Relationship Between Apparent Diffusion Coefficient and Subsequent Hemorrhagic Transformation Following Acute Ischemic Stroke

David C. Tong, MD; Alessandro Adami, MD; Michael E. Moseley, PhD; Michael P. Marks, MD

Background and Purpose—A method for identifying patients at increased risk for developing secondary hemorrhagic transformation (HT) after acute ischemic stroke could be of significant value, particularly in patients being considered for thrombolytic therapy. We hypothesized that diffusion-weighted MRI might aid in the identification of such patients.

Methods—We retrospectively analyzed 17 patients with ischemic stroke who received diffusion-weighted MRI within 8 hours of symptom onset and who also received follow-up neuroimaging within 1 week of initial scan. The apparent diffusion coefficient (ADC) for each pixel in the whole ischemic area was calculated, generating a histogram of values. Areas subsequently experiencing HT were then compared with areas not experiencing HT to determine the relationship between ADC and subsequent HT.

Results—A significantly greater percentage of pixels possessed lower ADCs (≤550×10⁻⁶ mm²/s) in HT lesions compared with non-HT lesions (47% versus 19%; P<0.001). Moreover, >40% of the pixels possessed values ≤550×10⁻⁶ mm²/s in all lesions experiencing secondary HT, compared with <31% of the pixels in the non-HT-destined lesions.

Conclusions—HT-destined stroke regions possess a significantly great percentage of low ADC values than non-HT-destined regions. Early measurement of ADC values may be a useful tool for assessing secondary HT risk. (Stroke. 2000;31:2378-2384.)

Key Words: cerebral hemorrhage ■ magnetic resonance imaging, diffusion-weighted ■ stroke, acute ■ thrombolyis

Hemorrhagic transformation (HT) after acute ischemic stroke is a common event, especially in the first week after symptom onset.1 Approximately 40% to 50% of all stroke patients experience some form of HT within the first week after symptom onset, although up to 95% of cardioembolic strokes will eventually exhibit this phenomenon.2-4 If symptomatic, HT is a major concern for physicians because of the potential effects of this cerebral bleeding on the course and outcome of stroke patients.1,5,6 This subject is of even greater importance since the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA (recombinant tissue plasminogen activator) Stroke Trial found that thrombolytic therapy significantly improves neurological outcome, but at the expense of increased hemorrhagic complications.7 Thus, the ability to identify patients at increased risk for secondary HT after acute stroke could potentially be helpful in increasing the effectiveness and safety of thrombolytic therapy.

Although a variety of clinical risk factors, including hypertension, embolic etiology, use of anticoagulant therapy, and increasing stroke severity, have been associated with a higher risk of hemorrhage,1,6-10 data regarding the use of neuroimaging to predict hemorrhage risk are limited. Early CT signs of major stroke such as hypodensity, edema, and mass effect have been identified as radiological risk factors for HT.6,9-13 In addition, contrast enhancement in the first hours after stroke onset is associated with subsequent HT.14,15 However, these findings are frequently subtle and the ability of clinicians to identify them is limited,16 even among expert observers.17

Diffusion-weighted MRI (DWI) may be particularly well suited to evaluate acute stroke patients because of its ability to detect ischemia in the first hours after symptom onset,18-22 when still viable tissue is believed to exist.23,24 However, the ability of DWI to predict secondary HT is uncertain. In animal models, lower apparent diffusion coefficient (ADC) values have been correlated with greater degrees of ischemia.25,26 Since severely ischemic or infarcted tissue is at higher risk for secondary hemorrhage because of breakdown of the blood-brain barrier,27 it is logical to hypothesize that there would be a relationship between acute ADC values and subsequent HT. If early ADC values were found to correlate with risk of secondary hemorrhage, this could potentially increase the clinical utility of DWI in the evaluation of acute stroke patients, particularly in those patients being considered for thrombolytic therapy.
In this study we evaluated the relationship between initial DWI findings and subsequent HT in patients with acute stroke. We hypothesized that the ischemic lesions of patients experiencing HT would have lower ADC values than ischemic lesions not experiencing HT and that this finding would be predictive of early (≤1 week) HT. In addition, we hypothesized that a frequency-based pixel-by-pixel analysis would be more predictive of the risk of secondary HT than traditional averaged ADC measurements because of the substantial heterogeneity of ADC values in acute stroke lesions.

