MRI Detection of Early Blood-Brain Barrier Disruption
Parenchymal Enhancement Predicts Focal Hemorrhagic Transformation After Thrombolysis

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Background and Purpose—Blood-brain barrier disruption may be a predictor of hemorrhagic transformation (HT) in ischemic stroke. We hypothesize that parenchymal enhancement (PE) on postcontrast T1-weighted MRI predicts and localizes subsequent HT.

Methods—In a prospective study, 33 tPA-treated stroke patients were imaged by perfusion-weighted imaging, T1 and FLAIR before thrombolytic therapy and after 2 and 24 hours.

Results—Postcontrast T1 PE was found in 5 of 32 patients (16%) 2 hours post-thrombolysis. All 5 patients subsequently showed HT compared to 11 of 26 patients without PE (P = 0.043, specificity 100%, sensitivity 31%), with exact anatomic colocation of PE and HT. Enhancement of cerebrospinal fluid on FLAIR was found in 4 other patients, 1 of which developed HT. Local reperfusion was found in 4 of 5 patients with PE, whereas reperfusion was found in all cases of cerebrospinal fluid hyperintensity.

Conclusions—PE detected 2 hours after thrombolytic therapy predicts HT with high specificity. Contrast-enhanced MRI may provide a tool for studying HT and targeting future therapies to reduce risk of hemorrhagic complications. (Stroke. 2008;39:1025-1028.)

Key Words: blood brain barrier • brain infarction • imaging • intracerebral hemorrhage • MRI • thrombolysis

Thrombolytic therapy of acute ischemic stroke increases the risk of hemorrhagic transformation (HT).1 A central mechanism is thought to be reperfusion of brain tissues, where prolonged, severe hypoperfusion damages the blood-brain barrier (BBB).2 In stroke, increased BBB permeability is observed as hyperintensities by contrast-enhanced T1-weighted MRI in the parenchyma3 and fluid-attenuated inversion-recovery (FLAIR) MRI in the cerebrospinal fluid (CSF), termed “hyperintense acute reperfusion marker” (HARM).4 By the dynamics of CSF, HARM may not be sensitive to subcortical BBB damage. On the other hand, parenchymal enhancement (PE) seen as postcontrast hyperintensity on T1-weighted imaging may provide a more direct localization of BBB disruption relative to the diffuse hyperintensity in HARM.

The purpose of this study was to compare the ability of contrast-enhanced T1 and FLAIR to predict HT in the first few hours after thrombolytic therapy. Secondly, we aimed to characterize the relation between early reperfusion, BBB disruption, and HT.
decrease of the MTT lesion volume of ≥30% from baseline to the follow-up study. Tissue with PE was characterized as showing local reperfusion if MTT values in the tissue volume had normalized after 2 and 24 hours (visual inspection). Postcontrast T1 PE had to be clearly distinct from vascular enhancement and not present on baseline images. HARM was defined as FLAIR hyperintensity in the CSF. Hemorrhagic transformation was classified as either hemorrhagic infarct (HI) or parenchymal hematoma (PH).

Results
Of 141 MRI-screened patients, 33 received tPA within 3 hours of symptom onset (age 68±9 years, NIHSS 11±6, time-to-MRI 104±33 min). Mean DWI lesion volume was 16 mL. Five patients (16%) displayed PE 2 hours post-tPA (Figure 1); hemorrhagic transformation occurred in those 5 patients, compared with 11 of 26 without PE (P=0.043, specificity=100%, sensitivity=31%). Three of 16 cases of HT were classified as PH. None of the hemorrhages were symptomatic (NIHSS increase of ≥4 during 24 hours).

Local reperfusion was found in 4 of 5 cases of PE 2 hours post-tPA (Figure 2). Reperfusion (≥30% MTT lesion shrinkage) was found in 1 of 4 patients after 2 hours compared with 10 of 19 without PE (P=0.59). There was no significant relationship between reperfusion and subsequent HT (Table). Reperfusion 2 hours post-tPA was found in 7 of 14 patients with subsequent HT. At 24 hours, local reperfusion had occurred in 12 of 13 patients with HT.

