Time Course of ADC<sub>w</sub> Changes in Ischemic Stroke: Beyond the Human Eye!

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Background and Purpose—Using newly developed computerized image analysis, we studied the heterogeneity of apparent diffusion coefficient of water (ADC<sub>w</sub>) values in human ischemic stroke within 10 hours of onset.

Methods—Echo-planar trace diffusion-weighted images from 9 patients with focal cortical ischemic stroke were obtained within 10 hours of symptom onset. An Iterative Self-Organizing Data Analysis (ISODATA) clustering algorithm was implemented to segment different tissue types with a series of DW images. ADC<sub>w</sub> maps were calculated from 4 DW images on a pixel-by-pixel basis. The segmented zones within the lesion were characterized as low, pseudonormal, or high, expressed as a ratio of the mean±SD of ADC<sub>w</sub> of contralateral noninvolved tissue.

Results—The average ADC<sub>w</sub> in the ischemic stroke region within 10 hours of onset was significantly depressed compared with homologous contralateral tissue (626.6±76.8 vs 842.9±60.4×10<sup>-6</sup> mm<sup>2</sup>/s; P<0.0001). Nevertheless, ISODATA segmentation yielded multiple zones within the stroke region that were characterized as low, pseudonormal, and high. The mean proportion of low:pseudonormal:high was 72%:20%:8%.

Conclusions—Despite low average ADC<sub>w</sub>, computer-assisted segmentation of DW MRI detected heterogeneous zones within ischemic lesions corresponding to low, pseudonormal, and high ADC<sub>w</sub> not visible to the human eye. This supports acute elevation of ADC<sub>w</sub> in human ischemic stroke and, accordingly, different temporal rates of tissue evolution toward infarction. (Stroke. 1998;29:1778-1782.)

Key Words: cerebral ischemia, focal ■ magnetic resonance imaging ■ signal processing, computer assisted ■ stroke, acute

Recent studies have highlighted the clinical value of diffusion-weighted imaging (DWI) in stroke diagnosis<sup>1,2</sup> and the potential of the apparent diffusion coefficient of water (ADC<sub>w</sub>) measurement to stage, quantify, and predict histopathologic damage in ischemic brain infarcts.<sup>3</sup> The precise staging of ischemic stroke evolution and prediction of cell death at very early times of clinical study with DWI remain challenging. Using computer-assisted image postprocessing and cluster analysis, we observed regions of elevated ADC<sub>w</sub> in human ischemic stroke within the first 10 hours after the symptom onset. Other investigators, who visually identified the ischemic focus and calculated an average ADC<sub>w</sub>, reported persistence of low ADC<sub>w</sub> values for 4 to 8 days after the onset of symptoms.<sup>1,2,4</sup> These disparate results may be explained in part by differences in the methods of diffusion imaging, direction of applied diffusion gradients, and differences in image processing.<sup>3,6</sup> Accordingly, we performed DWI using methods and equipment that more closely replicated the experimental measurement conditions of other centers and measured the orientation-independent trace ADC<sub>w</sub>. Again, using image postprocessing and an Iterative Self-Organizing Data Analysis Technique (ISODATA) clustering algorithm,<sup>7</sup> we report pseudonormalized and elevated ADC<sub>w</sub> in regions of acute stroke studied within 10 hours of the onset. We conclude that visually evaluating diffusion-weighted (DW) intensity changes may not accurately detect the heterogeneous nature of ADC<sub>w</sub> abnormalities in an acute ischemic stroke, or, accordingly, the changes in ADC<sub>w</sub> over time.

Subjects and Methods

Clinical Patients
We studied the first 9 patients who presented to us with acute onset of neurological symptoms and signs of focal cerebral ischemia and successfully completed the imaging protocol within 10 hours of onset. Their ages ranged from 45 to 83 years. Six were women and 3 were men. Clinically, 7 patients had middle cerebral artery (MCA) distribution infarct, 1 patient had anterior cerebral artery distribution infarct, and 1 had ischemia in the right inferior cerebellar artery. Four patients had MR angiography that confirmed occlusion of the MCA, 2 of whom had associated internal carotid artery occlusion as well. Two patients with MCA branch territory ischemia were diagnosed with embolic stroke on the basis of clinical as well as imaging information. In the other 7, the mechanism of arterial occlusion was considered thromboembolic, caused by atheromatous arterial disease with established risk factors.

