Multiparametric MRI ISODATA Ischemic Lesion Analysis Correlation With the Clinical Neurological Deficit and Single-Parameter MRI Techniques

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Background and Purpose—The purpose of this study was to show that the computer segmentation algorithm Iterative Self-Organizing Data Analysis Technique (ISODATA), which integrates multiple MRI parameters (diffusion-weighted imaging [DWI], T2-weighted imaging [T2WI], and T1-weighted imaging [T1WI]) into a single composite image, is capable of defining the ischemic lesion in a time-independent manner equally as well as the MRI techniques considered the best for each phase after stroke onset (ie, perfusion weighted imaging [PWI] and DWI for the acute phase and T2WI for the outcome phase).

Methods—We measured MRI parameters of PWI, DWI, and T1WI from patients at the acute phase (<30 hours) and DWI, T2WI, and T1WI at the outcome phase (3 months) of ischemic stroke. The clinical neurological deficit was graded with the National Institutes of Health Stroke Scale (NIHSS). We compared the ISODATA lesion size with the PWI, DWI, and T2WI lesion sizes measured within the same slice at each phase. The lesion sizes were also correlated with NIHSS score of each phase.

Results—We included 11 patients; 9 (82%) were women, and 7 (64%) were black. The mean ± SD age was 65.5 ± 9.3 years (range, 45 to 82 years). The median NIHSS score was 15 (minimum, 4; maximum, 24) at the acute phase and 3 (minimum, 0; maximum, 22) at the outcome phase. The median time interval from stroke symptom onset to the acute MRI study was 10 hours (range, 6 to 29 hours), and the mean time interval to the outcome study was 93 ± 11 days (range, 72 to 106 days). In the acute phase, the ISODATA lesion size had high correlation with the PWI lesion size (r = 0.95; 95% CI, 0.89 to 0.98; P < 0.0001), DWI lesion size (r = 0.83; 95% CI, 0.66 to 0.92; P < 0.0001), and T2WI lesion size (r = 0.67; 95% CI, 0.39 to 0.84; P = 0.008) and moderate correlation with NIHSS score (r = 0.59; 95% CI, 0.02 to 0.88; P = 0.06). In the outcome phase, the ISODATA lesion size had high correlation with the T2WI lesion size (r = 0.97; 95% CI, 0.94 to 0.99; P < 0.0001) and NIHSS score (r = 0.78; 95% CI, 0.34 to 0.94; P = 0.004).

Conclusions—The integrated ISODATA method can identify and characterize the ischemic lesion independently of time elapsed since stroke onset. The ISODATA lesion size highly correlates with the PWI and DWI lesion size in the acute phase and with the T2WI lesion size in the outcome phase of ischemic stroke, as well as with the clinical neurological status of the patient. (Stroke. 2002;33:●●●●●●.)

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

Standard neuroimaging techniques such as CT and T1-weighted (T1WI) and T2-weighted (T2WI) MRI give high false-negative rates for lesion identification during the first hours after onset of brain ischemia1–6; therefore, such negative scans are unreliable predictors of outcome. The new experimental interventions in ischemic stroke are best initiated during the first several hours after onset, when the potential for positive effects is greatest but diagnostic uncertainty also is greatest.

Within minutes after induction of cerebral ischemia in animal models and within a very short time in patients with acute ischemic stroke, perfusion-weighted imaging (PWI) can delineate areas of hypoperfusion, and diffusion-weighted imaging (DWI) can reveal areas of neuronal injury.4–6 In the acute phase of ischemic stroke, the lesion is usually larger in PWI than in DWI or T2WI.7–9 The acute-phase PWI lesion size correlates highly with the acute-phase clinical neurological status,7–9 and the acute-phase DWI lesion size correlates.
well with acute-phase clinical neurological status, neurological outcome, and final infarct volume. The exact significance of the acute-phase lesion defined by these 2 techniques, in regard to prediction of tissue viability and infarct size, remains to be determined.

