Impact of Baseline Tissue Status (Diffusion-Weighted Imaging Lesion) Versus Perfusion Status (Severity of Hypoperfusion) on Hemorrhagic Transformation

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Background and Purpose—The frequency of hemorrhagic transformation (HT) on gradient echo imaging and its impact on stroke outcomes continues to be debated. We investigated the factors associated with HTs and the influence of the HTs observed on gradient echo imaging on the early course after a stroke.

Methods—We analyzed the data from a prospectively maintained registry of patients who were eligible for recanalization therapy. Serial diffusion-weighted imaging and perfusion-weighted imaging were performed, and HTs were assessed on follow-up gradient echo imaging. T_{max} perfusion lesion maps were generated and hypoperfused regions were divided into severe (T_{max} ≥8 seconds) delay and mild (T_{max} ≥2 seconds but <8 seconds) delay. The factors associated with HTs, including the mode of recanalization therapy, pretreatment diffusion-weighted imaging and perfusion-weighted imaging lesion volumes, and reperfusion indices, were evaluated. The early clinical outcome was assessed during the first 7 days of admission.

Results—A total of 184 patients were included in this study. HTs were noted in 73 (39.7%) patients. Multiple logistic regression analysis identified aggressive treatment (OR, 5.12; 95% CI, 1.73 to 15.18) and a large area of severe perfusion delay (OR for highest quartile of T_{max} ≥8 seconds, 12.91; 95% CI, 3.69 to 45.17) as independent predictors of HTs. Neither risk factor profiles nor diffusion-weighted imaging lesion volumes were associated with HTs. There was a poor correlation between the radiological (HT types) and clinical (asymptomatic or symptomatic) categories of HTs. Even a parenchymal hematoma was not always associated with symptomatic worsening or affected the early clinical outcomes.

Conclusion—The results of this study indicate that the perfusion status (severe perfusion delay) rather than the tissue status (diffusion-weighted imaging lesions) and aggressive treatment were independently associated with HTs. HT on gradient echo imaging was common but usually associated with severe hypoperfusion and not always associated with clinical deterioration. (Stroke. 2010;41:e135-e142.)

Key Words: diffusion-weighted imaging ■ hemorrhagic transformation ■ ischemic stroke ■ MRI ■ perfusion-weighted imaging ■ thrombolysis

The most dreaded complication of thrombolytic therapy in patients with hyperacute stroke is hemorrhagic transformation (HT). The identification of predictors associated with HTs is important for the selection of patients for thrombolytic therapy so that HTs can be avoided. Clinical factors such as a high initial National Institutes of Health Stroke Scale (NIHSS), delayed treatment time, and high blood pressure are well known to cause a higher incidence of HTs and have been used as exclusion criteria for thrombolytic therapy.\(^1\)\(^-\)\(^3\) Although predictors found in currently available imaging methods are being studied, only the early ischemic sign on the pretreatment CT (more than one third of the middle cerebral artery territory) is widely used for the selection of patients for thrombolytic therapy.\(^1\) However, the sensitivity and reproducibility of the early ischemic sign is poor.\(^4\)\(^-\)\(^5\)

MRI, including diffusion-weighted (DWI), perfusion-weighted (PWI), and gradient-recalled echo (GRE) imaging, has increasingly been used in clinical practice in the management of patients with acute ischemic stroke. HTs and hemorrhagic stroke can be visualized with high sensitivity and specificity using GRE. The GRE accentuates the paramagnetic properties of blood products such as deoxyhemoglobin, intracellular methemoglobin, and hemosiderin and can detect hemorrhage and intravascular clots. A prospective multi-
center trial has shown that GRE is as accurate as CT for the
detection of acute hemorrhage in patients with acute stroke. A
However, information about the frequency of HT on GRE in
a large cohort with acute ischemic stroke is limited. In addition,
the pathogenesis of HT and the impact of the finding of an HT
on GRE, on stroke outcome, continues to be debated.7

One study has reported that thrombolytic therapies based
on MRI had a lower risk of HTs than those based on CT. A
large area of diffusion and perfusion abnormalities on MRI is
known to be associated with HT. A–15 A recent multicenter
study showed that symptomatic intracranial hemorrhage risk
increases gradually with increasing DWI lesion size, indicat-
ing that the potential benefit of therapy needs to be carefully
balanced against the risk for symptomatic intracranial hem-
orrhage, especially in patients with large DWI lesions.13

Hypoperfusion on pretreatment MRI was also reported to be
associated with HT. A–12 However, in most previous studies,
the severity of hypoperfusion and the degree of reperfu-
sion were not assessed.

