New Microbleeds After Thrombolysis

Contiguous Thin-Slice 3T MRI

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Abstract: We aimed to determine the frequency of new microbleeds after intravenous thrombolysis using contiguous thin-slice 3T magnetic resonance imaging. We retrospectively examined clinical and imaging data from 121 consecutive acute ischemic stroke patients who underwent magnetic resonance imaging before and 24 hours after intravenous thrombolysis. Of the included patients, 44 (36.4%) were women, with a median age of 69 years (range, 35–94 years). A total of 363 baseline microbleeds were observed in 57 patients and 8 new microbleeds in 6 patients. Multiple regression analysis indicated that baseline infarct volume (odds ratio, 0.99; 95% CI, 1.056–3.622; P = 0.03), but not the presence of baseline microbleeds, were independently associated with new microbleeds. The frequency of neither symptomatic intracranial hemorrhage nor remote hemorrhage or any hemorrhagic transformation was different between patients with and without new microbleeds (0.0% vs 1.7%; P = 0.99; 0.0% vs 28.7%; P = 0.36). New microbleeds developed rapidly 24 hours after intravenous thrombolysis. The significance of these new microbleeds and their effect on cognitive and functional outcome merits further investigation.

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INTRODUCTION

Cerebral microbleeds (CMBs), defined as small, rounded or circular, and hypointense lesions within brain parenchyma with clear margins on gradient-recalled echo (GRE) scans, are commonly detected in elderly individuals2 and patients with cerebrovascular diseases.3 Focal accumulation of hemosiderin-containing macrophages was noted in areas with signal loss on magnetic resonance imaging (MRI).4 CMBs might be a potential risk factor for intracranial hemorrhage (ICH) after ischemic stroke,5 or after thrombolysis.5,7 Generally, CMBs have been considered to be old microhemorrhages that develop over an individual’s lifetime,4 but recent studies indicated that CMBs might develop rapidly after acute ischemic stroke8 or after tissue-type plasminogen activator infusion.9 It is increasingly known that the presence, number, and size of CMBs may vary substantially with the parameters of GRE. Longer echo time (TE) (range, 25–50 ms), higher spatial resolution (3-dimensional [3D] Fourier transform technique, thinner scanning sections, and no interslice gap), and increased field strength can increase the sensitivity of CMBs detection.1 However, the GRE sequences used in these 2 studies had a relatively greater slice thickness (5-mm and 6-mm) and interslice gap (2-mm and 1-mm) and were performed on 1.5T MRI.1,7 We therefore deemed it worthy to detect the CMBs with a contiguous, thin-slice, and 3D multiecho GRE sequence performed with a 3T MRI unit. Based on such measurements, this study aims to delve into the variations in GRE characteristics and their influence on detecting new CMBs, and investigate the independent risk factors of new CMBs and the relationship between new CMBs and ICH after thrombolysis.

MATERIALS AND METHODS

Study Subjects

We retrospectively reviewed our prospectively collected database for consecutive patients with acute ischemic stroke who received thrombolytic therapy between June 2009 and September 2013. We then enrolled patients who had a diagnosis of acute ischemic stroke confirmed by diffusion-weighted imaging (DWI), received intravenous recombinant tissue-type plasminogen activator (rtPA) within 6 hours of symptom onset, underwent GRE sequence before rtPA infusion, and underwent follow-up GRE sequence 24 hours after rtPA infusion. The onset was considered to be the time when a patient was last known to be without ischemic symptoms. We excluded patients whose image quality was poor because of motion artifacts. No patient received antithrombotic agents within 24 hours after rtPA infusion.

We retrieved demographic, clinical, laboratory, and imaging data including age and sex; comorbid conditions such as history of hypertension, diabetes mellitus, hyperlipidemia, and functional outcome merits further investigation.
atrial fibrillation, and hyperhomocysteinemia; previous use of aspirin and warfarin; time interval from stroke onset to rtPA infusion; National Institutes of Health Stroke Scale (NIHSS) score, systolic blood pressure (SBP), diastolic blood pressure (DBP), serum glucose, serum creatinine, platelet and international normalized ratio (INR) before rtPA infusion; infarct volume before rtPA infusion, leukoaraiosis volume, presence of baseline and new CMBs, number of baseline and new CMBs, hemorrhagic transformation 24 hours after rtPA infusion, and modified Rankin Scale (mRS) score after 3 months. The follow-up MRI was done before any subject was started on antithrombotic therapy.