In most major academic clinical centers, DWI, T2WI, and T1WI studies are often obtained in the acute phase of stroke. Integration of the data obtained through each of these techniques into a single image may provide more information than would be obtained by the separate images on the degree, extent, and inhomogeneity of the ischemic brain injury. Therefore, the introduction of an objective computerized segmentation of the ischemic brain lesion would be expected to improve the identification and classification of the ischemic brain tissue. We have previously used unsupervised segmentation of the ischemic lesion in an experimental stroke model by using the Iterative Self-Organizing Data Analysis (ISODATA) method of postprocessing analysis and shown that the ISODATA is an objective, time-independent method for assessing the status of ischemic tissue, whereas all other methods are time dependent. In the present study, we use unsupervised segmentation of the ischemic lesion by using a standardized form of the ISODATA method of postprocessing analysis, and we seek to assess whether the unsupervised objective ISODATA method is capable of defining the size of the ischemic lesion in clinical stroke patients equally well as the currently used techniques (PWI, DWI, and T2WI) at the acute and chronic phases of ischemic stroke. Our hypothesis is that the ISODATA method is a time-independent method and, as such, can define the ischemic lesion at both the acute and chronic phases of ischemic stroke as well as the gold standard techniques for each phase, namely PWI and DWI for the acute phase and T2WI for the chronic phase.

Patients and Methods

Patients

The patients in this study were part of a larger cohort of 153 patients who had ischemic stroke and were enrolled in the MRI-Stroke Registry. For the MRI-Stroke Registry, patients with sudden focal neurological deficit consistent with ischemic stroke, within 24 hours of onset, and with no contraindications for MRI scanning were recruited prospectively from the Stroke and Inpatient Neurology Services of Henry Ford Hospital from January 1998 to January 2001. Patients treated with intravenous recombinant tissue plasminogen activator were recruited even past the first 24 hours up to 36 hours from onset. Stroke onset was defined as the last time the patient was known to be without neurological deficit. All patients were examined by the study neurologist. The clinical neurological deficit was graded with the National Institutes of Health Stroke Scale (NIHSS) score. The NIHSS was performed at the time of each MRI study. The clinical localization of stroke was based on the results of the neurological examination. The cause of the ischemic stroke was defined according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria. The MRI studies were performed according to the prespecified protocol (see below) at the following time intervals since stroke onset: acute, <24 hours from onset (patients treated with recombinant tissue plasminogen activator <36 hours from onset); subacute, 3 to 5 days from onset; and outcome, 90 days from onset. Patients were excluded if they had cerebral hemorrhage, preexisting significant neurological conditions, or history of prior stroke that would hamper interpretation of clinical and radiological data. All patients or appropriate family members gave informed consent before enrollment. The study was approved by the Human Rights Committee of the Henry Ford Health Sciences Center.

MRI Methods

MRI Data Acquisition

The MRI scans were performed at 2 time points, the acute (0 to 36 hours) and the outcome (3 months) phases after stroke onset. All MRIs were performed on a 1.5-T General Electric Signa MRI unit with echo-planar capability. This protocol takes ~35 minutes to complete (not including the PWI preparation and scan time). The MRI parameters were as follows: (1) sagittal T1WI: repetition time (TR), 600 milliseconds; echo time (TE), 14 milliseconds; field of view (FOV), 23 × 23 cm; matrix, 192 × 256; slice thickness, 6 mm; no interslice gap; (2) axial T2WI: TR, 2500 milliseconds; TE, 30, 60, 90, and 120 milliseconds; number of excitations (NEX), 1; FOV, 23 × 23 cm; matrix, 192 × 256; slice thickness, 6 mm; no interslice gap; (3) axial T1WI: TR, 450 milliseconds; TE, 1000 milliseconds; NEX, 2; FOV, 23 × 23 cm; matrix, 192 × 256; slice thickness, 6 mm; no interslice gap; and (4) axial DWI: TR, 10 000; TE, 101 milliseconds; b value, 1000, 600, 300, and 0 s/mm²; FOV, 23 × 23 cm; matrix, 128 × 128; slice thickness, 6 mm; NEX, 1; no interslice gap; on 3 orthogonal axes. Throughout the acquisition of the images, the patient was clinically monitored.