In this study, we evaluated whether the pretreatment
perfusion status, especially the severity of hypoperfusion,
was more important to the development of HTs on GRE than
the tissue status (the size of DWI lesions). Thus, we investi-
gated the frequency of the types of HTs on the GRE and the
association between the types of HTs and the PWI indices,
that is, severity of initial hypoperfusion and the degree of
reperfusion, in a relatively large cohort registered from 2
centers. In addition, early clinical outcome was assessed
during the first 7 days of admission to determine the associa-
tion of radiological HTs with clinical outcome.

Patients and Methods

Patient Selection

We analyzed the demographic, clinical, laboratory, and radiologi-
cal data collected prospectively at the University of California–Los
Angeles (UCLA) Medical Center (Los Angeles, Calif) from May
2002 through July 2007 and Samsung Medical Center (Seoul, Korea)
from June 2005 through September 2008.

Inclusion criteria for this study were as follows: (1) acute ischemic
lesions within the middle cerebral artery distribution on DWI; (2)
NIHSS scores of ≥4; (3) an onset to presentation interval of ≤6
hours; (4) PWI and DWI performed before recalibration therapy;
and (5) GRE performed within 7 days after onset of symptoms. The
local Institutional Review Boards approved the study.

MRI Methods and Image Analysis

All patients underwent MRI using a 1.5-T MRI machine (Siemens
Medical Systems) at the UCLA Medical Center or a 3.0-T MRI
machine (Achieva; Philips Medical Systems) at the Samsung Med-
ci cal Center. In both centers, the typical stroke MRI protocol
consisted of DWI, GRE, fluid-attenuated inversion recovery se-
quence, T2* PWI, and MR angiography of the cervical and intra-
cranial vessels (3-dimensional time-of-flight MR angiography and
contrast-enhanced MR angiography including extracranial carotid
and vertebral artery). DWI was obtained with 2 levels of diffusion
sensitization (b values of 0 and 1000 s/mm²; 5- to 7-mm slice
thickness; and no gap). PWI was performed with a timed contrast
bolus passage technique (0.1 mg/kg contrast administered into an
antecubital vein with a power injector at a rate of 5 cm³/s); PWI of
1.5 T performed with the following parameters: TR 2000 ms, TE 60
ms, flip angle 90°; matrix 128×128, field of view 24 cm, section
thickness 5 to 7 mm, and intersection gap 2 mm; whereas parameters
of 3T PWI were as follows: TR 1500 ms; TE 35 ms; flip angle 40°;

matrix 128×128, field of view 24 cm, section thickness 5 mm, and
intersection gap 2 mm.

Perfusion delay was defined based on the perfusion parameter
Tmax. Tmax is the time to the peak of the residue function map
generated by deconvolution of the tissue concentration over the time
curve using an arterial input function from the contralateral middle
cerebral artery.16 A 2-second (Tmax ≥2 seconds), 4-second (Tmax
≥4 seconds), and 8-second (Tmax ≥8 seconds) delay was used as the
lower thresholds for the perfusion defect. In a prior study using
both voxel-by-voxel and volume analyses of serial MRI, it was found
that the PWI measures of ischemia intensity could differentiate
irreversibly injured core from penumbral, salvageable tissue with the
best threshold for identifying core-infarcted tissue adjusted to a
Tmax of ≥6 or ≥8 seconds.17 Data analysis was performed with
software developed in-house, the Stroke Cerebral Analysis 2 (SCAN
2) software package. The software used the Interactive Data Lan-
guage produced by ITT Visual Systems (Boulder, Colo). MRI
volume measurements were performed by one of the investigators
who was blinded to the clinical information. For each patient, the
DWI and PWI lesion volumes were automatically outlined with
subsequent manual corrections. The volumes were calculated using
a computer-assisted volumetric analysis program (Medical Image
Processing, Analysis and Visualization, Version 3.0; National Insti-
tutes of Health, Bethesda, Md). For DWI lesion volume measure-
ment, raters outlined regions of acute diffusion abnormality on the
b=1000 s/mm² image by tracing around the visible hyperintense
lesions, a commonly used, clinical relevant technique.