Ethics Statement
All subjects conducting the research project in this manuscript had given written informed consent prior to the study and the protocols of MRI-guided intravenous thrombolysis had been approved by the human ethics committee of the Second Affiliated Hospital of Zhejiang University School of Medicine.

MRI Parameters
All subjects underwent MRI on a 3.0T system (Signa Excite HD; General Electric Medical System, Milwaukee, WI). The 3D multiecho GRE sequence covered the whole brain and used 11 equally spaced echoes: TE = 4.5 ms (first echo), interecho spacing = 4.5 ms, repetition time (TR) = 58 ms, field of view (FOV) = 24 × 24 cm², matrix size = 256 × 256, flip angle = 20°, slice thickness = 2.0 mm with no gap between slices, and in-plane spatial resolution of 0.4688 × 0.4688 mm/pixel. Magnitude images were acquired. Axial T2 fluid-attenuated inversion recovery sequence was used to measure the leukoaraiosis volume (TR = 10,000 ms, TE = 150 ms, FOV = 24 × 24 cm², matrix size = 256 × 256, inversion time = 2500 ms, slice thickness = 5.0 mm with no gap between slices, and in-plane spatial resolution of 0.4688 × 0.4688 mm/pixel). DWI sequence was used to measure the infarct volume before rtPA infusion (TR = 4000 ms, TE = 69.3 ms, b-value = 1000 s/mm² with 3 acquired diffusion directions, FOV = 24 × 24 cm², matrix size = 160 × 160, slice thickness = 5.0 mm, interslice gap = 1.0 mm, and in-plane spatial resolution of 0.9375 × 0.9375 mm/pixel); the segmentation threshold for infarct lesion was determined a priori as 3 standard deviations in pixel intensity above the mean of the fitted distribution of the contralateral brain parenchyma.

Detection Criteria of Baseline and New CMBs
We identified a CMB according to a field guide for the detection and interpretation of CMBs. Briefly, the signal of a CMB should be black or very hypointense on T2*-weighted MRI, round or ovoid with a size of ≤ 10 mm, blooming, devoid of T1- or T2-weighted hyperintensity, and at least half-surrounded by brain parenchyma. Mineralization of the basal ganglia and diffuse axonal injury are excluded based on appearance or clinical history.

New CMBs were defined as CMBs that newly appeared on the follow-up GRE scans compared with the initial scans. We described the locations, counted the number of all CMBs on baseline and follow-up GRE scans independently, and then performed slice-to-slice comparison to determine whether the CMBs on follow-up GRE scans were new or unchanged. DWI was used to confirm that the new CMBs occurred outside the infarct area. Newly appearing CMBs in the acute infarct area were not regarded as new CMBs. CMBs that were unquestionably hypointense on the initial GRE scans but became conspicuous on the follow-up were not regarded as new CMBs. The locations of CMBs were classified as lobar, deep, or infratentorial.

Evaluation of Outcome
Hemorrhagic transformation was classified by using clinical and imaging criteria as follows: hemorrhagic infarction (HI), parenchymal hemorrhage (PH), extracerebral hemorrhage, and symtomatic ICH (sICH). An ICH was defined as sICH if the patient had clinical deterioration causing an increase of NIHSS ≥ 4 points and if the hemorrhage was likely to be the cause of the clinical deterioration. An extracerebral hemorrhage was defined as the new appearance of hypointense lesions with a diameter of > 10 mm outside the infarct area on follow-up GRE scans and at least 1 aspect did not meet the detection criteria of CMBs. Outcome was dichotomized into good clinical outcome (mRS, 0–2) or poor clinical outcome (mRS, 3–6) at 3 months.

