Differential Pattern of Tissue Plasminogen Activator–Induced Proximal Middle Cerebral Artery Recanalization Among Stroke Subtypes

Carlos A. Molina, MD, PhD; Joan Montaner, MD, PhD; Juan F. Arenillas, MD; Marc Ribo, MD; Marta Rubiera, MD; José Alvarez-Sabín, MD, PhD

Background and Purpose—We aimed to evaluate the timing, speed, and degree of tissue plasminogen activator (tPA)–induced recanalization in patients with proximal middle cerebral artery (MCA) occlusion of different stroke subtypes.

Methods—We evaluated 72 patients with acute stroke caused by proximal MCA occlusion treated with intravenous tPA in <3 hours. Transcranial Doppler monitoring of recanalization was conducted during tPA infusion and at 6 hours. Strokes were categorized as large-vessel disease strokes, cardioembolic strokes, or strokes of undetermined origin according to Trial of Org 10172 in Acute Stroke Treatment criteria.

Results—During 1-hour tPA infusion, recanalization occurred in 34 patients (47%); 32% showed a sudden, 50% showed a stepwise, and 18% showed a slow pattern of recanalization. One-hour recanalization was more frequent in patients with cardioembolic stroke (59%) compared with large-vessel disease (8%) and undetermined origin (50%) strokes. A cardiac source of emboli was identified in 81% of patients who showed a sudden clot breakup during tPA infusion. Rate of complete recanalization at 6 hours was higher (P=0.006) in patients with cardioembolic stroke (50%) compared with other stroke subtypes (27%). Sudden recanalization was associated (P=0.002) with a higher degree of neurological improvement at 24 hours compared with stepwise, slow, and no recanalization. A graded response in long-term outcome was observed in relation to the speed of clot lysis during tPA administration.

Conclusions—We demonstrate that the pattern of tPA-induced MCA recanalization differs among stroke subtypes. Early recanalization was more frequent, faster, and more complete in patients with cardioembolic stroke compared with other stroke subtypes. (Stroke. 2004;35:486-490.)

Key Words: outcome ■ stroke classification ■ thrombolysis ■ ultrasonography

Although treatment with tissue plasminogen activator (tPA) has been demonstrated to be effective in unsellected stroke patients, response to tPA may vary, depending on the size, composition, and source of the offending clot. Specific structural aspects of clots have received attention with respect to lytic susceptibility and penetration of thrombolytic agents. Old, platelet-rich, and well-organized thrombi formed under flow conditions have been shown to be more resistant to thrombolysis than fresh, fibrin- and red cell–rich clots formed under conditions of stasis.1–3 Moreover, physical structure and biochemical and cellular composition of cerebral emboli may differ, depending on whether the embolic source is a thrombus engrafted in a proximal atherosclerotic lesion or a clot formed in cardiac cavities. Recanalization is a continuous process that usually begins early after tPA administration.4,5 However, the time until complete clot dissolution and restoration of blood flow may vary widely, depending on location of occlusion, clot position, area of clot surface exposed to blood flow, and pressure-driven permeation of tPA into the clot structures.6,7 Transcranial Doppler (TCD) monitoring provides a noninvasive tool for real-time measurement of the beginning, speed, timing, and degree of recanalization. In unsellected stroke patients, the speed of clot lysis during tPA infusion has been demonstrated to predict short-term improvement.8 Moreover, both timing and amount of recanalization on TCD have been correlated with clinical recovery and long-term outcome.4,8,9 However, whether stroke subtypes exhibit a differential profile of recanalization after thrombolysis remains unknown. Therefore, in the present study, we aimed to determine the timing, speed, and degree of tPA-induced recanalization in patients with proximal middle cerebral artery (MCA) occlusion in different stroke subtypes.

