Two Tales: Hemorrhagic Transformation but Not Parenchymal Hemorrhage After Thrombolysis Is Related to Severity and Duration of Ischemia

MRI Study of Acute Stroke Patients Treated With Intravenous Tissue Plasminogen Activator Within 6 Hours

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Background and Purpose—Intracerebral hemorrhage represents the most feared complication of treatment with intravenous tissue plasminogen activator. We studied whether perfusion-weighted imaging and diffusion-weighted imaging has the potential to identify patients at risk of severe intracerebral hemorrhage after treatment with intravenous tissue plasminogen activator.

Methods—We analyzed data of prospectively studied MRI selected acute ischemic stroke patients treated with intravenous tissue plasminogen activator within 6 hours. All patients were examined by perfusion- and diffusion-weighted imaging ≤6 hours. Perfusion- and diffusion-weighted imaging lesion volumes were calculated. Hemorrhagic transformation was assessed on follow-up CT or MRI and diagnosed as hemorrhagic transformation, parenchymal hemorrhage, or symptomatic intracerebral hemorrhage according to ECASS II criteria.

Results—Of 152 patients, hemorrhagic transformation was seen in 60 (39.5%), parenchymal hemorrhage in 15 (9.9%), and symptomatic intracerebral hemorrhage in 4 (2.6%). Multiple logistic regression analysis identified onset to treatment time after 3 to 6 hours (P<0.001), a larger perfusion-weighted imaging lesion volume (P=0.002), and, as a tendency, a higher score on the National Institutes of Health Stroke Scale on admission (P=0.068) as independent predictors of hemorrhagic transformation. Neither MRI lesion volumes nor severity of symptoms, but rather only an older age tended to be associated with parenchymal hemorrhage (P=0.087).

Conclusion—Our results further support the concept of a different pathogenesis for hemorrhagic transformation and parenchymal hemorrhage. Whereas hemorrhagic transformation should be regarded as a clinically irrelevant epiphenomenon of ischemic damage and reperfusion, parenchymal hemorrhage appears to be related to biologic effects of tissue plasminogen activator and other pre-existing pathologic conditions, which deserve further investigation. (Stroke. 2007;38:313-318.)

Key Words: magnetic resonance imaging, diffusion-weighted ■ magnetic resonance imaging, perfusion-weighted ■ outcome ■ stroke, acute ■ thrombolytic therapy ■ tissue plasminogen activator

The approval of intravenous thrombolysis with tissue plasminogen activator (IV-tPA) for the treatment of acute ischemic stroke has ended an era of therapeutic nihilism. Postapproval reports have demonstrated that IV-tPA can be given with similar effect and complications in the daily emergency setting as in the randomized controlled trials. However, symptomatic intracerebral hemorrhage still represents the most feared complication of treatment with IV-tPA and one of the reasons for the limited use of thrombolysis. Parenchymal hemorrhage after thrombolysis is associated with a higher mortality and worse outcome in surviving patients. However, asymptomatic hemorrhagic transformation is mainly considered to be an epiphenomenon of reperfusion into ischemic tissue without any clinical impact. At the same time, it is still uncertain by which means (if at all) patients at high risk of severe intracerebral hemorrhage after thrombolysis can be identified before the initiation of treatment.
In the present study, we aimed to test whether perfusion-weighted MRI (PWI) and diffusion weighted MRI (DWI) has the potential to identify patients at risk of severe intracerebral hemorrhage after treatment with IV-tPA. For this purpose, we analyzed data of a prospective multicenter study of IV-pa within 6 hours in MRI selected patients to determine whether pretreatment PWI and DWI lesion volumes can be related to symptomatic or asymptomatic intracerebral hemorrhage after thrombolysis within an expanded time window.

**Methods**

**Patients**

Between 1999 and 2003, the MRI in Acute Stroke Study Group of the “German Competence Network Stroke” conducted a prospective multicenter study in which MRI according to a standardized protocol was used as a tool to select acute stroke patients for treatment with IV-tPA within an expanded time window of up to 6 hours.8 In a secondary analysis, we aimed to look for imaging predictors of hemorrhagic transformation. For this study, all acute ischemic stroke patients with a complete stroke MRI study, including PWI and DWI, and a follow-up CT or MRI study within 36 hours were included. Patients enrolled in clinical trials of thrombolytics or neuroprotectives were excluded from the analysis.