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The patients were studied between 5.5 and 9.25 hours after stroke onset. All patients or appropriate family member or guardian signed informed consent. The study was approved by the Institutional Review Board of the Henry Ford Health Sciences Center.

**Imaging Methods**

Diagnostic DW images were acquired on a 1.5-T GE Signa whole-body scanner, coincident with routine MRI and MR angiography diagnostic imaging. Transaxial trace DW images were obtained with a single-shot, spin-echo, echo-planar imaging sequence. The FDA-approved echo-planar DWI sequence contained second-order eddy current compensation, which eliminated geometric distortions from the diffusion gradients. This was verified by overlaying the outlines (determined from the b=0 s/mm² image) of both the edges and the internal structures of the brain onto the DW images from the different b values. There was no mismatch in the images, thus indicating that eddy currents did not contribute to any distortion. Four sets (b=900, 600, 300, and 0 s/mm²) of trace DW images were obtained for all patients. Contiguous 6-mm-thick slices with a 230-mm field of view, with echo time of 99 ms and 128×128 matrix of the whole brain, were acquired. The single-shot DW images were obtained sequentially with X, Y, and Z diffusion weighting and then averaged. The scan time for trace DWI of the entire head per b value was 32 seconds, and the total scan time for the 3 sets of b values was 96 seconds. In addition, spin-echo T2-weighted images were obtained with echo time of 90 ms, repetition time of 2500 ms, 256×192 matrix, and other imaging parameters identical to those of DW images.

**Image Analysis**

Fourier-transformed, multiple-source DW MR images were processed for multispectral segmentation. Before segmentation, all image data sets were 3-dimensionally coregistered with a head and hat approach to compensate for patient motion between multiple scans. Next, the intracranial volume was segmented from the image background and skull by thresholding the signal intensity from recognized anatomic structures. The image background was discarded. Subsequently, white noise in the images was suppressed by multidimensional restoration filtering. For this, we used a nonlinear edge-preserving filter that maintained average partial volume information.

Tissue was segmented with the use of an ISODATA clustering algorithm. ISODATA is a robust segmentation algorithm that has the ability to self-adjust the number of clusters. It is an unsupervised clustering algorithm based on techniques of multivariate statistical analysis in which cluster centers are iteratively determined sample means. In addition, our algorithm includes a set of merging and splitting procedures. Image segmentation is based on both the spatial and feature domain properties of the MRI data. The spatial domain properties include the relationship between a pixel and its neighbor, for example, connectivity of pixels with similar gray levels or distance from the closest pixel with the same gray level. The feature domain properties include those of the image gray level distribution. In this algorithm, the euclidean distance in feature space between tissue patterns is used as a measure of their dissimilarity. To prepare the data for the clustering algorithm, a feature vector is constructed at each spatial location from the set of input data. The number of MR images per slice determines the dimension of the feature space in which the clusters are formed. The ISODATA algorithm identifies cluster centers in the multidimensional feature space (here, 4-dimensional feature space defined by the 4 DW images) and then classifies pixels to the closest cluster center. There is no specific shape associated with clusters in the feature space; they may have arbitrary shapes. If desired, the operator may generate a visualization of the partitioned feature space to examine cluster shapes (Figure 1d). Shape analysis is of interest in itself but beyond the scope of this report. A flowchart of the algorithm and its explanation are detailed in Reference 7. Calculation of ADCw maps is unnecessary for the ISODATA clustering algorithm; thus, a major advantage of ISODATA is that it segments the image using all the discriminating information implicitly available in the data.

