Predictors of Early Arterial Reocclusion After Tissue Plasminogen Activator-Induced Recanalization in Acute Ischemic Stroke

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Background and Purpose—We aimed to determine clinical and hemodynamic predictors of early reocclusion (RO) in stroke patients treated with intravenous tissue plasminogen activator (tPA).

Methods—We studied 142 consecutive stroke patients with a documented middle cerebral artery (MCA) occlusion treated with intravenous tPA. All patients underwent carotid ultrasound and transcranial Doppler (TCD) examination before tPA bolus. National Institutes of Health Stroke Scale (NIHSS) scores were performed at baseline and serially for <24 hours. TCD monitoring of MCA recanalization (RE) and RO was performed during the first 2 hours after tPA bolus and repeated when clinical deterioration occurred <24 hours after documented RE in absence of intracranial hemorrhage.

Results—After 1 hour of tPA administration, RE occurred in 84 (61%) patients (53 partial, 31 complete). Of these, 21 (25%) patients worsened after an initial improvement and 17 (12%) of them showed RO on TCD. RO was identified at a mean time of 65±55 minutes after documented RE. RO was associated (P=0.034) with a lower degree of 24-hour NIHSS score improvement than sustained RE, and a higher modified Rankin scale score at 3 months (P=0.002). Age older than 75 years (P=0.012), previous antiplatelet treatment (P=0.048), baseline NIHSS score >16 points (P=0.009), higher leukocytes count (P=0.042), beginning of RE <60 minutes after tPA bolus (P=0.039), and ipsilateral severe carotid stenosis/occlusion (P=0.001) were significantly associated with RO. In a logistic regression model, NIHSS score >16 at baseline (odds ratio [OR], 7.1; 95% CI, 1.3 to 32) and severe ipsilateral carotid disease (OR, 13.3; 95% CI, 3.2 to 54) remained as independent predictors of RO.

Conclusions—Stroke severity and ipsilateral severe carotid artery disease independently predict RO after tPA-induced MCA RE. (Stroke. 2005;36:1452-1456.)

Key Words: stroke ■ thrombolysis ■ transcranial Doppler ■ ultrasonography

Thrombolytic therapy has been demonstrated to be effective in acute stroke by dissolving the arterial occlusion and reestablishing tissue perfusion. However, the beneficial effect of tissue plasminogen activator (tPA)-induced recanalization may be eventually hampered by the occurrence of reocclusion (RO). In myocardial infarction, RO has been shown to be a frequent and important complication of thrombolytic therapy, reaching 15% during the in-hospital stay and 30% within the first year after the acute coronary event. In this setting, early RO has been associated with a 2- to 3-fold increased risk of heart failure and mortality, which has prompted the search and development of several preventive and therapeutic strategies.

Early RO has been increasingly recognized as a cause of clinical worsening and poor outcome in stroke patients treated with intravenous tPA. In the National Institute of Neurological Disorders and Stroke (NINDS) study, 13% of patients experienced an early clinical deterioration after an initial improvement, which in the absence of intracranial hemorrhage may represent a clinical surrogate of RO. Early RO has been documented on continuous transcranial Doppler (TCD) monitoring in up to 34% of stroke patients, leading to clinical worsening in 14% of cases. This proportion of symptomatic RO is higher than the rate of symptomatic intracranial hemorrhage (SICH) observed in most academic stroke centers. Although in the past few years extensive research has been focused on the development of new approaches to improve recanalization rates and on the identification of predictors of SICH, information about factors predisposing to RO in stroke patients is limited. Therefore, we aimed to determine clinical and hemodynamic predictors of early RO in stroke patients treated with intravenous tPA.