**Treatment Protocol**

All patients ≤3 hours were treated with IV-thrombolysis according to the European Stroke Initiative Recommendations for Stroke Management.9 After 3 to 6 hours, IV-thrombolysis was performed as an individual decision based on MRI findings.8 The study was approved by the local institutional review boards in all participating centers.

**Clinical Assessment**

Severity of neurological deficit at admission was assessed using the National Institutes of Health Stroke Scale (NIHSS).10 Outcome was assessed 90 days after stroke using the modified Rankin scale.11 Favorable outcome was defined as a score of 0 to 1; bad outcome as a score of 5 to 6 on the modified Rankin scale. All clinical assessments were made by experienced neurologists who were blinded to the imaging data.

**MRI Protocol**

Details for the standardized acute stroke MRI protocol used in this study have been described recently.12 All MRI studies were performed on 1.5-T clinical whole-body scanners with echo planar capabilities (Magnetom Symphony; Siemens, Hamburg, Heidelberg; Marconi Edge, Heidelberg; Philips Intera, Köln). The MRI protocol included an axial DWI sequence, a PWI sequence, a time-of-flight MR angiography of the intracranial arteries, a T2-weighted sequence, and a T2*-weighted sequence for the exclusion of intracranial hemorrhage with a scanning time of <20 minutes.

**MRI Lesion Volume Measurement**

Postprocessing of the PWI and DWI image data were performed offline in each participating center with locally established software as described previously. To summarize, DWI lesion volumes were delineated either on apparent diffusion coefficient maps or on diffusion-weighted (b=1000) images using standardized apparent diffusion coefficient thresholds or standardized window settings for manually tracing the lesion. For the PWI images, maps of the time to peak or of the mean transit time were calculated and standardized window settings or thresholds were used to delineate the perfusion lesion.

**Assessment of Hemorrhagic Transformation**

Hemorrhagic transformation was assessed on follow-up CT or MRI by experienced neuroradiologists blinded to clinical data. Following established definitions, 4 hemorrhagic transformation (HT) was diagnosed in cases of petechial or confluent hemorrhage within the ischemic lesion. Parenchymal hemorrhage (PH) was defined as blood clots in the infarcted area with at least slight space-occupying effect. Symptomatic intracerebral hemorrhage was defined as any signs of hemorrhage on follow up imaging associated with clinical deterioration of ≥4 points on the NIHSS within 36 hours, according to the definition used in the PROACT II trial.13

**Comparison With Pooled ATLANTIS, ECASS II, and NINDS Data**

Recently, a pooled analysis of the randomized controlled trials of IV-tPA in acute stroke within a 3- or 6-hour time window has been published.14 We compared the rates of hemorrhagic transformation within our study to those of the pooled placebo and pooled tPA patients from the clinical tPA trials (excluding ECASS I data, caused by the different tPA dose of 1.1 mg/kg body weight used in this trial, compared with 0.9 mg/kg used in the other trials and in our study).

**Statistical Analysis**

All values are presented as median (range) for continuous variables and counts (percentage) for categorical variables. Group comparisons were made using the Mann-Whitney U test for continuous variables and Fisher exact test for categorical variables. Univariate binary logistic regression analysis was performed to identify predictors of HT and PH. Parameters with P<0.1 in univariate analysis were entered into a multivariate logistic regression analysis. All statistical analysis was performed using statistical software (SPSS 13.0; SPSS Inc).

**Results**

Follow-up CT or MRI was available for 152 (87%) of 174 patients treated with IV-tPA within 6 hours included in the original study. Patients for whom follow-up imaging was not available were not different from those with follow-up imaging available regarding age, sex, onset to treatment time, NIHSS on admission, modified Rankin scale at day 90, and PWI and DWI lesion volumes. In 61% of patients (n=92), MRI was used for follow-up imaging, whereas in 39% (n=60) hemorrhagic complications were assessed on CT.