The resulting segmented regions were classified into normal (white matter, gray matter, and cerebrospinal fluid) and abnormal tissue (zones of stroke and partial volumes) by superimposing the clusters on the highest DWI and visually examining the location of the cluster (an example is illustrated in Figure 1d). Furthermore, the classification is based on both spatial and feature domain properties of MRI. The spatial domain properties included the relationship between a region and its neighbors, ie, size of connected pixels in a region and connectivity of the regions in 3 dimensions. The feature domain properties included similarity of the signature vectors associated with segmented regions (ie, the cluster centers) and the gradient and texture of the region. Clusters consisting of merely sparse pixels were assumed to be generated as a result of noise and thus were not classified as meaningful tissue types. Anatomic knowledge of the human brain was used to avoid misclassification.

An ADCw map of each slice was generated from the 4 sets of DW images. The ADCw was calculated on a pixel-by-pixel basis on the basis of the Stejskal and Tanner equation

\[
ADC_w = -\frac{\ln(SI_1/SI_0)}{b}
\]

where SI0 is the pixel signal intensity from image acquired with no diffusion gradients, ie, b=0 s/mm² image; SI1 is the pixel signal intensity with diffusion gradients on; and b is the diffusion sensitive factor that is dependent on the diffusion gradient strength, the gradient duration, and the diffusion time. The logarithm of intensity values for each pixel was used in a linear least-squares fit to obtain the map. The volume of each cluster was determined from the number of pixels. Regions of interest, corresponding to clusters comprising the ischemic tissue in each slice, were projected onto the map to obtain the mean and SD of the ADCw. The ADCw value of each cluster was compared and normalized to that of the contralateral noninvolved homologous region. Normalization eliminated the need for comparisons with a control group, avoiding intersubject variability, and minimized variability due to gradient eddy currents. It also avoided the use of absolute ADCw values because the accuracy in ADCw determination is inherently dependent on the range of b values used in the calculation.

Interoperator reliability measurements were performed; results of the ISODATA segmentation were identical, and the differences in the ADCw values were <1%. Also, ADCw maps were evaluated with the use of (1) unprocessed images and (2) processed (noise-filtered) images; the values obtained from the unprocessed and processed images for both normal tissue and ischemic regions had <1% difference.

**Data Analysis**

The ADCw of contralateral nonischemic tissue (N) and SD were used to classify the ISODATA segmented regions of the ischemic foci into 3 groups, namely, low (L), pseudonormalized (P), and high (H) ADCw. Regions of pixels in the ischemic region were classified as L if the ADCw was <N–SD, P if >N–SD but <N+SD, and H if >N+SD. Classification was also performed with the use of 1.5 and 2 SD to define the ranges of L, P, and H. Only 1 SD of the ADCw of normal tissue was used in the classification of the ischemic zones so as not to skew the data in favor of P and H (see Results). The percentage of L, P, and H of the total lesion volume was calculated. Finally, the average ADCw of the entire lesion volume was calculated.

**Statistical Analysis**

The average ADCw values of normal and ischemic tissue are presented as mean±SD. Statistically significant differences in ADCw of the ischemic tissue were tested against the noninvolved contralateral tissue with a paired t test; the significance level was set at P<0.05.

**Results**

In each patient, DW images (b=900 s/mm²) of the entire brain were reviewed visually. In all 9 patients, the ischemic region was conspicuous in ≥1 of the contiguous slices of the trace DW images. In the total patient group, the mean of the average ADCw in ischemic tissue (626.2±76.8×10⁻⁶ mm²/s) was significantly different (P<0.0001) from contralateral homologous noninvolved tissue (842.9±60.4×10⁻⁶ mm²/s) (Table). The numbers of pixels with high values according to
the 1-, 1.5-, and 2-SD classification were on average within 20% of each other, but there was an ~50% decrease in the number of pixels with low values (these pixels shifted to pseudonormal) when changing from the 1-SD to 2-SD classification. Thus, to avoid skewing the data toward pseudonormal and high values, the 1-SD classification was used in the analysis. The table also shows that the percentage of pixels with low ADCw in individual patients ranged from 56 to 91.