Pretreatment DWI and PWI were performed in all patients;
however, immediate posttreatment PWI was performed in selected
patients after approximately 2 hours after treatment. Posttreatment
GRE was also performed in all patients 24 hours after treatment.
Additional MRI scans were performed with any clinical worsening.

In the present study, GRE was used to identify HTs. HTs were
defined and classified into 4 subtypes: hemorrhagic infarct type 1
(HI-1), small petechiae along the margins of the infarct; hemorrhagic
infarct type 2 (HI-2), more confluent petechiae within the infarcted
area but without a space-occupying effect; a parenchymal hematoma
type 1 (PH-1), defined as a hematoma in <30% of the infarcted area
with some space-occupying effect; and a parenchymal hematoma
type 2 (PH-2), a hematoma in >30% of the infarct area with a
substantial space-occupying effect.18 Two investigators who were
blinded to the clinical information independently reviewed the MRIs
to determine the types of HTs on GRE. The clinical categories for
HTs were defined as follows: asymptomatic HT (no clinical wors-
ening on the NIHSS score despite HTs), minor symptomatic HT (a
one- to 3-point increase in the NIHSS score), and major symptomatic
HT (a ≥4-point increase in the NIHSS score).

Statistical Analysis

The differences in the clinical, laboratory, and radiological charac-
teristics among stroke subtypes were evaluated using the Student
T test, one-way analysis of variance, or Kruskal-Wallis test for
continuous variables, and Pearson χ² or Fisher exact test for
categorical variables.

Two multivariate logistic regression models were used to assess
for independent factors associated with any types of HTs. First, we
performed multivariate logistic regression analysis to determine
the independent predictors (causative variables) for any types of HTs
considering clinical and pretreatment MRI finding, and mode of
treatment, because these factors are known to influence the occur-
rence of HTs (Model 1). In addition, because endovascular treatment
was more likely performed in patients with severe neurological
deficits and perfusion delay, it could be that HT is associated with
increasing severities and not with aggressive treatment mode. Thus,
we calculated a model without entering treatment mode. Second, a
multivariable logistic analysis model was used to evaluate clinical–
radiological variables that may help to predict HTs controlling for
clinical and pre- and posttreatment MRI findings (Model 2). All
potential predictors were entered into a stepwise logistic regression
model as the dependent variable; entry was set with a univariate
association probability value of ≤0.2. Potential factors included in
Table 1. Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>Southern Californian (n=87)</th>
<th>South Korean (n=87)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>45 (46.4%)</td>
<td>54 (62.1%)</td>
<td>0.033</td>
</tr>
<tr>
<td>Age</td>
<td>67.1 ± 18.1</td>
<td>64.1 ± 12.4</td>
<td>0.186</td>
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<td>NIHSS score, points</td>
<td>16.0 ± 7.2</td>
<td>12.0 ± 6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recanalization therapy</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IV tPA</td>
<td>18 (18.6%)</td>
<td>11 (12.6%)</td>
<td></td>
</tr>
<tr>
<td>Endovascular therapy</td>
<td>56 (57.7%)</td>
<td>14 (16.1%)</td>
<td></td>
</tr>
<tr>
<td>IA tPA</td>
<td>11</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Mechanical</td>
<td>38*</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>IA tPA + mechanical</td>
<td>7*</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>IV tPA + endovascular therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conservative therapy</td>
<td>13 (13.4%)</td>
<td>36 (41.4%)</td>
<td></td>
</tr>
<tr>
<td>MRI time, onset of symptom to scan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment MRI, minutes</td>
<td>260.6 ± 203.0</td>
<td>198.8 ± 94.5</td>
<td>0.013</td>
</tr>
<tr>
<td>Posttreatment GRE, hours</td>
<td>28.1 ± 26.7</td>
<td>27.1 ± 7.1</td>
<td>0.737</td>
</tr>
<tr>
<td>HT</td>
<td></td>
<td></td>
<td>0.142</td>
</tr>
<tr>
<td>None</td>
<td>65 (67.0%)</td>
<td>46 (52.9%)</td>
<td></td>
</tr>
<tr>
<td>HI-1</td>
<td>7 (7.2%)</td>
<td>6 (6.9%)</td>
<td></td>
</tr>
<tr>
<td>HI-2</td>
<td>11 (11.3%)</td>
<td>17 (19.5%)</td>
<td></td>
</tr>
<tr>
<td>PH-1</td>
<td>4 (4.1%)</td>
<td>10 (11.5%)</td>
<td></td>
</tr>
<tr>
<td>PH-2</td>
<td>10 (10.3%)</td>
<td>8 (9.2%)</td>
<td></td>
</tr>
</tbody>
</table>

*Mainly MERCI clot retrieval.
IV indicates intravenous; tPA, tissue plasminogen activator; IA, intra-arterial.