Within the 152 patients included into the analysis, PH was found in n=15 (9.9%), HT in n=66 (39.5%), whereas in 77 (50.7%) no hemorrhagic transformation was seen (Table 1). In 4 patients (2.6%), PH was associated with clinical deterioration and assessed as symptomatic intracerebral hemorrhage. Patients with PH were slightly older than those without PH (median 66 versus 63 years; P=0.048), whereas there was no difference for sex, NIHSS on admission (NIHSS oA), MRI lesion volumes, onset to treatment time, or outcome between the 2 groups (Table 2). Compared with patients without any hemorrhagic transformation, those with HT were clinically more severely affected (NIHSS oA 15 versus 12; P<0.001), had larger DWI (23 versus 10 mL; P<0.001) and PWI (181 versus 83 mL) lesion volumes, and were treated later (onset to treatment time 185 versus 140 minutes; P<0.001). Patients with HT and those without HT were similar regarding age, sex, and outcome.

Results of logistic regression analysis are shown in Table 3. Only age tended to predict PH with an odds ratio of 1.55, denoting a 55% increased risk of PH for every 10 years of age. However, 95% confidence intervals include 1. Treatment within the 3- to 6-hour time window, PWI lesion volume, NIHSS on admission, and DWI lesion volume were identified...
as predictors of HT in univariate logistic regression analysis. After multivariate analysis treatment after 3 to 6 hours, PWI lesion volume and NIHSS on admission remained as independent predictors of HT. Odds ratios translate into a 3.5-fold increased hazard of HT for patients treated after 3 to 6 hours, whereas the risk of HT is increased by 8% for every 20-mL increase of PWI lesion volume, and by 54% for every 5 points on the NIHSS on admission.

The rate of symptomatic intracerebral hemorrhage in our study was similar to that in the pooled placebo group and lower than in the pooled tPA group from the clinical tPA trials (Table 4). The frequency of PH in our MRI selected patients was not different from the pooled tPA group, but higher than in pooled placebo patients. Finally, the rate of HT was clearly higher in our sample than in both pooled placebo and pooled tPA patients.

**Discussion**
The main finding of our study is that looking at the value of clinical and imaging parameters as predictors of intracerebral hemorrhagic complications after IV-tPA, completely different patterns are seen for the different types of hemorrhagic transformation. The parameters associated with HT in our study (perfusion lesion volume, neurological deficit on admission, onset to treatment time) can be regarded as reflection of severity and duration of ischemia, and this fits well with findings from previous studies. In acute ischemic stroke patients, a more severe diffusion and perfusion deficit was seen in regions, which later showed hemorrhagic transformation.5,15 However, no clear association was found between volumes of acute perfusion and diffusion lesion and HT,5,16 which may be attributable to small sample sizes in these studies. No association was reported between HT and outcome.5 Furthermore, HT was found more frequent in patients with early recanalization, and more frequent in patients showing clinical improvement after 48 hours.6 In the pooled data of the randomized trials of tPA in stroke, the rate of asymptomatic HT was not increased in patients treated with tPA14 (see also Table 4). As a result of these findings, HT is generally understood as an epiphenomenon of reperfusion into ischemic damaged tissue without any deleterious clinical impact, possibly even as a marker of reperfusion.5–7 Micro-
vascular damage has been identified as a link between ischemia and petechial hemorrhagic transformation,\(^\text{17}\) and an increasing endothelial damage during persisting ischemia might explain the higher frequency of HT in patients treated in the later time window.

In contrast to HT, PH was found to be related to bad outcome.\(^\text{3,4}\) We found similar results in our sample, with a clearly higher number of PH patients being severely disabled or dead after 90 days (33% versus 9%; \(P/<\text{H}110050.014\)). Neither pretreatment diffusion and perfusion lesion volumes nor the severity of neurological deficit on admission were associated with PH in our study. Previous MRI studies on hemorrhagic transformation after ischemic stroke have not reported results for PH type hemorrhages.\(^\text{5,6,15}\) From CT studies, one might have expected the extent of the initial ischemic lesion to be associated with severe parenchymal hemorrhage.\(^\text{4,18}\) However, this was clearly not the case in our study. Only an older age showed a tendency to predict PH in our study, which is in line with previous findings.\(^\text{4,14,19}\)