<table>
<thead>
<tr>
<th>Hours to Study After Ictus</th>
<th>Total No. of Pixels in Stroke</th>
<th>ADCw of Noninvolved Tissue, ×10^-6 mm²/s</th>
<th>Average ADCw in Stroke Lesion, ×10^-6 mm²/s</th>
<th>% of Pixels With Decreased ADCw</th>
<th>% of Pixels With Pseudonormal ADCw</th>
<th>% of Pixels With Elevated ADCw</th>
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<tr>
<td>5.50</td>
<td>5655</td>
<td>868.3</td>
<td>659.7</td>
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<td>5.80</td>
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<tr>
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<td>481.2</td>
<td>91.24</td>
<td>8.12</td>
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<td>2106</td>
<td>936.4</td>
<td>599.8</td>
<td>66.60</td>
<td>33.40</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Mean±SD ADCw of noninvolved tissue (n=9)=842.9±60.4×10^-6 mm²/s
Mean±SD ADCw of stroke (n=9)=626.2±76.8×10^-6 mm²/s

Range of L=56 to 91
Mean±SD of L=72.2±9.6

Range of P=4 to 33
Mean±SD of P=20.3±10.1

Range of H=0 to 17
Mean±SD of H=7.5±5.9

The heterogeneity of ADCw in the ischemic tissue is demonstrated by the percent volume of ischemic tissue with depressed (L), pseudonormalized (P), and elevated (H) values compared with that of contralateral noninvolved tissue. The group mean of the average ADCw of each stroke was significantly different from noninvolved tissue (P<0.0001).
to 91 with a mean of 72.2, the percentage of pixels with pseudonormal ADC<sub>n</sub> ranged from 4 to 33 with a mean of 20.3, and the percentage of pixels with high ADC<sub>n</sub> ranged from 0 to 17 with a mean of 7.5. These results show the heterogeneity of ADC<sub>n</sub> values in the ischemic focus.

Further evidence of ADC<sub>n</sub> heterogeneity was obtained when multiple zones were segmented within the ISODATA isolated ischemic lesion in all 9 patients. The following figures were chosen to illustrate patterns of segmentation observed in different patients. Figure 1a to 1d shows results from a patient with 2 separate zones of low but different ADC<sub>n</sub> values within the lesion that presumably reflected tissue at different stages of ischemic injury. One or more segmented zones of low but different ADC<sub>n</sub> was typical of each patient studied. Figure 1e and 1g are from the ischemic focus of a different patient and illustrate how image postprocessing is important to detecting pseudonormalized ADC<sub>n</sub>. Figure 1f shows 3 (blue, green, and yellow) zones of low ADC<sub>n</sub> and an outer zone (red) of pseudonormalized ADC<sub>n</sub>. The zone of pseudonormal ADC<sub>n</sub> was uniquely segmented from other brain regions. Despite having normal ADC<sub>n</sub> values, the signal strength of the pseudonormal zone compared with the signal strength of the contralateral noninvolved normal tissue was not the same for the 4 sets of DWI of this slice. Thus, this zone had a unique vector feature in the 4-dimensional feature space that uniquely distinguished it from normal tissue due to elevated T2 and that enabled its designation as pseudonormal. The pseudonormal zone was coincident with regions of hyperintensity on the T2 image (data not shown).

Figure 2 provides images from 2 patients, 1 of whom (Figure 2a, 2b, and 2c) exhibited high ADC<sub>n</sub> in marginal zones that surrounded a low ADC<sub>n</sub> core. In the other patient (Figure 2d, 2e, and 2f), the lateral zone had a low ADC<sub>n</sub> and the medial a region of high ADC<sub>n</sub>. Figure 3 illustrates that low, pseudonormal, and high ADC<sub>n</sub> zones often were not confined to a set pattern but were “jigsawlike” in composition and distribution. For example, zones of high ADC<sub>n</sub> were not confined to the periphery or to the interior of a lesion but randomly distributed in a pattern not attributable to partial volume effects. As shown in Figure 3b (the b=0 s/mm<sup>2</sup> DWI can be considered a T2-weighted image), the hyperintense areas were coincident with pseudonormal and high ADC<sub>n</sub> values of the lesion.