Reliability and Validity of the Radiological Data
Two investigators blinded to the patients’ clinical data jointly evaluated the MRI?findings. A trained observer (S.Y.) evaluated the images of all patients twice, at an interval of 3 months. Another observer (M.L.) independently made the same evaluation. The interobserver intraclass correlation coefficients (ICCs) were 0.96 and 0.95 for the number of baseline and new CMBs, respectively. The intraobserver ICCs were 0.93 and 0.94 for the number of baseline and new CMBs, respectively. ICCs were described in detail elsewhere. The interobserver and intraobserver reliabilities about the presence of CMBs (≥ 1) were also acceptable (k value = 0.86 and 0.81, respectively). Discrepancies were resolved by consensus.

Statistical Analysis
Fisher exact test was used to compare the dichotomous variables between groups, whereas independent samples of 2-tailed t test or Mann–Whitney U test was used for continuous variables. Variables with a P < 0.10 in univariate regression analyses were included in the binary logistic regression model, whereas NIHSS score before rtPA infusion, time from onset to treatment, previous use of aspirin or warfarin, infarct volume before rtPA infusion, which were thought to be potential factors associated with ICH after intravenous thrombolysis, and age, hyperhomocysteinemia, presence of baseline CMBs, leukoaraiosis volume, which were thought to be associated with small vessel disease, were forced into the model. Hosmer–Lemeshow test was used to evaluate the difference between observed and predicted event rates in the binary logistic regression model. Statistical significance was set at a probability value of < 0.05. All statistical analysis was performed with SPSS package (14.0 for Windows; SPSS Inc, Chicago, IL).

RESULTS
A total of 167 consecutive patients with acute ischemic stroke received MRI-guided intravenous thrombolysis during the study period. Among them, 39 did not undergo follow-up MRI 24 hours after treatment, MRI quality was poor for
analysis in 4, and 3 had hypointense lesion on GRE scans with suspicious cavernous malformations, which might affect CMBs evaluation. A total of 121 remaining patients were included for the final analysis. Demographic, clinical, and laboratory data were not different between included and excluded subjects, except that baseline NIHSS score was higher in excluded patients (13.3 ± 6.7 vs 9.5 ± 5.9), mainly because some severe stroke patients were transferred to intensive care unit or received surgical treatment, resulting in failure of follow-up GRE scans. Of the included patients, 44 (36.4%) were women, with a median age of 69 years (mean, 67.26 ± 12.53 years; range, 35–94 years).

On initial GRE scans, we observed 363 CMBs in 57 patients (47.1%). The median number of baseline CMBs was 2 (range, 1–65). On follow-up GRE scans 24 hours after treatment, 8 new CMBs in 6 patients (5.0%) were observed. The median number of new CMBs among these patients was 1 (range, 1–2). None of the baseline CMBs disappeared on follow-up GRE scans. New CMBs were found in 5 (7.8%) of 64 patients without baseline CMBs, 0 (0.0%) of 36 patients with baseline CMBs of 1 to 2, and 1 (4.8%) of 21 patients with microbleeds of >2 (Fisher exact test, P = 0.25).

There were 133 (36.6%) baseline CMBs in a lobar location, 178 (49.0%) in a deep location, and 52 (14.3%) in an infratentorial location. For the 8 new CMBs, 4 (50.0%) were lobar, 2 (25.0%) were deep, 2 (25.0%) were infratentorial, and 6 new CMBs were located in the ipsilateral hemisphere of infarction, whereas 2 were in the contralateral hemisphere. Among 57 patients with baseline CMBs, 13 had lobar CMBs, 15 had deep CMBs, 1 had infratentorial CMBs, 14 had lobar and deep CMBs, 2 had lobar and infratentorial CMBs, 1 had deep and infratentorial CMBs, and 11 had lobar, deep, and infratentorial CMBs. In addition, 11 patients had multiple baseline CMBs (>2) in the lobar location.