**Subjects and Methods**

**Patients**

All research was approved by the Stanford Medical Center institutional review board. Patients for this study were retrospectively drawn from the Stanford Stroke Center database encompassing all patients who have been evaluated by the inpatient Stanford Stroke Service between November 1996 and December 1998. Inclusion criteria included the following: (1) The initial DWI scan was performed within 8 hours of symptom onset. This early time point was chosen because these stroke patients are the most likely to be candidates for acute interventions such as thrombolytic therapy. (2) A repeated MRI or CT scan was performed within the first week after symptom onset to identify the presence of secondary HT.

Patients placed in the HT category were required to have received either an interpretable DWI scan with ADC mapping or a noncontrast head CT scan within 1 week of symptom onset that revealed evidence of secondary HT. These HT-positive patients were not required to undergo a repeated MRI scan at 5 to 7 days if secondary HT was detected before then, since the diagnosis of HT had already been established. Patients in the non-HT category were required to have received a technically adequate DWI scan with ADC maps at 5 to 7 days after stroke onset that did not reveal any MRI evidence of HT. Patients experiencing an MRI- or CT-detected hemorrhage >5 to 7 days after symptom onset were excluded because such hemorrhages were not believed to be clinically important for guiding initial therapies such as thrombolysis or anticoagulation. Susceptibility-weighted MRI sequences were not required because such sequences were not part of our routine acute stroke MRI protocol at the time of the study. Patients with evidence of hemorrhage on initial MRI or CT scan were excluded. Patients receiving either intravenous (n=14) or intra-arterial (n=2) rtPA were eligible. Patients involved in clinical trials of neuroprotective agents were also eligible for participation.

All DWI scans were performed as previously described. In brief, a General Electric Signa 1.5-T scanner with single-shot echo planar imaging was used. Acquisition parameters were as follows: repetition time, 8100 ms; echo time, 110 ms; matrix, 128×128; bandwidth, 100 kHz; field of view, 24 cm. Sixteen oblique slices with 5-mm thickness and a 2.5-mm gap were used. DWI scans were acquired in the X, Y, and Z directions and then averaged to minimize anisotropy. ADC maps were calculated at 2 different b values (b=0 and b=829 s/mm²). ADC values were then calculated to generate ADC maps as previously described.

HT was identified at successive time points using reported MRI characteristics of hemorrhage on the T2-weighted, fluid-attenuated inversion recovery (FLAIR), and DWI images. The main criterion was the presence of hypointense (dark) signal on DWI, T2-weighted, or FLAIR imaging within the brain parenchyma (Figure 1). This HT region could be either heterogeneous or homogeneous. Areas of high signal intermixed with low signal were included. The abnormal signal could not solely include regions of MRI susceptibility artifact. The presence of MRI signal consistent with HT on >1 slice was preferred but not essential. In cases in which a susceptibility-weighted sequence was performed (n=6), the hemorrhagic region had to be detected on that sequence. CT-detected hemorrhage was defined as heterogeneous or homogeneous high signal on a noncontrast CT scan not associated with artifact or calcification.

**Image Processing**

All images were processed off-line with a Sun Microsystems workstation with the aid of specialized image analysis software (MRVision). This software is capable of simultaneously visualizing the same slice on T2-weighted, FLAIR, DWI, and ADC maps. All measurements were performed by a single blinded observer (A.A.) to avoid interobserver variability. Regions of interest were generated by visual inspection of the DWI images. The regions of interest were

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**Figure 1.** HT in a patient who received rtPA treatment. Note that in this case HT was associated with a small infarction (volume=20 cm³). T1 indicates time of initial MRI scan, 4 hours and 23 minutes after symptom onset (1 hour and 43 minutes after rtPA administration); T2, 45 hours after initial scan. FSE indicates fast spin-echo MRI. Top left image is b=0 scan (DWI without diffusion weighting; FSE equivalent).
TABLE 1. Characteristics of Study Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>rtPA</th>
<th>HT Time</th>
<th>Size, mm³</th>
<th>Initial Stroke Volume, cm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>74</td>
<td>IV</td>
<td>3-6 h</td>
<td>0.84</td>
<td>89.87</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>70</td>
<td>IV</td>
<td>3-6 h</td>
<td>3.12</td>
<td>20.17</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>84</td>
<td>IV</td>
<td>24-36 h</td>
<td>13.48</td>
<td>57.10</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>85</td>
<td>IV</td>
<td>5-7 d</td>
<td>4.70</td>
<td>33.82</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>60</td>
<td>IV</td>
<td>5-7 d</td>
<td>1.75</td>
<td>50.48</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>76</td>
<td>IA</td>
<td>3-6 h</td>
<td>*</td>
<td>27.34</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>82</td>
<td>NO</td>
<td>5-7 d</td>
<td>0.64</td>
<td>26.13</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>74</td>
<td>NO</td>
<td>5-7 d</td>
<td>0.41</td>
<td>28.55</td>
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<tr>
<td>9</td>
<td>F</td>
<td>77</td>
<td>NO</td>
<td>5-7 d</td>
<td>9.69</td>
<td>136.66</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>70</td>
<td>NO</td>
<td>5-7 d</td>
<td>4.36</td>
<td>86.13</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>53</td>
<td>IV</td>
<td>NO</td>
<td>NO</td>
<td>31.82</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>49</td>
<td>IV</td>
<td>NO</td>
<td>NO</td>
<td>2.43</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>79</td>
<td>IV</td>
<td>NO</td>
<td>NO</td>
<td>8.46</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>68</td>
<td>†</td>
<td>NO</td>
<td>NO</td>
<td>19.93</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>59</td>
<td>IA</td>
<td>NO</td>
<td>NO</td>
<td>7.94</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>72</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>13.63</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>63</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>9.54</td>
</tr>
</tbody>
</table>