**Discussion**

Reports of the time course of ADC<sub>n</sub> changes in ischemic brain have differed between laboratories. This may be explained in part by the differences in the methods of the diffusion imaging and in the direction of applied diffusion gradients. Therefore, in the present study we measured the orientation-independent trace ADC<sub>n</sub> with imaging methods and equipment similar to that used by others. For example, we used an echo-planar imaging sequence and a 1.5-T scanner as opposed to a 3-T magnet. The mean ADC<sub>n</sub> value of contralateral noninvolved tissue obtained from our present study is in good agreement with the ADC<sub>n</sub> for control (normal) human brain (825 ± 170 × 10<sup>-6</sup> mm<sup>2</sup>/s). Another important explanation for the discrepancies may lie in visually identifying ischemic strokes by intensity increases on the DW images and in calculating its average ADC<sub>n</sub> and sampling regions of maximum intensity. Such visual selection may miss regions of pseudonormalization and be insensitive to regions of low intensity and correspondingly high ADC<sub>n</sub> within or outside the intense focus. Averaging the ADC<sub>n</sub> values may also average out pseudonormal or high values. To overcome these limitations, in past and present studies we performed computer analysis and segmentation of the total lesion.

Our present computer analysis eliminated user bias. ISODATA automatically isolated normal and abnormal clusters. There are no potential artifacts or weaknesses associated with the clustering algorithm, assuming that (1) data are free of artifacts, (2) the parameters for the algorithm are set appropri-
Zones of pseudonormal and high ADC were not confined to that pseudonormal and high ADC values were segmented islate total ischemic volumes. The ISODATA uted regions of pseudonormal or high ADC values. The ISODATA algorithm was trained to understand the mathematical basis of the algo-mathematical basis of the algorithm, and the operator of the algorithm, and the operator was trained to understand the mathematical basis of the algorith-r and its behavior through simulation and phantom studies for which the truth was known. We used this procedure to iso-total ischemic volumes.

When we calculated the average ADC\textsubscript{c} from each patient and the mean and SD of these averages from the total group of stroke patients studied within 10 hours, the ADC\textsubscript{c} was significantly reduced compared with nonischemic brain. Despite this, using ISODATA analysis of ischemic to contra-lateral noninvolved homologous tissue ADC\textsubscript{c} ratios, we showed that pseudonormal and high ADC\textsubscript{c} values were segmented throughout the ischemic volumes. Thus, averaging the values in the total lesion volume obscured heterogeneously distrib-uted regions of pseudonormal or high ADC\textsubscript{c}. The ISODATA pixel-by-pixel cluster analysis and segmentation routine therefore appear critical in discriminating normal tissue from abnormal ischemic regions and their heterogeneous distribution, especially in detecting pseudonormalized ADC\textsubscript{c} values. Also, accepting that pseudonormalized and high ADC\textsubscript{c} values reflect later stages in the evolution of ischemic cellular damage, our images reveal that the conventional notion of an infarcted core with potentially viable ischemic tissue in a penumbral location does not always pertain to human strokes.

To stage cerebral ischemic damage in clinical stroke independent of time, we proposed a MR signature model in which ADC\textsubscript{c} was combined with T2 and related to the histopathology of experimental ischemic infarction. The utility of this multiparametric model was questioned because of perceived differences in the time course of changes in ADC\textsubscript{c} between animal ischemia models and human strokes. Our present results suggest that the previously reported differences in ADC\textsubscript{c} values during the evolution of human ischemic strokes in part can be explained by difficulty in identifying accurately the heterogeneous nature of ADC\textsubscript{c} abnormalities on DWI, and they should not prohibit the validation of models that use MR signatures to stage, quan-ify, and predict histopathologic damage in ischemic infarcts.

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