Subjects and Methods
Our target group consisted of patients with acute ischemic stroke admitted within the first 3 hours after symptom onset. Stroke onset
was defined as the last time the patient was known to be without any neurological deficit. A total of 394 consecutive patients with nonlacunar stroke involving the vascular territory of the MCA were evaluated between March 2001 and January 2003. Of these, 302 (94.5%) underwent urgent carotid ultrasound and TCD examinations. Fifty-eight patients (16%) were excluded from the study because of insufficient acoustic temporal window for TCD examination. One hundred thirty-one patients (52.6%) with documented proximal MCA occlusion (excluding carotid T-occlusions) on TCD were initially included in the study. We excluded patients who were taking anticoagulants (n = 19), were > 88 years of age (n = 21), experienced dramatic spontaneous neurological improvement (n = 8), or showed early signs of infarction of > 33% of the MCA territory on baseline CT (n = 18). Finally, 75 patients (20.7%) with acute stroke caused by proximal MCA occlusion received intravenous tPA in a standard 0.9-mg/kg dose within 3 hours of symptom onset. For the analysis by stroke subtypes, we further excluded patients with carotid artery dissection (n = 1) and those with > 1-identified cause of stroke (n = 2).

Informed consent was obtained from all patients or their next of kin. The study protocol was approved by the local ethics committee.

Stroke Subtyping

All patients underwent a standard neurological examination, ECG, blood chemistry, extracranial carotid and vertebral ultrasound, and noncontrast CT before treatment. Emergent stroke MRI was also performed in 30 patients (40%). Transthoracic and transesophageal echocardiography (72%) and Holter ECG (68%) were performed when clinically indicated. All patients with severe carotid artery stenosis or occlusion on duplex ultrasound also underwent a cervical MR angiography. Using clinical, radiological, cardiac, and ultrasound test results, an experienced stroke neurologist assessed each patient according to modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria to determine stroke subtype. Large-vessel disease (LVD) was defined as > 50% stenosis or occlusion of the carotid artery ipsilateral to the proximal MCA occlusion in the absence of source of cardiac embolism. Cardioembolic (CE) stroke was defined as the presence of atrial fibrillation, myocardial infarction in the past 6 months, or a high-risk source of embolism on TCD. Source of cardiac embolism was defined as the presence of atrial fibrillation, myocardial infarction, or a high-risk source of embolism on TCD. Cardioembolic (CE) stroke is defined as the presence of atrial fibrillation, myocardial infarction, or a high-risk source of embolism on TCD.

TCD Assessment

A standard TCD examination was performed in the emergency room on admission before tPA administration with 1-channel, 2-MHz equipment (TCD 100 ML, Spencer Technologies, and DWL Multidop x4). TCD assessment was performed by 2 certified sonographers with extensive experience in monitoring recanalization in acute stroke who were blinded for clinical, radiological, and outcome data. A standard set of diagnostic criteria was applied to diagnose arterial occlusion. Proximal MCA occlusion was defined as the absence of flow or the presence of minimal flow signal throughout the MCA at an insonation depth between 45 and 65 mm, accompanied by flow diversion in the ipsilateral anterior and posterior communicating arteries, according to the Thrombolysis in Brain Ischemia (TIBI) grading system. In cases of concomitant cervical severe carotid stenosis or carotid occlusion, proximal MCA occlusion was diagnosed when TCD detected no flow or minimal flow (TIBI 0 or 1) in the MCA in the presence of collateral flow signals (anterior and posterior communicating arteries and ophthalmic artery), flow diversion signs, and compensatory velocity increase (≥ 20% increase in the contrastral hemispheric vessels or vertebrobasilar arteries) according to previously published criteria. After the site of MCA occlusion was identified, continuous monitoring of the residual flow signals was performed with a Marc 500 head frame (Spencer Technologies) or DWL metal head frame to maintain tight transducer fixation and a constant angle of insonation. Continuous TCD monitoring of recanalization was conducted during 1 hour after tPA administration. The speed of clot lysis during continuous TCD monitoring was categorized into sudden (abrupt appearance of a normal or low-resistance signal), stepwise (gradual flow improvement over 1 to 29 minutes), or slow (flow improvement over ≥ 30 minutes) recanalization. Changes on TCD in each patient were determined by 1 rater using direct visual control of monitoring display. The same rater carried out an additional TCD recording 6 hours after stroke onset to assess the degree of recanalization. Recanalization on TCD was diagnosed as partial when blunted or dampened signals appeared in a previously demonstrated absent or minimal flow. Complete recanalization on TCD was diagnosed if the end-diastolic flow velocity improved to normal or elevated values (normal or stenotic signals). No change in the TCD waveform indicated that no recanalization had occurred. Reocclusion was defined as a worsening in waveforms on TCD performed at the time of neurological deterioration after documented recanalization.