NO indicates no hemorrhage occurred.
*HT identified on CT scan; no MRI volume measurement performed.
†Patient enrolled in blinded randomized thrombolytic trial.

first drawn around hyperintense lesions in the brain parenchyma, as previously described. These regions of interest were then transferred to the ADC maps. Next, the distribution of ADC values within the ischemic lesion was determined with the use of built-in features of the image analysis software. With the use of computerized spreadsheet software (Excel, Microsoft Corporation), the ADC values were then separated into 11 distinct ranges with an interval of

8 mm²/s, creating a histogram of ADC values. Pixels with an ADC value of 6 mm²/s were rejected.

The paired t test or Mann-Whitney rank sum test was used as appropriate to compare same interval class frequency with computerized statistical software (SigmaStat, Jandel Scientific). Significance was accepted at the P=0.01 level.

Results

Between November 1996 and December 1997, 28 patients were identified who met the MRI criterion. During this same period, 568 patients were evaluated by the inpatient Stanford Stroke Service, and 368 subsequently received the diagnosis of acute ischemic stroke.

Of these 28 patients, 20 also received a follow-up MRI or CT scan within the first 5 to 7 days after symptom onset, fulfilling the second inclusion criterion. Three patients were subsequently excluded. One patient had small areas of HT detected on his initial MRI. Another experienced HT >30 days after stroke onset. The third patient had a very small lesion (1.08 cm³), which made accurate measurements difficult.

The mean age was 70±10 years (Table 1). There were 9 men and 8 women. The mean stroke volume was 38±36 cm³. Ten patients developed areas of HT on successive scans, while 7 did not. The HT patients were older than the non-HT patients (75±8 versus 63±11; P=0.016). However, HT was identified in 1 patient aged <70 years, and 7 patients aged ≥70 years did not develop HT.

Eleven patients received rtPA: 6 in the HT group and 5 in the non-HT group. Thrombolytics were administered according to NINDS guidelines in all patients treated with intravenous rtPA (n=8). In the intra-arterial cases, rtPA was administered at 2 hours (patient 6) and 1.5 hours (patient 15) after symptom onset.

HT was detected in 3 patients at 3 to 6 hours, in 2 patients at 24 to 36 hours, and in 5 patients at 5 to 7 days after the initial MRI. HT was symptomatic in only 1 case (patient 6). In this patient, HT was followed by worsening of the neurological deficit, prompting a head CT scan that revealed a hemorrhage into the area of initial DWI abnormality. The patient subsequently expired. In all other cases, no change in clinical status was detected.

Lesions subsequently experiencing HT were larger than non-HT lesions, with a mean size of 56±37 cm³ for hemorrhagic lesions versus 13±10 cm³ for nonhemorrhagic lesions (P=0.012). However, there was substantial overlap between groups (Table 1). There was no significant difference in the HT lesion size (P=0.76), initial stroke size (P=0.27), or incidence of HT between patients treated with rtPA (3/6) and those not treated with rtPA (2/5) (P=1.0). In addition, there was no significant difference between patients treated or not treated with rtPA in the percentage of pixels present in any of the ADC ranges.

