Evolution of Cerebral Infarct Volume Assessed by Diffusion-Weighted Magnetic Resonance Imaging

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Background: Knowledge of the natural evolution of ischemic brain lesions may be a crucial aspect in the assessment of future stroke therapies.

Objective: To establish daily changes of ischemic cerebral lesion volume using diffusion-weighted magnetic resonance imaging.

Design: Prospective cohort study.

Setting: Referral center.

Patients and Methods: Serial magnetic resonance imaging scans were performed in consecutive untreated stroke patients. The baseline scan was obtained within 48 hours after symptom onset; subsequent scans, 12 to 48 hours, 3 to 4 days, 5 to 7 days, and 30 days after baseline. Lesion volumes were measured on each scan by 2 independent observers.

Main Outcome Measure: Daily change in lesion volume.

Results: A total of 112 magnetic resonance imaging scans were obtained in 24 patients. An early increase in lesion volume was seen in all patients. Maximum lesion volume was reached at a mean of 74 hours. Lesion volumes increased by a mean (± SEM) of 21%±12% during day 2 and 10%±12% during day 3. No significant change occurred during day 4. During days 5, 6, and 7, statistically significant mean (± SEM) decreases of 6%±8%, 3%±4%, and 4%±5%, respectively, were observed.

Conclusions: Ischemic lesions follow a relatively consistent pattern of growth during the first 3 days and subsequent decrease in size. These data in conjunction with data regarding the evolution of lesion volume during the first 24 hours after symptom onset may be useful in the design of pilot studies of therapies for acute stroke.

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Several neuroprotective agents that have shown promising results in animal stroke models have not demonstrated beneficial effects in clinical stroke trials.\(^1\)\(^-\)\(^3\) Potential explanations for differing results in animals vs humans may be the more uniform infarct volumes and the possibility of initiating treatment soon after or even before stroke onset in animal models. Differences in collateral circulation between rodents and humans may be the reason why trials of neuroprotective agents in humans have not been successful.\(^4\) Another reason may be the use of different study end points. Animal studies typically use lesion volume as the primary outcome measure, whereas most clinical trials use a clinical stroke scale score. Unless the treatment dramatically affects clinical outcome, large trials are required to demonstrate efficacy using clinical scales. Most recent clinical stroke trials may not have been of sufficient size to detect a treatment effect on clinical stroke scales.\(^2\)

Although the most important end point in acute stroke trials is clinical outcome, an ancillary outcome measure may be useful if it can demonstrate a treatment effect in smaller clinical trials. Lesion volume evolution assessed by diffusion-weighted magnetic resonance imaging (MRI) (DWI) could be used as such an ancillary measure. Diffusion-weighted MRI is an imaging technique that can identify ischemic brain tissue in the hyperacute phase of stroke.\(^5\)\(^-\)\(^7\) The noninvasive nature of the technique facilitates the acquisition of multiple scans at different times, allowing ischemic lesion volumes to be followed up over time.

In several animal models, a treatment effect of neuroprotective agents has been demonstrated using DWI and subsequently confirmed by pathological assessment.\(^6\)\(^-\)\(^7\) The clinical relevance of re-
SUBJECTS AND METHODS

PATIENT ELIGIBILITY

Between January 1, 1997, and May 31, 1998, all patients who presented to the Stanford Stroke Center, Stanford University Medical Center, Stanford, Calif, with a presumed diagnosis of acute stroke underwent screening by a stroke neurologist for eligibility to participate in this longitudinal MRI study. Eligible patients were aged at least 18 years and presented for evaluation within 48 hours of symptom onset. Potential patients had to be able to comply with the MRI procedures and have a score of 1 or more on the NIHSS. Exclusion criteria included (1) enrollment in an investigational trial of a neuroprotective agent; (2) stroke treatment with thrombolytic therapy; (3) level-of-consciousness score of 3 on the NIHSS (responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and reflexless); (4) severe coexisting disease that limits life expectancy or may interfere with the conduct of the study; and (5) no acute ischemic lesion consistent with the presenting symptoms identifiable on the baseline DWI scan.