Four patients (12%) displayed HARM 2 hours post-tPA. After 24 hours, HARM was only found in those 4 patients; early reperfusion had occurred in all, but subsequent HT was only found in one of them. None of the patients displayed both PE and HARM at any time.

Predictors of Hemorrhagic Transformation
Logistic regression showed correlation between baseline DWI lesion volume and subsequent HT (P=0.04). Mean

| Table. Univariate Analysis of Association of Imaging Variables With Hemorrhagic Transformation |
|----------------------------------|-------|---------|-----|
| Hemorrhagic Transformation        | Yes   | No      | P   |
| Parenchymal enhancement, 2 hours  |       |         |     |
| Yes                              | 5 (100) | 0 | 0.04 |
| No                               | 11    | 15      |     |
| HARM, 2 hours                    |       |         |     |
| Yes                              | 1 (25) | 3 | 0.60 |
| No                               | 15    | 13      |     |
| Reperfusion, 2 hours             |       |         |     |
| Yes                              | 7 (64) | 4 | 0.70 |
| No                               | 7     | 6       |     |
| Reperfusion, 24 hours            |       |         |     |
| Yes                              | 12 (63)| 7 | 0.54 |
| No                               | 1     | 2       |     |

Percentages are shown in parentheses. Univariate tests of independence in 2×2 contingency tables by Fisher exact test.
DWI lesion volume at baseline was significantly higher in the HT-group than in the non-HT group (26.0 versus 6.6 mL, P=0.02, Student t test). Similarly, admission NIHSS was related to HT (P=0.04) and mean NIHSS was significantly higher in the HT group than in the non-HT group (13.3 versus 8.5, P=0.03). An exact anatomic relationship between PE and subsequent HT was found in all cases.

**Discussion**

This study of contrast agent (CA) leakage in tPA-treated stroke patients showed PE as early as 2 hours post-treatment. Furthermore, we found that local tissue reperfusion preceded BBB disruption in the majority of patients.

All patients with PE 2 hours after thrombolysis developed HT, confirming the high specificity and low sensitivity recently noted in a retrospective study. Parenchymal enhancement and subsequent HT colocalized in all of cases. In contrast, only 1 of 4 patients showing HARM developed HT. Latour et al retrospectively identified HARM in 53% of tPA-treated patients, of whom 46% developed HT, and found a correlation between HARM and reperfusion within 1 week. We extend that finding by demonstrating early reperfusion in all cases of HARM. We speculate that the number of cortical and periventricular infarctions accounts for differences in the occurrence of HARM between the 2 studies.

The sensitivity of PE was low; it failed to precede all cases of HT at 2 hours, perhaps due to the short half-life of gadobutrol (1.5 hour). Our preliminary data suggest that repeated T1-imaging immediately following 2-hour PWI increases sensitivity (results not shown). Furthermore, CA may not enter tissue with severe ischemia and hence fail to delineate BBB abnormality. The majority of patients were examined with a 3T scanner. No PE was recorded at 1.5T at 2-hour follow-up, and we speculate that 1.5T images may be less sensitive to CA leakage. All hemorrhages were asymptomatic. In contrast to thrombolysis-related “severe HT” (PH), “mild HT” (HI) may be a marker of successful recanalization without adverse impact on neurological outcome. Thomalla et al identified predictors of the 2 types of HT and suggested that they have different pathogenesis. The small number of PH in our study precludes us for stating whether specific BBB leakage patterns are associated with PH rather than HI. We speculate that the extent of PE and the severity of the subsequent HT are correlated. Indeed, studies using serial postcontrast T1-weighted imaging, PWI, and DWI may give insight into the pathology of BBB disruption in ischemic tissue and help target and monitor future adjunctive therapies for reducing hemorrhagic complications in thrombolytic treatment.

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**Disclosures**

None.
References

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