CT Studies

On admission, all patients underwent a CT within the first 3 hours after stroke onset, which was repeated after 36 to 48 hours (or earlier when rapid neurological deterioration occurred). The presence of a hyperdense MCA (HDMCA) sign, early focal hypodensity, or swelling as a result of developing infarction on baseline CT was assessed according to European Cooperative Acute Stroke Study (ECASS) criteria. The presence and type of hemorrhagic transformation were defined according to previously published criteria. CT scans were reviewed by a neuroradiologist with extensive experience in acute stroke who was blinded to the clinical and TCD details.

Clinical Assessment

We assessed clinical status at baseline and at 24 hours after symptom onset by means of the National Institutes of Health Stroke Scale (NIHSS), which was conducted by a neurologist or a senior neuroradiologist not involved in obtaining sonographic information. NIHSS was video-trained and certified for application of the NIHSS. Early neurological deterioration or improvement was defined as an increase or decrease of ≥ 4 points on the NIHSS score after 24 hours from baseline assessment. An intracranial hemorrhage was considered symptomatic (SICH) if the patient had clinical deterioration causing an increase of ≥ 4 points on the NIHSS and if the hemorrhage was likely to be the cause of neurological deterioration. Modified Rankin scale (mRS) was used to assess clinical outcome at 90 days. We defined good outcome as an mRS score ≤ 2.

Statistical Analysis

The analysis was performed with SPSS 9.0 software (SPSS Inc). Statistical significance for intergroup differences was assessed by the 2-tailed Fisher’s exact test and Pearson’s χ² test for categorical variables and by Student’s t test, Mann-Whitney U test, and Kruskal-Wallis test for continuous variables. A level of P < 0.05 was accepted as statistically significant.

Results

We studied a total of 72 patients (35 men, 37 women) with acute stroke caused by proximal MCA occlusion treated with intravenous tPA < 3 hours of stroke onset. Demographic data, risk factor profile, and baseline clinical findings are shown in the Table. Mean age was 68.6 ± 11.2 years (range, 31 to 85 years). Median NIHSS score of the series on admission was 18 points (interquartile range, 16 to 20 points). Time elapsed between symptom onset and drug administration was 154.4 ± 37.2 minutes (range, 82 to 178 minutes). The door-to-needle time was 63.2 ± 26.1 minutes, ranging from 51 to 106 minutes.

Thirty-eight patients (53.5%) were considered to have had a CE stroke: 24 (63.1%) from atrial fibrillation, 5 from atrioseptal aneurysm, 7 from dilated myocardopathy with a ventricular ejection fraction < 40%, and 2 from recent myo-
Demographic Data, Risk Factor Profile, and Baseline Clinical Findings of the Series