With regard to the pathogenesis of the different types of hemorrhagic transformation after thrombolysis, the results of our study indicate that PH cannot simply be regarded as a “more severe” form of HT, but that HT and PH are completely different stories. Asymptomatic HT appears to be a secondary phenomenon related to the severity of the ischemic lesion, a result of ischemic damage to the microvasculature, possibly related to reperfusion, not related to thrombolytic treatment and without any clinical impact. In contrast, parenchymal hemorrhage appears not to be related to the severity of pretreatment ischemia, is associated with tPA treatment, seems to be associated with older age, and is clearly associated with a bad outcome. Disturbances in the coagulation system attributable to the biological effects of tPA have been discussed as potential mechanisms of severe bleeding complications after IV-tPA.\(^\text{20,21}\) The impact of pre-existing structural pathologies such as a severe leukoariosis, or the presence of “cerebral microbleeds” detected by modern MRI techniques still remains blurred.\(^\text{16,22,23}\)

### TABLE 3. Predictors of HT: Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>(P)</td>
</tr>
<tr>
<td>Predictors of PH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>1.045 (0.994–1.099)</td>
<td>0.087</td>
</tr>
<tr>
<td>Age 10 y</td>
<td>1.553 (0.942–2.570)</td>
<td></td>
</tr>
<tr>
<td>PWI lesion (mL)</td>
<td>1.001 (0.997–1.005)</td>
<td>0.549</td>
</tr>
<tr>
<td>NIHSS oA</td>
<td>1.023 (0.934–1.120)</td>
<td>0.628</td>
</tr>
<tr>
<td>DWI lesion (mL)</td>
<td>0.997 (0.980–1.015)</td>
<td>0.757</td>
</tr>
<tr>
<td>OTT 3–6 h</td>
<td>0.927 (0.300–2.865)</td>
<td>0.895</td>
</tr>
<tr>
<td>Female</td>
<td>1.057 (0.356–3.135)</td>
<td>0.921</td>
</tr>
<tr>
<td>Predictors of HT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OTT 3–6 h</td>
<td>3.774 (1.802–7.874)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PWI lesion (mL)</td>
<td>1.007 (1.003–1.010)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PWI lesion 20 mL</td>
<td>1.150 (1.062–1.220)</td>
<td></td>
</tr>
<tr>
<td>NIHSS oA</td>
<td>1.127 (1.048–1.213)</td>
<td>0.001</td>
</tr>
<tr>
<td>NIHSS oA 5 patients</td>
<td>1.818 (1.264–2.626)</td>
<td></td>
</tr>
<tr>
<td>DWI lesion (mL)</td>
<td>1.010 (0.999–1.021)</td>
<td>0.073</td>
</tr>
<tr>
<td>DWI lesion 20 mL</td>
<td>1.220 (0.980–1.515)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>1.022 (0.993–1.051)</td>
<td>0.137</td>
</tr>
<tr>
<td>Female</td>
<td>0.859 (0.429–1.721)</td>
<td>0.668</td>
</tr>
</tbody>
</table>

Variables identified as predictors of PH or HT by univariate analysis (\(P/<\text{H}110210.1\)) were entered into a multivariate analysis. NA indicates not applied.

### TABLE 4. Frequency of Hemorrhagic Complications Compared to the Pooled tPA Trials Data

<table>
<thead>
<tr>
<th></th>
<th>MRI Selected tPA, n=152</th>
<th>Pooled Placebo, n=1081</th>
<th>MRI Selected tPA vs Pooled Placebo, (P)</th>
<th>MRI Selected tPA vs Pooled tPA, (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT</td>
<td>60 (39.5)</td>
<td>224 (20.7)</td>
<td>(&lt;0.001)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>PH</td>
<td>15 (9.9)*</td>
<td>34 (3.1)</td>
<td>(&lt;0.001)</td>
<td>0.888</td>
</tr>
<tr>
<td>SICH</td>
<td>4 (2.6)</td>
<td>21 (1.9)</td>
<td>0.537</td>
<td>0.013</td>
</tr>
</tbody>
</table>

