome, Department of Cognitive Neurology) on a Linux PC workstation. ADC maps from each slice were generated from the DWI for each slice. The ADC value was calculated as a 3-point fit pixel by pixel with the Stejskal-Tanner equation: 

\[ ADC = \frac{-\ln(S_{1000}/S_0)}{b} \]

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where SI is signal intensity. For PWI, the changes in T2* were expressed as a change in relaxation rate (\( R_2^* \)), and calculated as 

\[ R_2^* = \frac{1}{T_2^*} \]

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and as 

\[ \Delta R_2^* = \frac{1}{T_2^*} - \frac{1}{T_2^*} \]

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and determined from the signal intensity at time point 1 after injection of the contrast agent and S0 is the signal intensity without contrast agent. Principles of the indicator dilution theory for nondiffusible tracers were applied to the analyzed concentration-time curves. A γ-variate fit was used on a pixel-by-pixel basis to compute parameter images of time to peak of signal drop (TTP).

ADC maps of days 1 and 7 were realigned to day 0 with SPM 99 to improve spatial positioning. The average ADC values of the complete nonaffected hemisphere were determined by applying an upper threshold value of 1.00 × 10⁻³ mm²/s to eliminate partial volume effects caused by high ADC values from cerebrospinal fluid in cortical sulci. Additionally, ADC values >1.00 × 10⁻³ mm²/s were checked for early ADC increases within the ischemic tissue by use of a threshold function.

Even within a healthy brain, especially in the white matter, ADC values as low as 0.23 × 10⁻³ mm²/s can be found. Thus, it has to be corrected for these physiologically occurring low ADC values. Otherwise, these voxels within the affected hemisphere would be misinterpreted to represent ischemic tissue. Mean ADC values were calculated for each patient in 11 slices from the nonaffected hemisphere and defined as 100%. Pixels with ADC decreases within the ranges of <50%, 50% to 60%, 60% to 70%, and 70% to 80% were tagged by use of a semiautomatic segmentation technique based on thresholding and seed growing. For each of these ranges of highlighted pixels, we calculated volumes (ADC range volumes) by multiplying the pixel count by the voxel size in both the affected and nonaffected hemispheres. We then subtracted the numerical value of each of the different ADC range volumes of the nonaffected hemisphere from the volume of the affected hemisphere. The remaining volume differences in each single range were the subject of further analysis. In this way, the volume of the analyzed ADC decreases was clearly due to ischemic compromise. Accordingly, ADC range volumes for days 1 and 7 were calculated.

The initial perfusion deficit was determined on the basis of thresholding and seed growing as volume with a TTP delay of >2, >4, and >6 seconds compared with the nonaffected hemisphere by use of a threshold function. A TTP delay of >4 seconds was chosen for the definition of perfusion deficit because it seems to correlate best with acute clinical deficit. 26

Using an adapted TIMI classification, we defined recanalization depending on the TTP map and MRA on day 1 as complete when there was no detectable perfusion deficit, as extensive when there was reperfusion of >50%, as minimal when there was reperfusion of <50%, and as no reperfusion. Hemorrhagic transformation was evaluated on the basis of the T2* source images of the PWI. We used a semiquantitative classification: no hemorrhagic transformation, minor hemorrhagic transformation of less than one third of the lesion, and transformation exceeding one third of the lesion volume in the b=0 (T2-weighted) image on day 7. The b=0-images of the DWI scan of day 7 were used as T2-weighted images for the determination of terminal lesion volumes to prevent a bias of interindividual different dynamics in ADC pseudonormalization on ADC maps.

**Results**

Volumes with an ADC decrease (n=15), perfusion deficits (n=15), and partial hyperperfusion (n=1) in PWI were detected at the first imaging time point. Vessel occlusion of the middle cerebral artery (MCA) in M1 (n=5), M2 (n=6), the intracranial part of the internal carotid artery (n=2), and the distal extracranial internal carotid artery with secondary MCA embolism (n=2) was identified by MRA and PWI. There was no instance of conflict between MRA and PWI. In 4 patients, our time-of-flight MRA failed to reveal vascular occlusion. Because of the pattern in PWI, a peripheral M2 occlusion was diagnosed.