<table>
<thead>
<tr>
<th>Variable</th>
<th>CE (n=38)</th>
<th>LVD (n=12)</th>
<th>UD (n=22)</th>
</tr>
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<tbody>
<tr>
<td>Male sex, n</td>
<td>14 (37)</td>
<td>7 (58)</td>
<td>11 (50)</td>
</tr>
<tr>
<td>Age, y</td>
<td>68.1 (11)</td>
<td>70.1 (9)</td>
<td>68 (12)</td>
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<tr>
<td>Aspirin treatment, n</td>
<td>12 (32)</td>
<td>4 (33)</td>
<td>6 (27)</td>
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<td>Hypertension, n</td>
<td>17 (45)</td>
<td>5 (41)</td>
<td>11 (50)</td>
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<tr>
<td>Diabetes, n</td>
<td>10 (26)</td>
<td>3 (24)</td>
<td>6 (27)</td>
</tr>
<tr>
<td>Hyperlipidemia, n</td>
<td>4 (11)</td>
<td>3 (20)</td>
<td>5 (22)</td>
</tr>
<tr>
<td>CHD, n</td>
<td>9 (24)</td>
<td>2 (16)</td>
<td>4 (18)</td>
</tr>
<tr>
<td>Baseline NIHSS score, n</td>
<td>18 (16–19)</td>
<td>18 (15–19)</td>
<td>19 (16–20)</td>
</tr>
<tr>
<td>Right side, n</td>
<td>19 (50)</td>
<td>7 (58)</td>
<td>11 (50)</td>
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<tr>
<td>SBP, mm Hg</td>
<td>145 (21)</td>
<td>166 (37)</td>
<td>159 (16)</td>
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<tr>
<td>DBP, mm Hg</td>
<td>84.1 (11)</td>
<td>81.5 (10)</td>
<td>83.2 (9.5)</td>
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<tr>
<td>Body temperature, °C</td>
<td>35.9 (0.33)</td>
<td>36.1 (0.12)</td>
<td>35.8 (0.34)</td>
</tr>
<tr>
<td>Blood glucose, g/dL</td>
<td>156 (54)</td>
<td>206 (94)</td>
<td>143 (41)*</td>
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<tr>
<td>Hematocrit, %</td>
<td>39.1 (3.2)</td>
<td>40.1 (5)</td>
<td>42.3 (6)</td>
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<td>Platelet count, n</td>
<td>236.4 (124)</td>
<td>218.2 (71)</td>
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<td>Prothrombin time, %</td>
<td>95.3 (12.1)</td>
<td>93.8 (15)</td>
<td>0.55</td>
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<td>Fibrinogen, g/dL</td>
<td>3.3 (0.8)</td>
<td>2.9 (0.9)</td>
<td>3.2 (0.9)</td>
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<td>Occlusion depth (TCD), mm</td>
<td>55.5 (5.1)</td>
<td>53 (6.2)</td>
<td>55 (7)</td>
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<tr>
<td>Time to treatment, min</td>
<td>152 (33)</td>
<td>158 (36)</td>
<td>161 (38)</td>
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<tr>
<td>Door to needle time, min</td>
<td>70 (14)</td>
<td>81 (26)</td>
<td>72 (18)</td>
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<tr>
<td>Total tPA dose, mg</td>
<td>63 (6.4)</td>
<td>65 (8.6)</td>
<td>63 (5.2)</td>
</tr>
<tr>
<td>Early CT signs, n</td>
<td>18 (47)</td>
<td>4 (33)</td>
<td>13 (60)</td>
</tr>
<tr>
<td>HDMCA sign</td>
<td>19 (50)</td>
<td>6 (50)</td>
<td>12 (55)</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; SBP, systolic blood pressure; and DBP, diastolic blood pressure. Values are mean (SD), median (interquartile range), or n (%) as appropriate. *P<0.05.

cardiac infarction with ventricular hypocinesia. LVD was diagnosed in 12 patients (17%) in whom emergent carotid ultrasound and MRA revealed severe (>70%) cervical carotid artery stenosis (n=5) or carotid occlusion (n=7) ipsilateral to the MCA occlusion. Twenty-two patients (30.5%) without identified cause of stroke or who died without etiological diagnosis (n=4) were regarded as UD stroke.

On baseline TCD assessment, proximal MCA occlusion was detected at a mean insonation depth of 55±6.3 mm. During 1-hour tPA infusion, recanalization was seen in 34 patients (47%). Eleven patients (32%) showed a sudden, 17 (50%) showed a stepwise, and 6 (18%) showed a slow pattern of recanalization during tPA administration. No patient who recanalized in a slow manner completely recanalized at the end of tPA infusion. One-hour recanalization rate differed (P=0.012) among stroke subtypes: 22 CE (59%), 1 LVD (8%), and 11 UD (50%) strokes recanalized at 1 hour of tPA bolus. Moreover, the speed of clot lysis during tPA infusion differed markedly among stroke subtypes, being fastest in CE strokes (Figure 1). Sudden recanalization was seen in 9 (41%), 0, and 2 (20%); stepwise recanalization in 10 (36%), 0, and 6 (60%); and slow recanalization in 3 (14%), 1 (100%), and 2 (20%) patients with CE, LVD, and UD strokes, respectively (P=0.003). Recanalization at 6 hours after stroke onset was identified in 45 patients (62.5%). Six-hour recanalization was observed in 29 (76%), 4 (33%), and 12 (57.1%) patients with CE, LVD, and UD strokes (P=0.023).