This study was age, gender, hypertension, diabetes, statin use, and laboratory findings such as glucose levels, total cholesterol, and low-density lipoprotein cholesterol. In addition, method of recanalization therapy and volume of the DWI lesion as well as 3 degrees of the PWI lesion such as $T_{max}$ >2 seconds and >8 seconds were considered as potential factors. For DWI and perfusion lesions, we divided the lesion volumes into 4 groups according to interquartile cutoff points of the distribution of volumes of DWI lesions and perfusion delay. All statistical analyses were performed using commercially available software (SPSS for Windows, Version 13.0; SPSS Inc, Chicago, Ill). A $P<0.05$ was considered to indicate statistical significance.

Results

A total of 184 patients were included in this study (Table 1). Male gender was more prevalent in the South Koreans compared with the southern Californians ($P=0.033$). The NIHSS score on admission was lower in the South Koreans compared with the southern Californians, and endovascular treatment was more frequently performed in the southern Californians than in the South Koreans, whereas conservative treatment (including antiplatelet agents or anticoagulation as appropriate) was more frequently performed in the latter than in the former ($P<0.001$ in all cases). The frequencies and types of HTs were not different between the South Koreans and southern Californians ($P=0.142$). The time interval from last known well to MRI was shorter in the South Korean subjects compared with the southern Californian subjects ($P=0.013$). However, the interval to posttreatment GRE was not different ($P=0.737$).

Association of Hemorrhagic Transformations With Diffusion Restriction and Perfusion Delay

Among 184 patients, HI-1 was observed in 13 (7.1%) patients, HI-2 in 28 (15.2%), PH-1 in 14 (7.6%), and PH-2 in 18 (9.8%). The patient characteristics according to the HT types are shown in Table 2. Risk factor profiles and laboratory findings were not different according to the type of HT. The initial NIHSS was correlated with the type of HTs. It was lowest in patients with no HT and highest in patients with PH ($P<0.001$). The endovascular therapies with/without intravenous tissue plasminogen activator were associated with a higher frequency of HTs ($P=0.020$). Both the volumes of DWI lesions ($P=0.002$) and perfusion delay lesions ($P<0.001$) were associated with the presence of HTs. The volume of the DWI lesions and perfusion delay were increased in proportion to the category of the HTs (Table 2). Most HTs were located within the regions of severe perfusion delay; only 7 patients showed HTs located outside the regions of severe perfusion delay; 6 of them had received endovascular therapy and this finding suggested procedure-related complications.

Posttreatment PWI was performed in 88 patients, mostly in those who received recanalization therapy. The volume of perfusion delay lesions ($T_{max}$ >2 seconds) was associated with the presence and type of HTs. Compared with patients without HTs, patients with PH tended to have a larger area of perfusion delay on posttreatment MRI ($P=0.052$).

Table 3 shows the results of the multiple logistic regression models and the ORs for any HTs on the GRE. After adjustment for covariables (Model 1), an aggressive treatment mode (endovascular treatment with/without intravenous tissue plasminogen activator) and a larger area of severe perfusion delay ($T_{max}$ >8 seconds) on the pretreatment MRI were independently associated with any HTs ($P<0.05$ in both cases). We then calculated a model without entering treatment mode. Again, only a large area of severe perfusion delay ($T_{max}$ >8 seconds) on the pretreatment MRI were independently associated with any HTs ($P<0.05$ in both cases). When the volume of posttreatment perfusion delay was entered into the same model (Model 2), a larger area of perfusion delay on posttreatment MRI and s-glucose levels on admission were independently associated with any HTs ($P<0.05$ in both cases). In both models, the NIHSS on admission and pretreatment DWI lesion volumes did not significantly add value for the prediction of any HTs. An exemplary case is shown in Figure 1.