All values count (%). Two-tailed Fisher’s exact test was used for group comparison. *PH including SICH.
The frequency of PH was not increased in patients treated after 3 to 6 hours. This is in line with the results from previous studies, in which severe intracerebral bleeding complications after thrombolysis were not related to onset to treatment time.\textsuperscript{14,24,25} Moreover, the rate of symptomatic intracerebral hemorrhages in our group of MRI selected patients treated with IV-tPA did not exceed that in pooled placebo patients from the large clinical tPA trials. Fear of an increased risk of severe bleeding complications therefore should not serve as an argument against an extension of the time window for IV-tPA up to 6 hours, especially not when patients are selected by MRI.

The rate of HT was rather high in our sample compared with the data from the pooled tPA trials. This is most probably a result of the use of MRI as follow-up imaging modality in the majority of patients, whereas CT was used for follow-up in the tPA trials. With modern MRI sequences such as gradient echo and echo planar susceptibility-weighted imaging, MRI is known to be more sensitive to cerebral microbleeds or petechial hemorrhage than CT.\textsuperscript{12,23} In our sample, the rate of HT was clearly higher, when MRI was used as follow-up imaging (48.9\% compared with 25.0\% for CT; \textit{P}=0.004), whereas there was no significant difference in the rate of PH between both imaging modalities (7.6\% versus 13.3\%; \textit{P}=0.275).

Analysis of MR images in our study was focused on DWI and PWI lesion volume measurement, but there are further possibilities of using MRI for the prediction of hemorrhagic transformation. A more detailed analysis of perfusion and diffusion weighted images might provide additional markers of the severity of ischemia. Previous studies found a more severely decreased apparent diffusion coefficient\textsuperscript{5,15,16} and a more severe perfusion impairment\textsuperscript{5} within regions prone to secondary hemorrhagic transformation. Furthermore, other MRI sequences, such as T2-weighted, fluid attenuation inversion recovery, or gradient echo images, have shown a certain potential to identify patients at risk of severe hemorrhagic transformation. Severe leukoariosis\textsuperscript{26} and a lacunar state,\textsuperscript{16} diagnosed on T2-weighted images, were reported to be associated with intracerebral hemorrhage after thrombolysis, and there are controversial reports about the association of so-called microbleeds, usually diagnosed on gradient echo MRI, with secondary intracerebral hemorrhage.\textsuperscript{22,23,27} However, the analysis of these MRI techniques were not part of our study protocol. In future studies, a combined analysis of different MR images might further improve the understanding of the pathophysiology of hemorrhagic transformation in ischemic stroke and help identify patients at high risk for intracerebral hemorrhage after intravenous thrombolysis.

There are limitations to this analysis. The use of MRI as selection tool for IV-tPA treatment might introduce a certain bias, because we do not know how many patients were excluded from the study because of unavailability of the MRI scanner, unstable clinical condition, or contraindications against MRI. The use of different imaging modalities (MRI and CT) might have affected the classification of hemorrhagic transformation, because MRI might tend to overestimate the degree of hemorrhagic transformation compared with CT. The small number of patients with severe intracerebral hemorrhagic complications additionally limits the statistical power of our analysis. Finally, the focus of our study was the value of DWI and PWI in the prediction of hemorrhagic complications, and we did only include a small number of clinical parameters into our analysis. Additional clinical and laboratory parameters might have an additional value in the prediction of hemorrhagic transformation after IV-tPA.

**Conclusion**

We looked for predictors of hemorrhagic transformation after intravenous thrombolysis with tPA and identified different patterns for the different types of hemorrhage. Severity and duration of ischemia predicted HT-type, but not PH-type, bleeding. This further supports the concept of a different pathogenesis for HT and PH, with HT being a clinically irrelevant epiphenomenon of ischemic damage and reperfusion, whereas PH appears to be related to biologic effects of tPA and other pre-existing pathologic conditions, which deserve further investigation. With regard to the existing data, neither imaging nor clinical parameters seem to allow the identification of patients at high risk for severe parenchymal hemorrhage after IV-tPA treatment.

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**Disclosures**

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**References**


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