PWI Processing

PWI images were obtained at the acute time point by use of a dynamic first-pass bolus tracking of Gd-DTPA (Magnevist, Berlex) with an echoplanar imaging gradient-echo sequence (TR/TE, 1550/40 milliseconds; height, 12 mm). The Gd-DTPA bolus (25 cm³) was administered by a power injector over 5 seconds via an antecubital fossa cannula. The noise of the PWI images obtained was suppressed with a Gaussian low-pass filter. The parametric exponential model-dependent deconvolution method used to create the mean transit time (MTT) maps. We estimated the arterial input function by manually choosing 5 to 10 pixels on the unaffected hemisphere (contralateral to the lesion). The relative MTT images were used to define the perfusion deficit. To determine the MTT, the tissue concentration-time curve was numerically integrated between 2 points (t1 and t2), which were individually determined for each patient. The t1 was chosen from the arterial input function as a time point before the arterial arrival of the contrast agent, and t2 was chosen from the tissue concentration-time curve as a time point at which the signal returned completely or almost completely to the baseline. The concentration-time curve obtained was processed on a voxel-by-voxel basis to determine the MTT.

MRI Image Preprocessing

The MRI data analyses were performed on a SUN Ultra2 Workstation (Sun Microsystems Inc). The MRI data were processed with the Image Processing Laboratory of the Image Analysis Laboratory of Henry Ford Health Sciences Center, which has a comprehensive set of functions for displaying, restoring, enhancing, and analyzing images. After reconstruction, all data were preprocessed to segment the intracranial volume (subimaging) and to suppress noise. Subimaging of the intracranial volume was done with thresholding and morphological operations to segment the image background, skull, scalp, eyes, and other extracranial structures, which may affect the image processing. After subimaging, the images were noise reduced by use of a nonlinear restoration filter that reduces noise while preserving edges and partial volume effects.

Coregistration

Coregistration and warping methods were used to correct for the misalignment and mismatch among the different imaging modalities.
caused by patient movement or other factors. After registration, maps of the trace apparent diffusion coefficient (ADC) and T2 were created for each time point by use of a least squares fit from the slope of the signal intensity on a pixel-by-pixel basis. The ADC and T2 maps were used to overlay the region of interest of the signatures made by ISODATA and to obtain the mean ADC and T2 values.

**Warping**

Because coregistration alone may not accurately match the hat to the head set, warping 1 data set to the other introduces a nonlinear spatial transformation required to correct for the anatomic variations seen among the various MRI sets. Because DWI is more distorted than other parameters, those parameters were warped to fit the T2WI. The warping program creates the boundary around the target image (T2WI) and around the image that will be warped (DWI). Then, the inverse-distance weight interpolation method is used to calculate the projection from 1 image onto another. The anatomic structures are then visually checked between the warped DWI and the T2WI for accuracy of the warping procedure. Similarly, T1WI was warped to fit the T2WI if needed.