To compensate for the volume differences, the number of pixels for each ADC interval was calculated as a percentage of the total number of pixels for all patients (Table 2). The mean ADC of the HT-destined lesions was nonsignificantly lower than in the non-HT-destined lesions (627±52×10⁻⁶ versus 717±122×10⁻⁶ mm²/s) (P=0.051). However, ischemic lesions experiencing HT had a significantly higher percentage of pixels in the lower ADC ranges than ischemic areas not experiencing HT. The greatest relative percentage of low ADC values occurred in the ADC range from 450 to 550 mm²/s (Table 2, Figure 2). The percentage of pixels in the range ≤550×10⁻⁶ mm²/s was significantly lower in the HT than in the non-HT-destined group in all ranges of ADC ≤550×10⁻⁶ mm²/s (Table 2). Overall, the mean cumulative percentage of pixels in the lower range (≤550×10⁻⁶ mm²/s) was 47% for HT-destined lesions versus 19% for non-HT-destined lesions (P<0.001). In addition, the percentage of pixels with ADC values between 750 and 850×10⁻⁶ mm²/s was significantly greater in the non-HT group than in the HT group (P<0.001; Table 2, Figure 2).

Moreover, >40% (range, 40.63% to 53.74%) of the pixels in each HT-destined lesion had ADC values ≤550×10⁻⁶ mm²/s (Figure 3). In contrast, <31% (range, 6.88% to 30.37%) of the pixels in the non-HT lesions had an ADC value below this level. Thus, the percentage of pixels below an ADC value of 550×10⁻⁶ mm²/s seems to discriminate between HT- and non-HT-destined lesions.

Discussion

This study suggests that a pixel-by-pixel ADC analysis may be helpful in identifying patients at increased risk for HT.
within the first week after stroke onset. Lesions destined to experience HT possessed a greater percentage of ischemic tissue in a low ADC range than non-HT-destined lesions (47% versus 19%; \( P < 0.005 \)). This effect was present even after we compensated for the generally larger stroke volumes of the HT-destined patients compared with the non-HT patients. In addition, at least 40% of pixels in the HT-destined lesions possessed an ADC \( \leq 550 \times 10^{-6} \) mm\(^2\)/s, compared with <31% of pixels in the non-HT-destined lesions. This suggests that a cutoff value can be identified that differentiates HT-destined from non-HT-destined ischemic lesions. To our knowledge, this is the first report of a potential ADC

### Table 2. Correction of ADC Values for Lesion Volume

<table>
<thead>
<tr>
<th>ADC Range</th>
<th>HT Pts</th>
<th>Non-HT Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>(100-250)</td>
<td>5.95</td>
<td>0.50</td>
</tr>
<tr>
<td>(350)</td>
<td>8.89</td>
<td>1.82</td>
</tr>
<tr>
<td>(450)</td>
<td>13.05</td>
<td>5.97</td>
</tr>
<tr>
<td>(550)</td>
<td>12.00</td>
<td>10.27</td>
</tr>
<tr>
<td>(650)</td>
<td>11.53</td>
<td>16.40</td>
</tr>
<tr>
<td>(750)</td>
<td>12.20</td>
<td>18.56</td>
</tr>
<tr>
<td>(850)</td>
<td>8.68</td>
<td>26.09</td>
</tr>
<tr>
<td>(950)</td>
<td>6.01</td>
<td>8.70</td>
</tr>
<tr>
<td>(1050)</td>
<td>5.40</td>
<td>3.26</td>
</tr>
<tr>
<td>(1150)</td>
<td>4.37</td>
<td>5.43</td>
</tr>
<tr>
<td>Mean</td>
<td>4.37</td>
<td>5.40</td>
</tr>
<tr>
<td>SD</td>
<td>2.34</td>
<td>1.54</td>
</tr>
</tbody>
</table>

Volume-corrected ADC values for individual patients (Pts) within each ADC range \( (\times 10^{-6} \) mm\(^2\)/s) are shown. The number of pixels is expressed as a percentage of the total number of pixels in each ADC range. The percentage of pixels in the range \( 100-550 \times 10^{-6} \) mm\(^2\)/s was significantly greater for HT lesions, while in the ranges 850 and 1050 the percentage was significantly greater in the non-HT lesions.

Figure 2. Graphic comparison between ADCs of HT- and non-HT-destined acute stroke lesions. *Statistically significant (\( P < 0.01 \)) (see Table 2).
threshold value associated with an increased risk of secondary HT.

A number of previous experimental and clinical studies of secondary HT support these findings. In experimental models, the severity of brain ischemia is directly related to the intensity and duration of the cerebral blood flow reduction, and HT risk is associated with both these variables. In addition, the degree of capillary damage and endothelial tight junction disruption in the first 24 hours is also related to the severity and duration of initial ischemia. Similarly, a severe deficit in focal brain perfusion as measured by hexamethylpropyleneamine oxime single-photon emission CT (HMPAO-SPECT) or xenon CT has been reported to predict a high risk of both secondary HT and adverse outcomes in acute stroke patients.