Table 1 shows the characteristics of patients with and without new CMBs for comparison. There were no significant differences in the risk factors between patients with and without new CMBs in univariate analysis. Only increased SBP and INR were marginally associated with new CMBs. Patients with baseline CMBs didn’t have more new CMBs than those without baseline CMBs (1.8% vs 7.8%, P = 0.21).

Age, hyperhomocysteinemia, the presence of baseline CMBs, baseline NIHSS, time from onset to treatment, previous use of aspirin or warfarin, baseline infarct volume and leukoaraiosis volume, SBP, and INR were included in the binary logistic regression model. Baseline DWI infarct volume and SBP were the independent factors associated with new CMBs (Table 1). The Hosmer–Lemeshow test showed no significant difference (P = 0.99) or remote hemorrhage (0.0% vs 1.7%, P > 0.99) or any hemorrhagic transformation (50.0% vs 28.7%, P = 0.36) was not different between patients with and without new CMBs. Patients with baseline multiple lobar CMBs (>2) also did not reveal higher risk of sICH (0.0% vs 1.8%, P > 0.99), remote hemorrhage (0.0% vs 1.8%, P > 0.99), or any hemorrhagic transformation (9.1% vs 31.8%, P = 0.17). The presence of new CMBs was not associated with poor clinical outcome after adjusting for baseline NIHSS score and age in the binary logistic regression model (odds ratio, 0.557; 95% CI, 0.072–4.286; P = 0.57).

**DISCUSSION**

In the current study, we found that new CMBs developed rapidly in 5.0% of acute ischemic stroke patients received intravenous thrombolysis. However, the occurrence of new CMBs was not independently related with the presence of baseline CMBs, and patients with new CMBs

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**TABLE 1. Univariate Comparison of Characteristics Between Patients With and Without New CMBs**

| Variable                          | With (n = 6) | Without (n = 115) | P Value |
|-----------------------------------|-------------|------------------|---------|
| Age, y                            | 72.17 ± 12.92 | 67.01 ± 12.51 | 0.33    |
| Sex                               | 2 (33.3%)   | 42 (36.5%)     | >0.99   |
| Past medical history              |             |                 |         |
| Hypertension                      | 6 (100%)    | 78 (67.8%)     | 0.18    |
| Diabetes mellitus                 | 1 (16.7%)   | 22 (19.1%)     | >0.99   |
| Hyperlipidemia                    | 0 (0.0%)    | 6 (5.2%)       | >0.99   |
| Atrial fibrillation               | 2 (33.3%)   | 40 (34.8%)     | >0.99   |
| Hyperhomocysteinemia              | 2 (33.3%)   | 34 (29.6%)     | >0.99   |
| Clinical variables                |             |                 |         |
| NIHSS score                       | 9.00 ± 7.35 | 9.56 ± 5.90    | 0.82    |
| Onset to treatment, min           | 200.00 ± 43.00 | 242.43 ± 78.44 | 0.19  |
| Previous use of aspirin or warfarin| 1 (16.7%)   | 14 (12.2%)     | 0.56    |
| SBP, mm Hg                        | 172.67 ± 18.06 | 155.74 ± 23.71 | 0.09    |
| DBP, mm Hg                        | 85.67 ± 18.60 | 86.78 ± 14.23  | 0.85    |
| Glucose, mmol/L                   | 7.66 ± 3.67  | 7.86 ± 2.94    | 0.87    |
| Creatinine, µmol/L                | 74.33 ± 15.15 | 71.81 ± 16.65  | 0.72    |
| Platelet (10^9/L)                 | 187.33 ± 44.86 | 185.62 ± 60.73 | 0.95    |
| INR                               | 1.10 ± 0.11  | 1.04 ± 0.08    | 0.08    |
| Radiological data                 |             |                 |         |
| Baseline infarct volume, mL       | 26.1 ± 51.8  | 11.4 ± 26.2    | 0.57*   |
| Leukoaraiosis volume, mL          | 15.94 ± 15.75 | 11.01 ± 11.52  | 0.37*   |
| Presence of baseline CMBs         | 1 (16.7%)   | 56 (48.7%)     | 0.21    |
| Number of baseline CMBs           | 0.50 ± 1.23  | 3.13 ± 9.15    | 0.19*   |
| Hemorrhagic transformation        |             |                 |         |
| HI                                | 2 (33.3%)   | 26 (22.6%)     |         |
| PH                               | 1 (16.7%)   | 7 (6.1%)       |         |
| sICH                              | 0 (0.0%)    | 2 (1.7%)       | >0.99   |
| Extraischemic hemorrhage          | 0 (0.0%)    | 2 (1.7%)       | >0.99   |