The rate of complete recanalization at 6 hours was significantly (P=0.006) higher in patients with CE stroke (n=19, 50%) compared with other stroke subtypes (n=9, 27%). Moreover, the 4 patients with a proximal MCA occlusion resulting from LVD who recanalized at 6 hours did so only partially.

Recanalization was seen in 6 patients (8.5%); in 4 patients, recanalization was partial, and in 2, it was complete. Recanalization occurred at a mean time of 35±26 minutes after documented recanalization. In 5 cases, reocclusion was detected during 1-hour continuous TCD monitoring. Although reocclusion was more frequent in strokes caused by LVD (16.3%) than in CE (7.7%) and UD (5%) strokes, this difference did not reach statistical significance.

Clinical assessment revealed that 15 patients (20.8%) worsened, 33 (45.8%) improved, and 24 (33%) remained stable during the first 24 hours of admission. Neurological improvement was significantly (P=0.02) more frequent in CE (54%) and UD (48%) than in LVD (8.3%) stroke patients. Figure 2 illustrates variation of NIHSS score at 24 hours according to the sonographic pattern of recanalization during tPA infusion. Sudden recanalization was significantly (P=0.002, Kruskal-Wallis test) associated with a higher degree of neurological improvement at 24 hours compared with stepwise, slow, and no recanalization. All but 1 patient who recanalized suddenly improved >10 points in NIHSS score at 24 hours.

HDMCA sign on baseline CT was seen in 38 patients (52.7%); 20 (52%) CE, 6 (50%) LVD, and 12 (54%) UD strokes (P=0.82). No differences were found in the timing, speed, and degree of tPA-induced recanalization regarding the presence or absence of HDMCA sign. Hemorrhagic transformation on CT was detected in 21 patients (29%). SICH occurred in 7 patients (9.7%). Four (10.5%), 3 (13.6%), and 0 patients with CE, UD, and LVD stroke, respectively, experienced SICH (P=0.49). SICH occurred in 1 patient who recanalized suddenly, in 1 who recanalized in a stepwise manner, and in 5 patients who did not recanalize at the end of tPA infusion or at 6 hours.

The median mRS score at 3 months was 3 points (interquartile range, 1 to 5 points). As shown in Figure 3, a graded response on long-term outcome was observed in relation to...
the speed of maximum completeness of recanalization during tPA administration. Sudden reperfusion was significantly (P<0.001, Kruskall-Wallis test) associated with better long-term outcome than stepwise and slow recanalization. Median mRS score was 1 (range, 1 to 3), 2.5 (range, 1 to 4.5), and 5 (range, 4 to 6) in patients who showed complete, partial, and no recanalization at 6 hours (P<0.001). Consequently, the proportion of patients who became independent at 3 months was significantly (P=0.012) higher in CE (59%) compared with UD (40%) and LVD (11%) strokes. On the other hand, mortality rate was higher in patients with stroke resulting from LVD (41%) than in those with UD (19%) and CE (13%) strokes.

**Discussion**

The present study demonstrates that in patients with proximal MCA occlusion treated with intravenous tPA, early recanalization is more frequent, faster, and more complete in patients with CE stroke. A cardiac source of emboli was identified in most patients who experienced sudden clot breakup during tPA administration. Sudden recanalization was associated with a higher degree of neurological improvement and better long-term outcome than stepwise and slow recanalization. On the other hand, the presence of a concomitant ipsilateral severe carotid artery disease was associated with low MCA recanalization rate and poor clinical outcome.

The National Institute of Neurological Disorders and Stroke (NINDS) trial demonstrated a beneficial effect of tPA regardless of stroke subtypes. However, in the NINDS trial, stroke subtypes were established from information available before randomization without systematic neurovascular assessment before tPA administration. Moreover, stroke subtypes were not adjusted by stroke severity and location of arterial occlusion, which precluded any direct comparison of the effect of tPA among stroke subtypes. Our study shows that the pattern of tPA-induced clot lysis differs among stroke subtypes independently of possible confounders such as stroke severity on admission, location of intracranial occlusion, time to treatment, and total tPA dose. We focused on patients with a proximal MCA occlusion excluding T-occlusions, which have been shown to be more resistant to thrombolysis than isolated proximal MCA occlusions. So, we evaluated several aspects of the recanalization process in patients with a similar location of arterial occlusion and different embolic sources. Differential patterns of the speediness, degree, and temporal profile of clot dissolution may reflect structural differences of clots. Both in vitro and animal models demonstrated that clots formed under a variety of biochemical and physical conditions exhibit a differential susceptibility to lysis. Moreover, composition of embolic material may vary, depending on specific endothelial and flow conditions of the embolic source. In this context, stroke subtypes may represent a surrogate of clot composition and differential response to tPA in term of recanalization.