STUDY PROCEDURES

A baseline MRI scan was obtained within 48 hours of symptom onset, and follow-up MRI scans were obtained at 12 to 48 hours, 3 to 4 days, 5 to 7 days, and 30 days after the baseline examination. Scans were cancelled or delayed if scan time was not available or if requested by the patient or their family. The NIHSS score was determined by a certified neurologist at the time of the baseline scan. The study was approved by the Stanford University Human Subjects Committee. Informed consent was obtained from each patient or from an appropriate family member.

MRI VARIABLES AND DATA PROCESSING

Magnetic resonance imaging was performed by echo planar imaging using a 1.5-T Signa Magnet (General Electric, Milwaukee, WI). The whole-brain echo planar imaging–DWI examination acquired 16 slices (slice thickness, 5 mm; 2.5-mm gap between slices; repetition time, 6000 milliseconds; echo time, 110 milliseconds; field of view, 24 cm; matrix size, 128 × 128 pixels; b values, 0 and 849 s/mm²). The DWI images were acquired in x, y, and z planes and were processed off-line to generate trace-apparent diffusion coefficient maps and isotropic DWI images.

Lesion volumes were determined on the DWI image for the acute scans and on the echo planar imaging T2-weighted (b=0) image for the 30-day scans. On the baseline MRI scan, the acute lesion was identified by means of high signal on the DWI image and hypointensity on the apparent diffusion coefficient map in a region that was consistent with the clinical presentation. Lesion volume was determined with the aid of an image analysis software program (MRVision, Menlo Park, Calif) on a computer workstation (Sun Microsystems, Palo Alto, Calif). Lesion areas were outlined and measured for each slice. If multiple lesions were present in the same hemisphere, they were outlined separately. The area measurements were used to calculate lesion volume. Lesion volume at each time was determined by 2 independent observers, whose results were averaged. Lesion volumes at 1, 2, 3, 4, 5, 6, 7, and 25 days after symptom onset were calculated by linear interpolation. After analysis of the data to determine the median time to maximal lesion volume, lesion volumes at each time were expressed as a fraction of the volume at 72 hours (closest 24-hour time to the time of maximal lesion volume) to control for the large variation in lesion volumes among patients. Mean percentage of changes in lesion volume were determined for each 24-hour period.

STATISTICAL ANALYSIS

Statistical analyses were performed using commercially available software (SigmaStat; Jandel, San Rafael, Calif). Mean lesion volumes, SDs, and SEMs were calculated for each 24-hour period. The paired t test was used to assess the changes in lesion volume for each 24-hour period.

RESULTS

Twenty-seven patients were enrolled in the study. Three patients died before the end of the study and are excluded from this analysis. A total of 112 scans were obtained in the 24 patients (average, 4.7 scans per patient) included in this analysis. The median time from symptom onset to the baseline MRI scan was 23 hours (range, 8-48 hours). Thirteen patients received their baseline scan within the first 24 hours; 11, between 24 and 48 hours. The median time until the final MRI scan was 31 days (range, 26-72 days).

At enrollment, the patients’ median age was 73 years (range, 37-93 years) and the median NIHSS score was 5 (range, 1-24). In 17 patients, the infarction involved the middle cerebral artery territory; 2 of these were deep subcortical infarcts. One patient had an infarct that involved...
the middle and the anterior cerebral artery distribution, and 6 patients had an infarct in the posterior cerebral artery.