**Multiparameter Segmentation Technique: The ISODATA Algorithm**

Tissue characterization was performed on multiparameter MRI data with a segmentation algorithm that requires minimal user intervention. The study neuroradiologist and the neurologist selected at most 3 slices from each ischemic lesion for multiparametric segmentation analysis. (They were blinded to the clinical data but not to the data from single-parameter MRI techniques.) The slice that showed the largest lesion area (on DWI for the acute phase and on T2WI for the chronic phase) and the slices above and below that level were selected for analysis. Obviously, in cases of small ischemic lesions such as lacunar infarcts, 2 slices or even 1 slice could show the lesion, and those were used for analysis. The ISODATA is an unsupervised segmentation method related to the K-means algorithm with additional splitting and merging steps that allow adjustment of cluster centers. The main advantage of the ISODATA method is that it requires no initial training procedure for segmentation. In this study, the multiparameter MRI data set used in the unsupervised segmentation algorithm consisted of 2 T2WI (TE, 30 and 90 milliseconds), 1 T1WI, and 2 DWI (b = 600 and 1,000 s/mm²). Our modified ISODATA algorithm consisted of the following steps: (1) The clustering parameters are entered into the program; (2) the MRI data are partitioned into random clusters; (3) cluster centers and intra-Euclidean and inter-Euclidean distances are calculated between pixel vectors and cluster centers; (4) splitting and merging of clusters are performed on the basis of the intra-Euclidean and inter-Euclidean distances; and (5) steps 3 and 4 are repeated until the algorithm converges or reaches the maximum number of iterations allowed (see Reference 23 for details on the analysis methods).

**Statistical Analysis**

For the acute-phase studies, we compared the ISODATA lesion size with the PWI, DWI, and T2WI lesion sizes measured in the same slice. For the outcome-phase studies, we compared the ISODATA lesion size with the T2WI and DWI lesion sizes measured in the same slice. To study the relationship between the NIHSS score and lesion size at the acute and outcome phases, a single slice containing the largest lesion size was selected on the basis of the DWI lesion for the acute phase and the T2WI lesion for the outcome phase.

Descriptive analyses were performed for the data collected at the acute phase, including the patients’ characteristics and stroke classification. Normality of each MRI measurement at each time point was evaluated. Data transformation was considered if the data were not normal. As a result, a log transformation was conducted for the NIHSS scores, and square-root transformation was carried out for lesion size variables. Because in most cases the DWI lesion size would be 0 (89% based on the data) at the outcome time point, the DWI lesion size was categorized as lesion present or absent with Spearman’s correlation between MRI measurements and NIHSS scores. We calculated Pearson’s correlation coefficients from the transformed data. Correlation coefficients between MRI measurements (lesion size) were calculated from slice information for data illustration. The test of significance of correlation coefficient from 0 between MRI lesion size parameters was performed with the fixed- and random-effect (mixed) model using all data from each slice and taking the correlation among slices for each patient into account.

We also calculated the correlation coefficient between MRI lesion size and the NIHSS score at the acute and outcome time points, respectively, on the basis of a single slice per person, as described earlier.

The correlation coefficient, in a range of −1 to 1, was classified as low if |r| < 0.4, moderate if |r| was in the range of 0.4 to 0.7, or high if |r| > 0.7. Pearson’s correlation was used to calculate the correlation coefficient of NIHSS with MRI measures. The 95% confidence limits were calculated. A 95% confidence limit not including 0 indicates a significant correlation between 2 measurements compared with no correlation at all.

**Results**

**Clinical Data**

We identified 11 patients for this study; 9 (82%) were women, and 7 (64%) were black. The mean age was...
The outcome-phase ISODATA lesion had a high correlation with the DWI lesion size (r=0.76; 95% CI, 0.53 to 0.88; P<0.001).

The ISODATA lesion size had moderate correlation with the acute-phase NIHSS score (r=0.59; 95% CI, 0.02 to 0.88; P=0.06). Similarly, moderate correlation was observed between the acute-phase NIHSS score and PWI lesion area (r=0.65; 95% CI, 0.08 to 0.90; P=0.03) and the DWI lesion area (r=0.57; 95% CI, −0.05 to 0.62; P=0.07). There was no correlation between the acute-phase NIHSS score and the T2WI lesion size (r=0.04; 95% CI, −0.58 to 0.62; P=0.91) (Table 2).

Outcome-Phase Correlations
In the outcome phase, 33 slices from 11 patients were processed and included in the analyses and comparisons. There was high correlation between the ISODATA lesion size and the T2WI lesion size (r=0.97; 95% CI, 0.94 to 0.99; P<0.0001). There was weak negative correlation between the ISODATA lesion and the DWI lesion (r=−0.34; 95% CI, −0.67 to −0.04; P=0.11) and no correlation between the T2WI lesion size and the DWI lesion size (r=0.30; 95% CI, −0.58 to −0.05; P=0.38).