Intravenous (n=7) and intra-arterial (n=1) thrombolysis was performed immediately after MRI in case of vessel occlusion and mismatch between DWI and PWI. Patients not treated with thrombolytic therapy met the following exclusion criteria: low
NIHSS score (n=1), disabling disease (n=4), lesion size on CT scan less than one third of the lesion (n=1), or lack of DWI-PWI mismatch by visual inspection (n=1). In 9 of 15 patients, reperfusion had occurred on day 1 [complete (n=6), extensive (n=1), minimal (n=2)]. In 6 patients, reperfusion was absent on day 1. Mean absolute ADC within the nonaffected hemisphere was 0.82±0.02×10⁻³ mm²·s⁻¹, which is in line with ADC values from previous reports. 16,28 Referring to the T2-weighted lesion size on day 7 as final infarct, the size of the area with an ADC decrease >80% (total ADC-based lesion volume) showed a weak correlation on day 0 (r=0.42, P<0.05) but a strong correlation on day 1 (r=0.82, P<0.05). Manually delineated lesions in ADC maps showed a good correlation (r=0.97, P<0.05) with total ADC-based lesion volumes determined by subtraction of the nonaffected hemisphere from the affected hemisphere. There was a tendency for underestimation of the lesion volume by the threshold technique, because the mean total ADC-based lesion volume accounted for 88±12% (mean±SD) of the manually delineated volume on the ADC map.

Development of Total ADC-Based Lesion Volume
As far as the development of the absolute size of the total ADC-based lesion volumes from day 0 to 1 is concerned, 2 patterns could be distinguished: an increase [n=11 (group A)] to a mean total ADC-based lesion volume of 257±14% (mean±SD) and a considerable reduction [n=4 (group B)] to a mean total ADC-based lesion volume 14%; range 0% to 44%] of the total ADC-based lesion volume. Within group A, patients with either a further increase in initial total ADC volume from day 1 to 7 or an unchanged ADC lesion volume [n=4 (group A1); mean compared with day 0 (day 1/7), 354/705%] could be distinguished from patients in group A2 who showed a secondary drop in the extent of the total ADC-based lesion volume from day 1 to 7 (n=7; 201/57%). Mean initial total ADC-based lesion volumes and final lesion volumes on day 7 (T2 weighted) were 43/166 mL (ADC/T2 weighted) in group A1, 22/72 mL in group A2, and 24/8 mL in group B. Group A1 showed a mismatch between ADC and T2-weighted lesions (121/80 mL) on day 1 with consecutive further lesion growth to 166 mL in T2-weighted lesions (Figure 1), whereas group A2 had no ADC/T2-weighted mismatch.
mismatch (50/53 mL) and presented only minor lesion growth to 72 mL.

Initial perfusion deficit determined by the volume of TTP delay >4 seconds was 181±70 mL (mean±SD in group A1, 91±51 mL in group A2, and 50±48 mL in group B (see the Table). The relative mismatch between ADC and TTP >4 seconds was 0.20±0.13 mL in group A1, 0.35±0.32 mL in group A2, and 0.86±0.60 mL in group B. Accordingly, the volume of TTP delay >2 seconds/>6 seconds was 264±58/136±66 mL in group A1, 148±67/61±39 mL in group A2, and 93±76/32±32 mL in group B.

Group A1 had no reperfusion (n=3) and 1 patient with minimal reperfusion on day 1 as determined by PWI and MRA (see the Table). In group A2, complete (n=2), extensive (n=1), minimal (n=1), and absent (n=3) reperfusion was observed. Exclusively complete (n=4) reperfusion was found in group B. Group A1 did not improve neurologically (mean NIHSS, 12.3±3.1 to 11.3±3.9) from day 0 to 7 (Figure 1), whereas groups A2 and B improved considerably (9.2±3.5 to 5.2±4.0 and 4.7±2.4 to 1.0±0.8, respectively).

Hemorrhagic transformation was detected in 4 patients in group A2 and 1 patient each in groups A2 and B. In 4 of 6 cases of hemorrhagic transformation, extensive or complete reperfusion was detected on day 1. A late occurrence of hemorrhagic transformation <1/3 on day 7 was detected in 1 case (patient 4). There was no further increase in hemorrhagic transformation volume and no case of symptomatic hemorrhage.

Development of ADC Range Volumes
In group A1, the initial mean <50% ADC range volume accounted for 12% of the total ADC volume. The proportion of this <50% ADC range volume increased to 30% on day 1, whereas the ADC range volume of 70% to 80% dropped from 30% to 18% (Figure 1). This reflects the spread of decreased ADC values to adjacent areas during the absolute increase in total ADC-based lesion volume (Figure 2). As in group A1, within a slightly increasing total ADC-based lesion volume in group A2, the ADC range volume of 70% to 80% dropped from 29% to 16%, whereas the <50% ADC range volume increased from 19% to 27% (Figure 1). On day 0 in group B, the ADC range volume of 70% to 80% represented 33% of the initial composition. The mean <50% ADC range volume and 50% to 60% ADC range, both of which represent absolute ADC values of <0.50×10⁻³ mm²·s⁻¹, accounted for 8% and 23% of the total ADC-based lesion volume. In group B, 86% of the initial total ADC-based lesion volume was normalized on day 1. Because of the low number of voxels (n<210) within the total ADC-based lesion volume on day 1 (<1.2 mL in 3 patients) and the resulting partial volume effects, no statistical comparisons between the ADC range volumes were performed in group B on days 1 and 7. The total ADC-based lesion volume on day 1 is less than half of the initial <60% ADC range volume.