All lesions initially expanded and subsequently shrank during the course of the study. Figure 1 shows an example of the initial increase and subsequent decrease in lesion size. The mean (±SEM) lesion volume on the baseline DWI scan was 25±32 cm³. Maximum lesion volume was observed at a median of 74 hours (range, 43-170 hours) after symptom onset. The mean (±SEM) maximum lesion volume was 31.4±37.1 cm³. Figure 2A displays the mean lesion volumes at each time for patients with a baseline scan obtained within 24 hours after symptom onset (n=13) and for patients with a baseline scan obtained between 24 and 48 hours after symptom onset (n=11). The mean lesion volume was smaller in the group of patients with baseline scans obtained within 24 hours compared with the group with baseline scans obtained between 24 and 48 hours; this difference was not statistically significant (t test; P=.13). However, the pattern of evolution was similar for both groups. This is also illustrated in Figure 2B, where lesion volumes are expressed as fractions of the volumes at 72 hours (the
time point closest to the time of maximal lesion volume), and the curves for both groups overlap.

The mean daily percentage of change in lesion volume is shown in Figure 3. Lesions significantly increased in size by a mean (± SEM) of 21%±12% (P<.01) during day 2 and an additional 10%±12% (P<.01) during day 3. No significant change occurred during day 4. During days 5, 6, and 7, statistically significant decreases in lesion volume by a mean (± SEM) of 6%±8% (P<.01), 3%±4% (P<.1), and 4%±0% (P<.01), respectively, were observed. A further decrease of 34%±22% (P<.01) was seen from days 7 through 25, representing a mean daily change of 3%±3%, assuming that the rate of change was uniform each day.

This study describes the daily changes of DWI lesion volume in untreated stroke patients. The data show a relatively consistent pattern of volume change in this population. The DWI lesion volumes typically increase substantially during the first 3 days after stroke onset, plateau during day 4, and slowly decrease in size during the next 3 to 4 weeks.

Our finding of the early expansion of DWI lesion volumes agrees with the results of others. Sorensen et al13 reported that final infarct volumes were larger than baseline DWI lesion volumes in 8 of 9 patients who underwent scanning within 10 hours after symptom onset. Baird et al14 compared acute DWI lesion volume with follow-up T2-weighted lesion volume and found evidence that substantial enlargement of human cerebral ischemic lesions can occur beyond the first 24 hours after symptom onset. Both groups of investigators speculated, based on data from perfusion-weighted MRI, that the observed early lesion growth represented recruitment of tissue at risk into the infarct. Schwamm et al15 published the time course of DWI lesion evolution in a smaller series of stroke patients. They found a progressive increase in lesion volume in most patients in the first days after symptom onset, with maximum DWI lesion volume typically occurring after 3 days.

Expansion of DWI lesion volume likely reflects 2 pathophysiological processes: an increase in ischemic brain tissue injury and the formation of vasogenic edema. The largest increase in ischemic brain injury likely occurs during the first hours after stroke onset,8,9 whereas formation of edema may play a more important role during the following 2 to 3 days.16,17 The increase in lesion volume during the second and third days, however, could also reflect a prolonged period when the ischemic core expands into surrounding tissue. This hypothesis is supported by the observation in positron emission tomographic studies that ischemic but viable tissue may be present up to 48 hours after stroke onset.18,19 The decrease in lesion volume between 4 and 25 days after symptom onset is likely explained by a combination of resolution of edema10,11 and a decrease in inflammatory infiltration. Reversal of some penumbral ischemia and atrophy of the infarct may also be contributing factors. Mean lesion volume at 25 days was somewhat smaller than the 24-hour volume. In studies that obtained the baseline scan sooner after symptom onset, final T2-weighted lesion volume has been larger than baseline DWI lesion volume.13,15

The use of MRI findings as a surrogate end point for studies of therapies for acute stroke is in its infancy. For this surrogate to be useful, lesion volume assessed by means of MRI must be shown to be correlated to clinical outcome. Our study is of insufficient size to determine the correlation between lesion volume and clinical stroke scale scores. Previous studies have found a good correlation between lesion volume as assessed by DWI and clinical outcome as assessed by clinical stroke scales.10-12 More recently, a moderate correlation has been reported between computed tomographic lesion volume and NIHSS score.20 It is generally believed that lesion location is an important factor that weakens the correlation between lesion volume and clinical stroke scale score. For example, a comparison of lesion volumes in patients with equal NIHSS scores has shown significantly larger lesions in patients with a right hemisphere stroke compared with patients with a left hemisphere stroke.21