The outcome-phase ISODATA lesion had a high correlation with the outcome-phase NIHSS score (r=0.78; 95% CI, 0.34 to 0.94; P=0.004). The T2WI lesion size also had a high correlation with the NIHSS score (r=0.85; 95% CI, 0.51 to 0.96; P=0.009). There was no correlation between the NIHSS score and the DWI lesion at the outcome phase (r=0.07; 95% CI, −0.61 to 0.58; P=0.82) (Table 3).

Discussion
In this study, the primary finding is that the size of the ischemic lesion defined by the multiparametric MRI inte-
grated ISODATA method correlates highly with the size of the ischemic lesion defined by monoparametric techniques best for either the acute (PWI, DWI) or the outcome (T2WI) phase of ischemic stroke, indicating that the multiparametric ISODATA analysis technique can define the ischemic lesion regardless of time elapsed since the onset of vascular occlusion and ischemia. In addition, this report shows that in the acute phase of ischemic stroke, the ISODATA method can detect heterogeneous zones of ischemia not necessarily identifiable by DWI. This present study expands further the findings of our previous report \(^2\) to include the comparison with PWI findings.

The MR parameters used for the ISODATA analysis in this study were based on results obtained from a model of experimental cerebral ischemia \(^1\) in which we demonstrated that identification and segmentation of the ischemic lesion on a MRI data set combining T2WI, T1WI, and DWI and incorporating the ISODATA approach highly correlated with the histological status of the tissue. In the clinical setting of this study, we selected the neurological status of the patient, defined by the NIHSS, to test the ISODATA model. The ischemic lesion identified by the multiparametric ISODATA method exhibited the features of evolving cerebral ischemia \(^2\) namely decreased mean relative ADC and increased mean relative T2 in the acute phase and increased mean relative ADC and mean relative T2 in the outcome phase of ischemic stroke.

In the acute phase of stroke, the ISODATA lesion size correlated highly with the PWI \((r=0.95, P<0.0001)\) and DWI \((r=0.83, P<0.0001)\) lesion size; in the outcome phase, the ISODATA lesion size highly correlated with the T2WI lesion size \((r=0.97, P<0.0001)\). Therefore, the ISODATA method is capable of defining the ischemic lesion at either the acute or the late outcome phase of its evolution equally as well as the single-parameter MRI techniques that are considered the best for each phase of ischemic stroke, namely PWI and DWI in the acute and T2WI in the late outcome phase. These points strongly support the concept that the multiparametric MRI ISODATA analysis is a time-independent method for assessing cerebral ischemic lesions at any phase of their evolution.

In the acute phase, the PWI lesion size was on average 70% larger than the DWI lesion size, indicating the presence of PWI-DWI mismatch; the ISODATA lesion size was on average 31% larger than the DWI lesion size. Figure 2 shows the composite PWI, ISODATA, DWI, and T2WI lesion size in the acute phase of ischemic stroke for all 11 patients. Often, in the acute phase of stroke, the PWI lesion size is significantly larger than the DWI lesion volume (mismatch), and the DWI lesion tends to enlarge in the first days after stroke onset.\(^\text{6,9}\) However, the final infarct volume is almost always smaller than the initial PWI volume.\(^\text{6,9}\) This indicates that not all acutely hypoperfused tissue becomes infarcted and that the acute PWI lesion size, in the absence of reperfusion, could represent the sum of hypoperfused tissue at risk for infarction and tissue that is hypoperfused but not below a critical threshold. Given the difference between the PWI-ISODATA-DWI lesion sizes, we indicate here that the use of multiple MRI parameters by the ISODATA algorithm allows identification of tissue that is ischemic but not yet visible by DWI studies. Additionally, we speculate that, in the acute phase of cerebral ischemia, the ISODATA method may actually define the cerebral tissue that is hypoperfused below a critical threshold and at risk for infarction and that the difference between the PWI and ISODATA lesion sizes may simply reflect tissue that is not critically hypoperfused. This is certainly highly speculative, but we will explore this concept further by performing additional analyses comparing the acute-phase ISODATA, PWI, and DWI lesion sizes and their individual parameter characteristics with the outcome-phase T2WI lesion size in a larger number of patients and MRI studies. These data demonstrate PWI-DWI mismatch and that the composite ISODATA lesion size is close to the composite PWI and DWI lesion size.