Thus, normalization must have included, at least partially, the severely reduced ADC range volumes (<50% and 50% to 60%; eg, see Figure 2, patient 7). In 2 patients (patients 5 and 7), the terminal lesion (T2 weighted) on day 7 was less than half of the initial 60% ADC range volume, reflecting true normalization within this range. Mean ADC values in the <50% lesion volume were 401±15×10⁻⁶ mm²/s (mean±SD) in group A1, 424±41×10⁻⁶ mm²/s in group A2, and 411±49×10⁻⁶ mm²/s in group B without significant difference between the groups.

The mean relative composition of the ADC range volumes seemed to be more or less stable within the small total ADC-based lesion volume on days 1 and 7.
Discussion

We followed the temporal and spatial development of ADC values after acute ischemia in stroke patients to determine the fate of the tissue with respect to the severity of the ADC decrease. Areas with severe ADC decreases expanded into the periphery if timely reperfusion did not occur. Early pseudonormalization on day 1 was observed in patients with reperfusion. We found that ADC values within the time window for thrombolysis do not predict tissue viability. Although areas with severe ADC values are found mainly within the ischemic core and are severely malperfused, severe ADC decreases may completely normalize. This is likely to depend mainly on the time point of reperfusion. ADC normalization is not a rare event (4 of 15 patients in the present series), and it is not limited to tissue with moderately decreased ADC values (at least more than half of the area with ADC values <60% normalized).

ADC Normalization

We have shown that ADC values do not serve as a viability threshold at an early time point after ischemia, and even within the <50% ADC range volume, we observed complete recovery as defined by normal T2-weighted imaging on day 7 (n=1). Our results reconfirm recent reports that ischemic tissue with severe ADC decreases may well recover. Absolute ADC values represent a moving target and reflect the dynamics of specific stages of the ischemic cascade and histomorphological development. In animal studies of MCA occlusion, the degree of the ADC decrease was related to the location and extent of neuronal injury, with the most dramatic changes occurring within the areas displaying the most severe histological damage. It was shown recently that the initial ADC decrease is correlated with not only swelling of astrocytes, dendrites, and endothelial cells but also shrinkage of the neuronal soma. Kuroiwa et al reported that a significant decrease below a specific ADC threshold value is not necessarily associated with histological changes indicating irreversible injury after 3 hours of MCA occlusion in cats, whereas others described a strong association in newborn rats. Animal studies did not find ADC thresholds to be associated with irreversible tissue injury independent from the duration of ischemia. After 2 hours of ischemia, the degree of ADC decrease was significantly correlated with the degree of ischemic cell damage documented by histopathology but not at later time points.

The reversibility of signal hyperintensities in DWI does not necessarily reflect complete salvage of brain tissue from ischemic injury, and in cases of reverse DWI lesions and normal-appearing tissue in T2-weighted MRI, a partial neuronal necrosis was observed. Thus, the true extent of neuronal damage may be underestimated by T2-weighted MRI. It therefore has to be evaluated whether normal-appearing T2-weighted MRI in humans on day 7 after stroke is a reliable measure of ischemic tissue recovery. Preliminary data show that selective neuronal necrosis may occur after resolution of mismatch areas that may be depicted by iomazenil SPECT.