Subjects and Methods
Our target group consisted of patients with acute ischemic stroke admitted within the first 3 hours after symptoms onset. Stroke onset...
was defined as the last time the patient was known to be without any neurological deficit. A total of 343 consecutive patients with <3-hour nonlacunar stroke involving the vascular territory of the middle cerebral artery (MCA) were evaluated between May 2002 and November 2004. Of these, 304 (91.1%) underwent urgent carotid ultrasound and TCD examinations. Sixty-six (16%) patients were excluded from the study because of insufficient acoustic temporal window for TCD examination. We excluded patients who exhibited a normal TCD examination on admission (n = 27), experienced dramatic spontaneous neurological improvement with very mild neurological deficits (National Institutes of Health Stroke Scale [NIHSS] score <4 points) despite evidence of occlusion on TCD (n = 14), who were using anticoagulants (n = 32), or showed early signs of infarction >33% of the MCA territory on baseline CT (n = 23). Finally, 142 (41.3%) patients with a documented MCA occlusion on TCD who received intravenous tPA in a standard 0.9 mg/kg dose (10% intravenous bolus followed by 90% continuous intravenous infusion during 60 minutes, according to the NINDS protocol) <3 hours after symptom onset were included in the study. Informed consent was obtained from all patients or their next of kin. The study protocol was approved by the local ethics committee.

All patients underwent a standard neurological examination, electrocardiography (ECG), blood chemistry, extracranial carotid ultrasound, and noncontrast CT before treatment. Transthoracic and transesophageal echocardiography and Holter ECG were performed when clinically indicated. All patients with a severe carotid artery stenosis or occlusion on duplex ultrasound also underwent a cervical MR angiography. Carotid artery stenosis was defined a stenosis ≥70% on carotid artery ultrasound. With the use of clinical, radiological, cardiac, and ultrasound test results, each patient was assessed, by an experienced stroke neurologist, according to modified Trial of Org 10172 in Acute Stroke Treatment (TOAST)* criteria to determine stroke subtype.

**Clinical Assessment**

We assessed clinical stroke severity at baseline and at 24 hours after symptom onset by means of the NIHSS score, which was conducted by a neurologist or a senior neurology resident not involved in sonographic information and who were 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 during 24 hours from baseline assessment. Deterioration after improvement was defined as an increase ≥4 points on the NIHSS score after an initial improvement. An intracranial hemorrhage was considered as symptomatic (SIC) 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 score was used to assess clinical outcome at 90 days. We defined good outcome as modified Rankin scale score ≤2.

**TCD Assessment**

A standard TCD examination was performed in the emergency room on admission before tPA administration using 1-channel 2-MHz equipment (TCD 100 mol/L; Spencer Technologies, and DWL Multidop X4). TCD assessment was performed by 2 certified sonographers with extensive experience in monitoring RE in acute stroke. 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 to 65 mm, accompanied by flow diversion in the ipsilateral ACA and PCA, 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) on the MCA in the presence of collateral flow signals according to previously published criteria. Distal MCA occlusion was defined as blunted or dampened signals (TIBI 2 or 3) in the symptomatic artery with <30% flow than the contralateral MCA, and flow diversion signs in ipsilateral neighboring arteries.

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 the first 2 hours of tPA bolus (during the hour of tPA administration and another hour after tPA). Changes on TCD in each patient were determined by one rater using direct visual control of monitoring display. An additional TCD examination was performed if a neurological worsening was detected within the 24 hours after stroke onset.

Recanalization (RE) 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). 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), and slow (flow improvement over ≥30 minutes) recanalization pattern. No change in the abnormal flow waves indicated that no recanalization had occurred.

RO was defined as a worsening in >1 grade in the TIBI flow grading system after a previously documented RE. RO was considered as symptomatic when a clinical deterioration (increase of ≥4 points on NIHSS score) occurred at the time of RO on TCD.

**CT Studies**

On admission, all patients underwent a CT scan 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 early focal hypodensity or swelling caused by 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.