CMBs = cerebral microbleeds, DBP = diastolic blood pressure, HI = hemorrhagic infarction, INR = international normalized ratio, NIHSS = National Institutes of Health Stroke Scale, PH = parenchymal hemorrhage, SBP = systolic blood pressure, sICH = symptomatic intracranial hemorrhage.

*Mann–Whitney U test.
did not experience more hemorrhagic transformation than those without new CMBs.

Generally, CMBs are regarded as old microhemorrhage and follow a slow process of development because histopathological analysis shows that CMBs consist of hemosiderin accumulations from red blood cells that presumably have leaked out of small vessels. However, a recent systematic review report stated that 12.9% of CMBs contained erythrocytes rather than hemosiderin, which indicated that not all CMBs are chronic in nature.14 Indeed, Jeon et al8 reported that 12.7% of acute ischemic stroke patients developed new CMBs 24 hours after rtPA infusion. Our results are similar to the findings of Kimura et al9 where 4.9% of acute ischemic stroke patients developed new CMBs within 1 week of stroke onset, whereas Kimura et al9 reported that 4.9% of acute ischemic stroke patients developed new CMBs 24 hours after rtPA infusion. Our results are similar to the findings of Kimura et al9 and confirm that CMBs could occur in the acute stage of ischemic stroke.

However, our findings did not repeat the previous findings that the presence of CMBs before rtPA therapy was associated with new CMBs. When we reviewed and compared the parameters of GRE scans in different studies (Table 3), including field strength, echo time, slice thickness, and interslice gap, we found that new CMBs may be misidentified even though slice-to-slice comparison between initial and follow-up GRE scans was done. Usually, CMB detection depends on lesion size, slice thickness, lesion position relative to slice, thickness of gap between slices, and inherent contrast between lesion and background. Image co-registration is not reliable with a relatively greater slice thickness and an interslice gap. As shown in Figure 1, if there is an interslice gap in the GRE protocol, the unchanged CMBs may be undetected or misidentified as “new” or “disappeared” CMBs because of even a minor head motion. The images of our patient with initial and follow-up GRE scans presented in Figure 2 further confirm this misidentification. Thus, the misidentified “new” CMBs would only appear in the patients with baseline CMBs, which leads to the bias that more “new” CMBs occurred in the patients with the presence of CMBs. Similarly, this reason could also explain the phenomenon that new baseline CMBs in 7 patients were disappeared on follow-up GRE scans in the study by Jeon et al.9 Furthermore, radiological size of the missed CMBs might be larger than the thickness of interslice gap (such as 1- or 2-mm) because of the so-called “blooming” effect. Therefore, a contiguous thin-slice imaging study is particularly important in determining whether a CMB is new or not. Our study, the first to use contiguous 2-mm slice-to-slice comparison to detect CMBs, confirms that the presence of baseline CMBs is not a predictor for the development of new CMBs after thrombolytic therapy.

We found that large baseline DWI infarct volume and high SBP were the independent factors associated with new CMBs. The cellular mechanism that underlies the formation of new CMBs remains to be elucidated. It is suggested that CMBs result from 2 main pathogenic mechanisms: leakage from damaged vessels in cerebral small vessel diseases associated with hypertension and other cerebrovascular risk factors, or from vessels damaged by vascular amyloid deposition. “New” CMBs have been reported to occur in 38% of patients with cerebral amyloid angiopathy and previous lobar hemorrhage during the 1.5-year follow-up period and in 30% of hypertensive patients with ICH after a median period of 23 months. New CMBs appearing