Some investigators have also explored the possibility of predicting secondary HT using conventional CT alone. Several thrombolytic studies have reported that regions of early hypodensity and cerebral edema are associated with an increased hemorrhagic risk. These regions probably represent areas of early predominantly irreversible ischemic injury. However, the reported ability of clinicians to correctly identify these early CT changes is low. In addition, some studies have reported that acute extravasation of contrast media on either CT or MRI is associated with secondary HT. However, other studies have shown a poor correlation between contrast enhancement, the degree of blood-brain barrier disruption, and HT. Thus, an alternative diagnostic approach such as DWI could have significant potential value in better identifying ischemic areas at risk for secondary HT.

Previous MRI studies have shown that ADC values within hyperacute ischemic lesions are quite heterogeneous and that averaging the ADC of the entire lesion does not accurately discriminate the inherent variations in ADC between different ischemic regions. The simultaneous categorization of ADC values into distinct ranges helps to solve this heterogeneity problem. The findings in this study suggest that careful attention to ADC values may be of significant importance in determining the risk of HT associated with a particular ischemic lesion. Fortunately, these analytical methods are not complicated and require little additional data processing. In theory, such calculations could easily be added to current MRI protocols, making rapid, automated data analysis of this kind readily available.

This study is subject to some limitations. Despite the magnitude and consistency of the results, the relatively small sample size and retrospective design require that the findings be validated in a larger number of patients. Moreover, the possibility of a selection bias for patients who could tolerate multiple MRIs cannot be ignored. A larger sample would also allow further refinement of the ADC cutoff values and potential improvement in the predictive power of the techniques used.

In addition, the relationship between asymptomatic and symptomatic hemorrhage after acute ischemic stroke remains uncertain. In this study no distinction was made between symptomatic and asymptomatic hemorrhage because only 1 patient suffered a symptomatic hemorrhage. Although symptomatic hemmorhages are clearly of the most clinical significance, it is has been hypothesized that the difference between symptomatic and asymptomatic hemorrhage may be related more to the degree of bleeding than to differences in pathophysiology. Nevertheless, a separate study of the relationship between ADC values and symptomatic hemorrhage alone would be necessary to fully resolve this issue. However, such a study may be difficult to perform because of the relatively small number of symptomatic hemorrhages after acute ischemic stroke, even in patients receiving thrombolytic therapy.

HT-destined patients were also found to be significantly older than non-HT-destined patients. Some studies have detected a relationship between age and risk of HT. However, in other studies this association has not remained after multivariate analysis or no such relationship has been found. Because of the size of this study, we cannot determine whether age is independently associated with secondary HT. However, considerable overlap in age was evident between the HT- and non-HT-destined patients, suggesting that age alone is an imperfect predictor of HT risk.

The sensitivity of MRI for detecting cerebral hemorrhage has also been a subject of recent debate. Several studies have reported a high sensitivity of MRI to hyperacute ischemic lesions. In the present study, the use of a 1.5-T scanner at 3-mm intervals allowed the detection of hemorrhage in all patients.
hemorrhage. These studies suggest that MRI is more sensitive to acute hemorrhages than previously believed, particularly if susceptibility-weighted sequences are used. Although susceptibility-weighted studies were not consistently performed in this study, it is unlikely that this would have any substantial effect on the results because most hemorrhages were detected many hours to days after stroke onset. Moreover, there was concordance between the susceptibility-weighted sequences and the other MRI techniques used in all cases in which both were performed. It is also unlikely that bleeding was missed in the HT-negative group because all of them had a negative repeated MRI at 5 to 7 days. However, future studies should be performed with susceptibility-weighted sequences at all time points to more completely rule out the possibility that subtle hemorrhages were missed. Such sequences are now integrated into all of our current acute stroke MRI protocols.

Conclusion

In summary, acute stroke lesions destined to result in HT appear to be different and potentially identifiable from non-HT lesions by DWI. Ischemic lesions experiencing HT had lower ADC values and a significantly larger percentage of pixels in lower ADC ranges than ischemic lesions not experiencing HT. These findings suggest a possible added utility of MRI in the evaluation of acute stroke patients, particularly those being considered for therapies that can increase the risk of bleeding, such as thrombolysis. These findings also suggest that future DWI studies must account for the heterogeneity of ADC during the hyperacute phases of cerebral ischemia.

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