Correlation Between Radiological and Clinical Categories of HTs

Symptomatic HTs, either major or minor, were more common in PH-type HTs (17 of 32 patients) than in HI-type HTs (11 of 41 patients). However, 15 of 32 patients with PH-type
HTs on GRE had clinically asymptomatic HTs (Figure 2A–B). The relationship between radiological and clinical categories of HTs was stronger in patients with milder disabilities (initial NIHSS <14 points) than in those with severe disabilities (≥14 points) on admission (Figure 2A–B).

Moreover, deterioration in NIHSS was frequently observed during the early course of hospitalization regardless of the presence of HTs; the reduction in the NIHSS score during the first 7 days after the onset of stroke was not significantly different according to the HT types on GRE (P=0.147; Figure 2C). The Spearman correlation analysis showed no relationship between types of HTs and NIHSS reduction (r=−0.015, P=0.863).

Table 2. Clinical and MRI Factors According to Severity of HTs

<table>
<thead>
<tr>
<th>Type of HT</th>
<th>No HT (n=111)</th>
<th>HI-1 (n=13)</th>
<th>HI-2 (n=28)</th>
<th>PH-1 (n=14)</th>
<th>PH-2 (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66.7±15.6</td>
<td>65.2±11.4</td>
<td>61.1±17.1</td>
<td>65.2±15.1</td>
<td>67.0±17.4</td>
<td>0.556</td>
</tr>
<tr>
<td>Male gender</td>
<td>58 (52.3%)</td>
<td>7 (53.8%)</td>
<td>13 (46.4%)</td>
<td>9 (64.3%)</td>
<td>12 (66.7%)</td>
<td>0.638</td>
</tr>
<tr>
<td>Hypertension</td>
<td>68 (61.8%)</td>
<td>8 (61.5%)</td>
<td>15 (53.6%)</td>
<td>9 (64.3%)</td>
<td>12 (66.7%)</td>
<td>0.912</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17 (15.5%)</td>
<td>3 (23.1%)</td>
<td>9 (32.1%)</td>
<td>4 (28.6%)</td>
<td>4 (22.2%)</td>
<td>0.314</td>
</tr>
<tr>
<td>Statin use before admission</td>
<td>19 (17.8%)</td>
<td>1 (8.3%)</td>
<td>3 (11.1%)</td>
<td>3 (21.4%)</td>
<td>5 (27.8%)</td>
<td>0.567</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
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<tr>
<td>Glucose</td>
<td>129.3±40.2</td>
<td>121.9±39.5</td>
<td>134.0±40.8</td>
<td>158.6±69.5</td>
<td>138.7±29.6</td>
<td>0.131</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>169.7±39.8</td>
<td>168.6±41.5</td>
<td>165.3±37.0</td>
<td>157.2±46.8</td>
<td>163.2±42.0</td>
<td>0.830</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>104.4±29.5</td>
<td>109.5±39.1</td>
<td>105.0±40.6</td>
<td>98.8±34.9</td>
<td>102.8±44.6</td>
<td>0.957</td>
</tr>
<tr>
<td>Recanalization therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>0.020</td>
</tr>
<tr>
<td>None</td>
<td>37 (74.0%)</td>
<td>3 (6.0%)</td>
<td>5 (10.0%)</td>
<td>3 (6.0%)</td>
<td>2 (4.0%)</td>
<td></td>
</tr>
<tr>
<td>Intra-venous tPA</td>
<td>24 (82.8%)</td>
<td>0 (0%)</td>
<td>2 (6.9%)</td>
<td>0 (0%)</td>
<td>3 (10.3%)</td>
<td>0.887*</td>
</tr>
<tr>
<td>Endovascular</td>
<td>38 (54.3%)</td>
<td>8 (11.4%)</td>
<td>14 (20.0%)</td>
<td>3 (4.3%)</td>
<td>7 (10.0%)</td>
<td>0.061*</td>
</tr>
<tr>
<td>Combined</td>
<td>12 (33.3%)</td>
<td>3 (8.3%)</td>
<td>7 (19.4%)</td>
<td>8 (22.2%)</td>
<td>6 (16.7%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Pretreatment MRI findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWI lesion, mL</td>
<td>20.8±30.9</td>
<td>25.3±21.1</td>
<td>44.3±64.4</td>
<td>42.3±51.9</td>
<td>59.0±69.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Tmax &gt;2 seconds, mL</td>
<td>84.3±85.9</td>
<td>146.6±85.4</td>
<td>168.8±107.4</td>
<td>183.4±104.7</td>
<td>173.0±79.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tmax &gt;4 seconds, mL</td>
<td>59.6±68.2</td>
<td>108.4±66.6</td>
<td>126.4±87.9</td>
<td>141.8±91.8</td>
<td>132.6±66.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Posttreatment MRI</td>
<td>(n=47)</td>
<td>(n=8)</td>
<td>(n=15)</td>
<td>(n=8)</td>
<td>(n=10)</td>
<td></td>
</tr>
<tr>
<td>Tmax &gt;2 seconds, mL</td>
<td>45.3±61.5</td>
<td>50.3±65.2</td>
<td>100.9±103.0</td>
<td>100.9±93.3</td>
<td>91.2±81.8</td>
<td>0.052</td>
</tr>
<tr>
<td>NIHSS score</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>On admission</td>
<td>12.2±6.6</td>
<td>12.1±5.1</td>
<td>15.6±6.2</td>
<td>16.1±7.2</td>
<td>19.2±5.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reduction after 7 days</td>
<td>5.0±7.2</td>
<td>3.4±8.5</td>
<td>2.7±8.7</td>
<td>7.9±6.0</td>
<td>1.8±11.3</td>
<td>0.224</td>
</tr>
</tbody>
</table>