Figure 2. ADC maps of patients representing groups A1 (patient 11), A2 (patient 10), and B (patient 7) on days 0, 1, and 7. With the use of a threshold function, areas within <50%, 50% to 60%, 60% to 70%, and 70% to 80% vs the nonaffected hemisphere are color coded (see legend). Note the concentric lesion development in patients in groups A1 and A2 and the recovery independent of initial ADC in patient 7.
The ADC behavior of group A2 in our study follows the previously described temporal development of pseudonormalization (normal ADC, lesion in T2-weighted MRI)14,15,39 1 to 10 days after acute stroke, which is attributed to the increased extracellular water content with early development of vasogenic edema. On day 7, the lesion in T2-weighted MRI was considerably larger than the ADC lesion volume in groups A and B, indicating that the mismatch of ADC and <T2-weighted lesion volume represents the tissue with pseudonormalization. It was hypothesized that pseudonormalization of ADC as early as 1 day after intravenous thrombolysis represents reperfusion injury with early cell lysis.17 Because the volume of hemorrhagic transformation did not increase in patients in group A2 from day 1 to 7, this aspect cannot account for the considerable pseudonormalization of ADC values in this group. In a recent article, Kidwell and colleagues25 reported a late secondary ADC decrease on day 7 that occurred after transient ADC normalization 3 hours after intra-arterial thrombolysis. Secondary ADC decrease after initial ADC normalization is known from animal experiments and underlines the fact that ADC values are a poor predictor of tissue recovery.19,32,35,40

A major target in stroke imaging remains the prediction of the functional stroke outcome.41 It was previously reported that the neurological status correlated well with both with DWI lesion volume4,22–44 and the degree of the ADC decrease.44,45 In our study, the neurological outcome measured by the NIHSS was correlated with the temporal development and degree of ADC decrease. Additionally, with comparable initial NIHSS scores in groups A1 and A2, the outcome was better in group A2, in which considerable pseudonormalization of ADC values was found on day 7 (Figure 1). In patients with good clinical recovery (group B), there is a gross transformation of areas with severe diffusion impairment toward normal values at day 1 and a comparably small or even absent lesion in T2-weighted MRI.

A perfusion deficit determined by a TTP delay >4 seconds was shown to correlate with acute clinical deficit, whereas a TTP delay >6 seconds correlated best with lesion volume.26 We found considerable differences in the mismatch between ADC and TTP >4 seconds (group A1, 0.20±0.13 mL; A2, 0.35±0.32 mL; and group B, 0.86±0.60 mL). Thus, volume with a severe TTP delay exceeding the total ADC volume indicated further lesion growth beyond the initial total ADC volume.

Development of ADC Range Volumes
Under experimental conditions, the core of the ischemic lesion with lowest ADC values continuously spread over time to adjacent areas.8 We made a similar observation and found a concentric expansion of low ADC values (ADC range volume <50%) in the absence of recanalization (Figure 2, patient 10) accompanied by an increase in total lesion size and less favorable outcome. Group A1 showed a mismatch between ADC and T2-weighted lesion volumes (ADC>T2 weighted) on day 1 with consecutive further lesion growth by 101% in T2-weighted lesions (Figure 1). A possible explanation of this ADC/T2-weighted mismatch on day 1 might be the prolonged presence of tissue at risk of infarction46 (Figure 1). The less pronounced lesion growth (35% in T2-weighted MRI) in group A2 in the absence of this mismatch might be predominantly due to edema.47 In all patients, the total ADC-based lesion volume shows a relatively weak correlation with terminal lesion volume in T2-weighted lesion on day 0, whereas on day 1, there was a strong correlation. This might be due to the early imaging time point in our study. The very good correlation between initial lesions in DWI and terminal lesions in former investigations44 might be explained by the later time point of the first MRI study, by which the fate of the tissue was already determined. Correspondingly, in our study, total ADC-based lesion volume on day 1 correlated much better with T2-weighted lesion volume (day 7) compared with total ADC-based lesion volume on day 0. Thus, ADC decreases may have been meaningful in terms of tissue viability at later time points.

Recovery of ADC values does not show a concentric development (Figure 2, patient 7). As was observed in group A, an increase in lesion size beyond 24 hours is a well-described phenomenon,43,44,48,49 with a maximum DWI lesion volume around day 3.44 For comparisons with these previous investigations, it is important that we had a good correlation between the manually delineated lesion volumes and the volumes determined by thresholding. Compared with the manually delineated terminal lesion volumes in T2-weighted MRI, our ADC range areas were rather underestimated. Thus, the initial severely decreased ADC range volumes would have been even larger with more pronounced normalization if manually delineated.

Differences in absolute ADC values50 and dynamics of ADC changes23 between gray and white matter were not considered because the separation seemed complex for the stroke subtypes included in our study. Although there is regional heterogeneity in the development of absolute ADC values,23,40 the spreading rate of the ADC decrease to adjacent areas seems to be similar in all regions.47

Conclusions
Our data suggest that ADC values of human stroke measured at a time point relevant for thrombolysis do not serve as absolute indicators of tissue viability in individual patients. We found ADC normalization in tissue with even severely decreased ADC at a rate not expected from the literature. The normalization of ADC values is in line with the concept that ischemic tissue with an ADC decrease may include the penumbra.

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