In the acute phase, the correlation between the ISODATA lesion size and the clinical neurological deficit, as assessed with NIHSS score, was moderate \((r=0.59, P=0.06)\) and of a magnitude similar to that between the NIHSS score and PWI \((r=0.65, P=0.03)\) or DWI \((r=0.57, P=0.07)\) lesion size. In the outcome phase, the ISODATA lesion size highly correlated with NIHSS score \((r=0.78, P=0.004)\), as was the case with the T2WI lesion size and NIHSS score \((r=0.81, P=0.009)\). The correlations between ISODATA and clinical neurological scores in our study are of similar magnitude to the correlations demonstrated by other investigators\(^\text{9,11}\) who used total ischemic lesion volume in their MRI clinical comparisons. These correlation coefficients also are compa-

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**TABLE 3. Pearson Correlation Coefficients, \(P\) Value, and 95% CIs Between NIHSS and MRI Measurements in the Outcome Phase of Stroke**

<table>
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<th>ISODATA</th>
<th>DWI</th>
<th>T2WI</th>
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<tbody>
<tr>
<td>Correlation coefficient</td>
<td>0.78</td>
<td>-0.07</td>
<td>0.85</td>
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<tr>
<td>(P) value</td>
<td>0.004</td>
<td>0.82</td>
<td>0.0009</td>
</tr>
<tr>
<td>CI</td>
<td>0.34 to 0.94</td>
<td>-0.64 to 0.58</td>
<td>0.54 to 0.96</td>
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*Based on the transformed data; \(n=11\).*
rable to those observed between NIHSS score and ischemic lesion size on CT scan in the NINDS rt-PA Study ($r=0.64$ acutely and $r=0.59$ 3 months after stroke onset),\textsuperscript{27} despite the small number of patients included in our study. Our approach, using the single slice that contained the largest lesion instead of measuring the entire lesion volume in the comparisons with NIHSS score, may have actually resulted in weaker-than-actual correlations, especially in regard to larger ischemic lesions.

This preliminary study certainly has a number of limitations. The number of patients included is small, and the patients underwent the MRI studies over a rather heterogeneous time window. In addition, for the correlations between MRI findings and clinical scores, we used the size of the ischemic lesion from a single MRI slice. These factors may have weakened the correlations between ischemic lesion size and clinical scores. Despite this, these correlations remain strong.

**Conclusions**

This preliminary study provides strong evidence that the multiparametric MRI integrated ISODATA method can identify and characterize the ischemic lesion independently of time elapsed since the onset of stroke. The ISODATA lesion size highly correlates with the size of the lesion defined with the most sensitive MRI technique for each phase (DWI and DWI in the acute, T2WI in the outcome phase) and with the size highly correlates with the size of the lesion defined with time elapsed since the onset of stroke. The ISODATA lesion size on CT scan in the NINDS rt-PA Study ($r=0.64$ acutely and $r=0.59$ 3 months after stroke onset),\textsuperscript{27} despite the small number of patients included in our study. Our approach, using the single slice that contained the largest lesion instead of measuring the entire lesion volume in the comparisons with NIHSS score, may have actually resulted in weaker-than-actual correlations, especially in regard to larger ischemic lesions.

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**Acknowledgment**

This work was supported by NIH PO1 grant NS/23393.

**References**

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Stroke. published online November 14, 2002;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2002/11/14/01.STR.0000043072.76353.7C.citation

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