The established correlation between DWI lesion volume and clinical stroke scale scores makes DWI lesion volume a potentially good end point for pilot trials of therapies for acute stroke. If pilot trials do not demonstrate any evidence of a treatment effect, much larger trials powered for clinical end points may be avoided. The optimal timing of the MRI scans and the best imaging sequences for clinical trials remain to be determined. Our data demonstrate that ischemic lesions follow a consistent pattern of evolution, despite large variation in lesion volumes among patients. Therefore, the change in lesion volume over time is likely to be a much more sensitive end point than absolute lesion volume at any specific time. To determine change in lesion volume, the acquisition of at least 2 scans in each patient is required. The first scan should be acquired before or immediately after the initiation of treatment to demonstrate the baseline lesion. At present, DWI appears to be the most suitable imaging modality for this purpose, because ischemic lesions can be visualized using DWI before they become apparent using conventional imaging techniques.13,22-24 Because DWI lesion volumes change rapidly in the acute phase of stroke, it is essential that the time from symptom onset to performance of the baseline scan be well matched between treatment and control groups. The follow-up scan, ideally, should provide an accurate measure of the final infarct volume. The lesion volume on a chronic T2-weighted scan is generally believed to be
a reasonable reflection of final infarct volume. Early DWI lesion volume has been shown to correlate well with lesion volume on later T2-weighted MRI as well as with infarct volume at autopsy and may therefore be used as a surrogate measure of final infarct volume. Because DWI lesion volumes typically increase until day 3 and plateau during day 4, infarct volumes may be best estimated by means of DWI performed approximately 3 to 4 days after symptom onset. However, at this time, both cytotoxic and vasogenic edema contribute to the size of the maximum DWI lesion, resulting in an overestimation of the infarct volume. In contrast, the T2-weighted MRI lesion volume at a later time may underestimate the actual volume because of atrophy. If treatment of an acute stroke has an impact on early lesion growth, then DWI lesion volume, obtained a few days after treatment is begun, might be as suitable a study end point as late T2-weighted lesion volume. Logistically, a second scan at 3 to 4 days, when many stroke patients are still in the hospital or in the rehabilitation unit, may be more convenient than a follow-up scan several weeks or months after symptom onset.

This study has several limitations. The MRI scans were not obtained at exact 24-hour increments. However, because linear interpolation and no extrapolation was used for volume estimations, we expect that the introduced error is relatively small. Another limitation is that no data points were collected between the 5- to 7-day scan and the late follow-up. The calculated mean daily changes in lesion volume of 3% assume a uniform change in lesion volume during this period. Further studies are necessary to describe the evolution of lesion volume during this period in more detail. Patients presenting very early after stroke onset were typically excluded because they were treated with recombinant tissue-type plasminogen activator or investigational neuroprotective agents. Volume changes occurring during the first day after symptom onset could, therefore, not be addressed. Further studies investigating the change in lesion volume during the first 24 hours in untreated patients would be very valuable. The most dramatic increases in lesion volume may be observed during this time, and sample size calculations for acute stroke studies may thus yield even smaller numbers than those that could be calculated based on the data in this study. In addition, the change in lesion volume during the first 24 hours is more likely to reflect expansion of the ischemic region and less likely to reflect the formation of potentially reversible cerebral edema, and most clinical stroke trials now initiate treatment very early after stroke onset. Efforts are currently under way to establish the pattern of evolution during the first 24 hours after symptom onset and, from these data, to estimate required sample sizes for placebo-controlled studies of hypothetical stroke treatments.

The results of this study demonstrate that ischemic lesions follow a relatively consistent pattern of volume evolution with a significant increase in size during days 2 and 3, no change during day 4, and subsequently a slow decrease in volume. These data suggest that DWI lesion volume may be a sensitive measure of the efficacy of agents that attenuate early lesion expansion and may be a useful end point in preliminary trials of stroke therapies.

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REFERENCES