*Compared with no recanalization therapy, linear-by-linear analysis.

LDL indicates low-density lipoprotein; tPA, tissue plasminogen activator.

Discussion

The Frequencies of HT Types on GRE

HTs of brain infarction occur even in patients not treated with interventional stroke therapy; however, they occur more frequently in actively treated patients. Comparisons across trials are limited by varying definitions of HTs. Most previous studies have focused on the symptomatic HTs. There is a significant difference in the frequencies of clinical and radiological categories of HTs (Supplemental Table I; available at http://stroke.ahajournals.org). Symptomatic HTs have been reported to range from 6% to 20% among patients receiving thrombolysis treatment.1–5 It is possible that the prevalence of symptomatic HTs in previous reports might have been underestimated; in most previous studies, CT or MRI was performed only when patients showed clinical signs of worsening in their neurological status. It is often difficult to identify clinical worsening, by HTs, when patients already have severe neurological disabilities. There is a significant difference in the frequencies of HTs between CT- and GRE-based studies; HTs on CT have been reported to range between 25% and 37%; however, they are more commonly observed on GRE ranging between 37% to 43% (Supplemental Table I). The frequencies of HTs in the present data were consistent with those of previous GRE-based studies.

The Size of DWI Lesions Versus Perfusion Defects and HTs

Most previous studies have focused on the relationship between the extent of early changes on CT or DWI (tissue status) and subsequent HTs after thrombolysis.1–3,13 However, studies on the relationship between the severity of the hypoperfusion on the pretreatment MRI and subsequent HTs are limited.10,27 The Diffusion and Perfusion Imaging for...
Understanding Stroke Evolution (DEFUSE) trial studied the severity of perfusion delay (Tmax/H11022 8 seconds) as well as DWI lesion volume for the identification of patients at risk for HTs after recanalization therapy (the malignant profile). The results of the present study indicated that a large volume of severe perfusion delay was an independent predictor over pretreatment DWI lesion volume or the extent of the regions with mild hypoperfusion. The findings of the present study suggest that in patients with a large area of severe perfusion delay, the risk of HTs should be considered, even if the patient shows no extensive early CT or DWI changes suggesting tissue damage.

HTs have at times been regarded as a reperfusion marker. Molina et al reported that HTs were found more frequently in patients with early recanalization and with clinical improvement after thrombolysis. In the present study, the rates of HTs were different depending on the mode of recanalization therapy. Aggressive treatment (endovascular treatment with/without fibrinolysis) was independently associated with HTs. Further studies controlling mode of treatment are needed.

### Radiological and Clinical Findings Associated With HTs

Except symptomatic HTs, the role of HTs in stroke outcomes remains unsettled. In the present study, there was a poor correlation between radiological and clinical categories of HTs. Patients with PH-type HTs on GRE often showed no clinical worsening in neurological status. Moreover, the early hospital course was not different depending on the radiological categories of the HTs. These findings are consistent with a previous study that showed that there was no correlation between HTs on imaging and clinical outcomes.