**Statistical Analysis**

The analysis was performed with the use of SPSS 9.0 software (SPSS Inc). Statistical significance for intergroup differences were assessed by the 2-tailed Fisher exact test and Pearson χ² test for categorical variables and Student t test and Mann–Whitney U test and Kruskal–Wallis test for continuous variables. A level of P<0.05 was accepted as statistically significant.

**Results**

A total of 142 patients (72 men and 70 women) with an acute ischemic stroke caused by MCA occlusion treated with intravenous tPA <3 hours of stroke onset were studied. Demographic data, risk factor profile, and baseline clinical findings are shown in the Table. Mean age was 69.6±12.2 years (range, 31 to 87 years). Median NIHSS score on admission was 17 points (interquartile range, 15 to 19 points). The time elapsed between symptom onset and drug administration was 156.4±37.4 minutes (range, 81 to 178 minutes). The door-to-needle time was 62.1±24.1 minutes, ranging from 47 to 109 minutes.

On baseline TCD assessment, proximal MCA occlusion was detected in 84 (59%) patients and distal occlusion in 58 (41%). Emergent carotid artery ultrasound revealed a severe carotid artery stenosis in 14 and a carotid artery occlusion in 13 patients. During the first 2 hours after tPA bolus, MCA recanalization was seen in 84 (61%) patients: 53 (64%) recanalized partially and 31 (36%) did it completely. Ten (11%) patients showed a sudden, 43 (52%) a stepwise, and 31 (37%) a slow pattern of RE during tPA administration. No
patient who recanalized in a slow manner did it completely at the end of tPA infusion.

Of 84 patients who recanalized, 53 (63%) showed a sustained neurological improvement during the first 24 hours, 10 (12%) did not improve, and 21 (25%) patients experienced deterioration after improvement. RO on TCD was detected in 17 (20.2%) patients who recanalized during the first 2 hours after tPA bolus (12% of the series). RO occurred in 15 of 21 (71%) deterioration after improvement patients (symptomatic RO), in 2 of 10 (20%) of those who recanalized without clinical improvement, and in no patient who showed a sustained neurological improvement. SICH was seen in 9 (6.3%) of patients. SICH occurred in 5 patients who remained occluded and in 4 patients who recanalized on TCD. Three patients who experienced deterioration after improvement and no patient who reoccluded had SICH.

RO occurred at a mean time of 65±55 minutes after tPA bolus (range, 22 to 283 minutes) after tPA bolus and at a mean time of 43±41 minutes (range, 9 to 208 minutes) after documented RE. In 13 cases, RO was detected during 2-hour TCD monitoring, and in 4 patients it was assessed by TCD examination at the time of clinical deterioration during the first 24 hours after stroke onset. Mean time to RO was similar between patients with and without ipsilateral carotid artery disease (68±57 versus 61±58; P=0.56). RO was more frequent after a partial (60%) than after a complete (40%) RE. The occurrence of RO varied according to the speed of clot lysis after tPA bolus. RO was more frequent after stepwise (53%) and slow (40%) RE patterns as compared with sudden (7%) RE.

Patients with RO had more severe stroke at onset (NIHSS >16 at baseline 86.7 versus 48.1%; P=0.009). Patients who experienced RO were treated conservatively without any additional or adjuvant therapy to re-open the re-occluded vessel. At 24 hours after tPA-bolus, RO was associated with a lower degree of NIHSS improvement than patients with a sustained RE (P=0.034); the degree of improvement in RO patients was equivalent to patients that remained occluded (Figure 1). At 3 months, patients with RO and patients with a persistent occlusion had a significant worse long-term outcome than patients with a stable RE (P=0.002; Figure 2). The relative contribution of different factors associated with RO on univariate analysis is shown in the Table. Age older than 75 years (P=0.012), previous antiplatelet therapy (P=0.048), baseline NIHSS >16 points (P=0.009), high