### Table 3. Clinical Studies Investigating New CMBs in Acute Ischemic Stroke Patients

| Study            | Jeon et al8 | Kimura et al9 | Current Study |
|------------------|-------------|---------------|---------------|
| Population       | Stroke patients | Stroke patients treated with tPA | Stroke patients treated with rtPA |
| Number of participants | 237 | 224 | 121 |
| Age, y           | 64.0 ± 12.8 | 76.2 ± 10.6 | 67.3 ± 12.6 |
| Parameters of GRE scans | | | |
| Field strength, tesla | 1.5 | 1.5 | 3.0 |
| Echo time, ms    | 30 | 20 | 11 echoes, first 4.5; interecho spacing 4.5 |
| Slice thickness, mm | 5 | 6 | 2 |
| Interslice gap, mm | 2 | 1 | 0 |
| CMBs              | | | |
| Baseline prevalence | 31.6% | 32.1% | 47.1% |
| New prevalence   | 12.7% | 4.9% | 5.0% |
| Disappeared      | 8 | Not reported | 0 |

CMBs = cerebral microbleeds, GRE = gradient-recalled echo, tPA = recombinant tissue-type plasminogen activator, rtPA = tissue-type plasminogen activator.
within 24 hours after rtPA treatment would be fresh. Hence, the presence of large DWI infarct volume in the acute ischemic stage may precipitate abnormal permeability of the arteriolar blood–brain barrier leading to extravasation of blood components, providing a possible explanation for its association with the formation of new CMBs. Previous studies showed blood pressure elevation was associated with hemorrhagic transformation in patients with rtPA therapy. The arterioles are vulnerable to the effects of high blood pressure, resulting in damage to the smooth muscle cells and microbleeding. Thus, blood pressure lowering treatment during rtPA infusion should be important to reduce the occurrence of new CMBs.

It has been questioned whether the presence of microbleeds is a risk factor for sICH after tPA therapy. However, it was underpowered to detect the relationship between CMBs and sICH in our study due to the small number of sICH patients. We did not find the difference between patients with and without new CMBs in the frequency of hemorrhagic transformation both in the infarct and extraischemic area, which is inconsistent with the previous finding that extraischemic hemorrhage was associated with new CMBs.9 Indeed, it was difficult to discriminate new CMBs from extraischemic hemorrhage sometimes. Microbleeds and macrobleeds may fall in a naturally bimodal size distribution that does not strongly depend on the precise cut point chosen to differentiate them. The size of a CMB is relatively less important for correctly categorizing lesions because it depends on imaging parameters on MRI.1 Furthermore, the presence of new CMBs may have little clinical implication in the prevention of hemorrhagic transformation after thrombolysis, considering that new CMBs and hemorrhagic transformation are both detected on follow-up imaging scans.

The present study had limitations. First, our study had a retrospective design and might have a potential risk of selection bias. Some severe stroke patients might transfer to intensive care unit or receive surgical treatment next day so that they were unable to undergo follow-up GRE scans, leading to the small sample of patients with sICH. Second, some new CMBs outside the infarct area might be covered by remote hemorrhage. This limitation made it more difficult to detect new CMBs and investigate the relationship between new CMBs and postthrombolytic hemorrhage. Third, inter-slice gap has been used sometimes to minimize interference from adjacent slices (“cross-talk”), which is a cause of reduced signal intensity, so we used a 3.0 tesla field strength magnet to provide a high signal-to-noise ratio and high spectral resolution, in order to minimize this limitation.18 Fourth, we did not perform follow-up computed tomography (CT) scans, which might discriminate new CMBs from tiny remote hemorrhage after rtPA infusion.

In summary, we found that new CMBs developed in 5% of thrombolytic patients. The baseline DWI infarct volume and SBP, but not the presence of baseline CMBs, were independent factors associated with new CMBs. We highlight the effect of variation in slice thickness and inter-slice gap on new CMB detection. It is still uncertain whether the new CMBs are caused by thrombolysis or just ischemic stroke. The significance of
these new CMBs and their effect on cognitive and functional outcome requires further investigations.

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