The possible explanations for this unexpected finding include the following. First, it may be caused by the fact that...
the GRE is too sensitive in the detection of HTs. Second, and more important, most patients who are eligible for recanalization therapy had severe neurological deficits, which would not permit the early identification of HT-related deterioration clinically. The recent European Cooperative Acute Stroke Study (ECASS) III trial used a new definition for symptomatic HT, that is, any blood in the brain or intracranially associated with a clinical deterioration ≥4 NIHSS points that was identified as the predominant cause of neurological deterioration. However, it is often difficult to differentiate the predominant cause of neurological deterioration in clinical practice. Our results showed that PH-related deterioration was less frequently observed in patients with severe disabilities than in those with milder disabilities. Third, HTs restricted to regions with severe hypoperfusion may be asymptomatic regardless of the volume or type of HT. In the present study, HTs were more frequently observed in patients with large severe perfusion delay areas, and most HTs were located within these regions. Thus, the presence of HTs, within the severely hypoperfused regions, could be asymptomatic and may have little impact on early stroke outcomes. These findings suggest that in patients with large regions of severe perfusion delay, follow-up neuroimaging studies may show HTs, especially when patients have severe neurological deficits with no further improvement after recanalization therapy. Lastly, although symptomatic HTs were the main causes of neurological deterioration during the early stage of a stroke, other factors such as stroke evolution should be considered. Worsening of symptoms can be caused by the stroke per se (stroke evolution) or other medical conditions.

Limitations and Conclusions
The strengths of this study include the prospective recruitment of patients from 2 centers and serial MRI-based studies, including the GRE and pretreatment perfusion status. In the present study, immediate posttreatment PWI was performed to evaluate the reperfusion status rather than measurement of the vascular recanalization. However, the results of this study should be interpreted with caution. Limitations include the modest numbers of patients in the cohort. Second, not all (88

Figure 1. A case with hemorrhagic transformation. A, Pretreatment DWI and PWI images show a marked diffusion–perfusion mismatch area with severe perfusion delay. B, Posttreatment PWI images show areas with severe perfusion delay. The day after recanalization with intravenous and endovascular treatment, GRE findings revealed a PH, but the patient showed no clinical worsening. The PH was located within the severely hypoperfused regions. C–E, The volume in the regions with baseline severe perfusion delay (Tmax >8 seconds) and posttreatment perfusion delay, but not the baseline DWI lesions, correlated with the type of HTs. Q1 represents the patients with the lowest quartile volume, whereas Q4 indicates patients with the highest quartile volume.
of 184), patients underwent serial PWI. Moreover, patients were treated with a variety of recanalization therapies, including those with high systemic (intravenous), high local (intrararterial) as well as those without exposure to pharmacological thrombolysis (thrombectomy or conservative treatment). Third, long-term outcomes were not measured. Instead, we used seventh day NIHSS to measure clinical improvement. To reflect clinical outcomes more properly, longer-term follow-up data are needed. Fourth, DWI lesions were identified by visual inspection and apparent diffusion coefficient thresholding was not used in the present study. Last but not least, only time-domain perfusion parameter ($T_{\text{max}}$) was used, and other perfusion parameters such as cerebral blood volume and cerebral blood flow were not considered in the present study. Decreased cerebral blood volume was reported to be associated with HTs.

In conclusion, the results of this study indicate that the perfusion status (severe perfusion delay) rather than tissue status (DWI lesion volume) and aggressive treatment was independently associated with HTs. Perfusion-enhancing strategies may be important not only for the fate of cerebral tissues, but also for the prevention of HTs. Further studies are needed for a better understanding of the pathogenesis and clinical implications of radiological HTs. The factors affecting the differences in the frequency between symptomatic and radiological HTs require further investigation.

Figure 2. HT on GRE and symptomatic worsening. Relationship between radiological and clinical categories of hemorrhagic transformation in patients with (A) milder (NIHSS < 14) and (B) severe (initial NIHSS ≥ 14) disabilities on admission; (C) reductions in the NIHSS scores during the first 7 days and the distribution of radiological categories of HT.

Appendix

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Disclosures
None.

References


Impact of Baseline Tissue Status (Diffusion-Weighted Imaging Lesion) Versus Perfusion Status (Severity of Hypoperfusion) on Hemorrhagic Transformation

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