<table>
<thead>
<tr>
<th>Variables</th>
<th>Yes, n=15</th>
<th>No, n=127</th>
<th>P</th>
</tr>
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<tbody>
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<td>Age &gt;75 y</td>
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<td>37 (27.8%)</td>
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<td>Sex, male</td>
<td>9 (60%)</td>
<td>63 (47.3%)</td>
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<td>Diabetes mellitus</td>
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<td>Antiplatelet therapy</td>
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<td>38 (28.6%)</td>
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<tr>
<td>NIHSS &gt;16 points</td>
<td>13 (86.7%)</td>
<td>64 (48.1%)</td>
<td>0.009*</td>
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<td>Proximal occlusion</td>
<td>11 (73.3%)</td>
<td>73 (54.9%)</td>
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<td>Time to treatment, min</td>
<td>151±20</td>
<td>162±24</td>
<td>0.34</td>
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<td>SBP, mm Hg</td>
<td>163±69</td>
<td>168±46</td>
<td>0.54</td>
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<td>DBP, mm Hg</td>
<td>82±9</td>
<td>84±10</td>
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<td>Glucose, mg/dL</td>
<td>153±69</td>
<td>147±20</td>
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<td>Leukocytes count</td>
<td>9.8±1.3</td>
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<td>Platelet count</td>
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<td>INR</td>
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<td>Partial recanalization</td>
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<td>Beginning of recanalization &lt;60 min</td>
<td>13 (86.7%)</td>
<td>42 (31.6%)</td>
<td>0.039*</td>
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<tr>
<td>Cardioembolic stroke</td>
<td>3 (20%)</td>
<td>63 (44%)</td>
<td>0.065</td>
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<tr>
<td>Severe ipsilateral carotid artery disease</td>
<td>10 (66%)</td>
<td>17 (13%)</td>
<td>0.001*</td>
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</tbody>
</table>

DBP indicates diastolic blood pressure; SBP, systolic blood pressure; tPA, tissue plasminogen activator; INR, international normalized ratio.

Figure 1. Change of NIHSS score at 24 hours in patients who experienced reocclusion, sustained recanalization, and persistent arterial occlusion.

Figure 2. Clinical outcome at 3 months in patients who experienced reocclusion, sustained recanalization, and persistent occlusion. Sustained recanalization was associated with a better long-term outcome compared with reocclusion and persistent arterial occlusion.
leukocyte count \((P=0.042)\), beginning of RE <60 minutes after tPA bolus \((P=0.039)\), and ipsilateral carotid severe stenosis/occlusion \((P=0.001)\) were significantly associated with RO after tPA-induced RE. Of these, baseline NIHSS >16 points \((OR, 7.1; 95\% CI, 1.3 to 32)\) and the presence of a severe ipsilateral carotid artery disease \((OR,13.3; 95\% CI, 3.2 to 54)\) remained as independent predictors of RO in a logistic regression model.

**Discussion**

The present study demonstrates that early RO with clinical worsening occurs in up to 12\% of MCA stroke patients treated with intravenous tPA. Stroke severity on admission and the presence of an ipsilateral severe carotid artery disease independently predict RO in patients treated with intravenous tPA.

In our study, the rate of RO of 12\% from all tPA-treated patients and of 17\% of those who achieved recanalization. In the NINDS trial,\(^6\) deterioration after improvement was found as 13\% of tPA and placebo-treated patients. Early RO has been shown to occur as frequently as in 34\% of stroke patients after standard tPA administration leading to clinical worsening in 14\% of cases,\(^7\) which is in consonance with our findings. Patients with RO had a worse in-hospital clinical course and a poorer long-term outcome than patients with a sustained RE, and it was similar to patients with a persistent occlusion.