Our findings are in consonance with clinical and experimental studies indicating that early and complete reperfusion is associated with reduced infarct. Sudden recanalization reflects rapid and complete restoration of flow; stepwise and slow recanalization indicate proximal clot fragmentation, downstream embolization, and continued clot migration. CE stroke probably represents the stroke subtype with more uniform fibrin-rich clots. Given the high binding affinity of tPA for fibrin, in fibrin-rich clots, tPA penetrates and distributes homogeneously, leading to an entire and rapid clot dissolution (sudden recanalization). In contrast, in well-organized and platelet-rich clots, penetration and distribution of tPA are limited, which may result in nonuniform clot softening and degradation from the outside of the clot. As a result, the clot shrinks and moves distally, lodging in smaller arteries (stepwise or slow recanalization), which would prolong ischemia. This may explain our observation that the stepwise and slow patterns of recanalization were associated with a lower degree of neurological improvement and worse
long-term outcome than sudden recanalization shortly after tPA administration.

In our study, although sudden recanalization showed a high specificity (81%) for CE stroke, up to 20% of UD strokes recanalized suddenly during tPA infusion. This may suggest that in a proportion of patients with UD stroke, an occult unidentified cardiac embolic source exists. However, whether the stroke mechanism may be inferred by the pattern of speed of clot lysis during tPA infusion requires further investigation.

Transport of tPA into the thrombus represents a rate-limiting step in thrombolysis. Experimental studies have demonstrated that effective delivery and distribution of tPA into the clot accelerate fibrinolysis and that the fibrinolytic rate is dependent on the pressure gradient to which the clot is exposed.\textsuperscript{1–3,21} Systemic thrombolysis has been shown to be more effective in coronary artery thrombi of normotensive and hypertensive patients. In contrast, thrombolysis was much less successful in clots that are exposed to an insufficient pressure gradient such as venous thrombi and coronary thrombi of patients in cardiogenic shock.\textsuperscript{21} Pressure-driven permeation of tPA into the clot may differ among stroke subtypes, being particularly limited in cases of a regional decrease of cerebral perfusion pressure. The presence of an extracranial ICA occlusion might hamper the delivery of an adequate dose of tPA into the ipsilateral occluded MCA. This is in consonance with a previous study showing that the presence of a proximal ICA occlusion represents an independent predictor of poor outcome in patients treated with intravenous tPA.\textsuperscript{22} We hypothesize that proximal MCA occlusions related to severe carotid artery disease represent main platelet-rich clots exposed to an insufficient pressure gradient to ensure adequate permeation of tPA, which may explain their relatively poor response to lysis.

The present study has certain limitations. The source of the tandem MCA lesion may not necessarily be an ipsilateral occluded ICA via an artery-to-artery embolism. Alternatively, MCA clots may be cardiogenic emboli via the contralateral internal carotid artery and anterior communicating artery. On the other hand, some patients with proximal MCA occlusion classified in this study as UD stroke according to TOAST criteria may correspond to MCA atherothrombosis in situ. In our study, the designation of LVD referred only to internal carotid artery atherothrombosis. Therefore, the relatively poor response to tPA in patients with LVD observed in our study should not be extrapolated to patients with suspected MCA atherothrombosis in situ.

In conclusion, we demonstrate that the pattern of tPA-induced recanalization differs among stroke subtypes. Early recanalization was more frequent, faster, and more complete in patients with CE stroke compared with other stroke subtypes. Because the presence of a concomitant ipsilateral severe carotid disease was associated with a lower rate of recanalization in the MCA and poor clinical outcome, emergent carotid ultrasound plus TCD may be helpful in the selection of patients for more aggressive reperfusion strategies.

References
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