More than half of our patients with RO had a severe stenosis or occlusion in the ipsilateral extracranial carotid artery. Severe carotid disease has been previously associated with a low rate recanalization and poorer clinical outcome.\(^17\) Experimental studies have demonstrated that effective delivery and distribution of tPA into the clot accelerates fibrinolysis and that fibrinolytic rate is dependent on the pressure gradient to which the clot is exposed.\(^18\)–\(^20\) The presence of an extracranial carotid severe stenosis or occlusion leads to a regional decrease of cerebral perfusion pressure, which may not only hamper MCA clot dissolution but also favor blood stasis, increasing the likelihood of rethrombosis after incomplete recanalization. Furthermore, in vitro and animal models had demonstrated that clots formed under a variety of biochemical and physical conditions exhibit a differential susceptibility to lysis.\(^18\)\(^,\)\(^19\)\(^,\)\(^21\) In carotid atherothrombosis, the presence of an ipsilateral MCA occlusion usually is related to an artery-to-artery embolism, with a clot proceeding from the carotid plaque.\(^22\) Clots formed in arterial bifurcations had usually been considered as platelet-rich clots.\(^7\) Platelet-rich clots may be not only more resistant to lysis but also more prone to rethrombosis. It is known that the tPA itself promotes thrombosis by stimulating the plasmin production, which activates platelets and transforms prothrombin in its active form. Thrombin has been also demonstrated to mediate platelet activation and to convert fibrinogen to fibrin. The activated-platelets secrete native plasminogen inhibitor 1, which is opposed the intrinsic–fibrinolytic cascade and the administrated tPA.\(^23\) The presence of a platelet-rich clot probably enhances these mechanisms, as demonstrated in patients with acute MI in whom an augmented platelet aggregation was a powerful predictor of RO after thrombolysis.\(^23\) Finally, the presence of a severe stenosis or occlusion in the carotid artery may represent a marker of a diffuse atherosclerotic disease. In this context, the presence of a concomitant in situ atherothrombosis over an underlying MCA plaque (tandem atherosclerotic lesion) may lead to an incomplete RE and eventually to rethrombosis.

Our results are in line with previous studies showing that partial recanalization frequently preceded RO.\(^7\)\(^,\)\(^23\) Partial, and probably stepwise or slow, recanalization patterns imply a residual clot, which may provide an adequate surface to fibrinogen deposit promoting RO.

We observed that baseline stroke severity independently predicted early RO after successful recanalization. Stroke severity as measured by means of the NIHSS has been correlated with the location of angiographic MCA occlusion.\(^16\) Thus, stroke severity may represent a clinical surrogate of clot burden. Interestingly, in our study baseline stroke severity was a better predictor of RO than occlusion location on TCD, which may indicate that stroke severity more accurately reflects clot burden than dichotomization of occlusion into proximal or distal on TCD. Large MCA clots are shown to be more resistant to thrombolysis,\(^16\) which may lead to incomplete clot dissolution and greater tendency to RO.

In our study, patients who experienced RO were treated conservatively. However, a rapid initiation of aggressive rescue reperfusion strategies including intraarterial administration of thrombolytics or GP IIb/IIIa antagonists,\(^24\) angioplasty plus stenting, or mechanical clot retrieval may potentially improve the clinical course and outcome of RO.

The present study has limitations. Both frequency and predictors of RO may vary depending on clot burden, location of arterial occlusion, and vascular territory involved. Therefore, because our study was focused on patients with MCA occlusion, our findings should not be extrapolated to patients with stroke involving other vascular territories. Moreover, TCD is an operator-dependent technique and experienced sonographers are required for the assessment of RE and RO. However, although RE and RO may be diagnosed with other noninvasive neurovascular techniques (ie, MRA or CTA), TCD provides rapid, accurate, and real-time information on the dynamic nature of the RE/RO phenomenon in stroke thrombolysis.

In conclusion, admission stroke severity and the presence of a severe extracranial carotid artery disease represent independent predictors of early arterial RO after tPA-induced recanalization. RO associates with worse clinical course and poorer long-term outcome compared with sustained recanalization. Therefore, emergent carotid ultrasound plus TCD may be useful to identify patients at high risk for RO and for selecting alternative or combined reperfusion approaches to prevent RO after arterial recanalization.

**References**


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