Effect of Incomplete (Spontaneous and Postthrombolytic) Recanalization After Middle Cerebral Artery Occlusion

A Magnetic Resonance Imaging Study

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Background and Purpose—Early reperfusion is one of the best predictors of good outcome after acute middle cerebral artery (MCA) occlusion. The purpose of this study was to analyze the frequency and relevance of incomplete recanalization for tissue and clinical outcome.

Methods—From a larger acute stroke database (Kompetenznetzwerk Schlaganfall B5), all patients (n=82) with MCA main stem occlusion (excluding carotid T-occlusions) were selected. These patients had received a multiparametric stroke MRI protocol including diffusion- and perfusion-weighted imaging (DWI, PWI) and MR angiography (MRA) within 6 hours after symptom onset, at day 1 and after 1 week. Recanalization status was determined with MRA on day 1 (according to Thrombolysis In Myocardial Infarction flow grades) and used to group patients into those with persistent occlusion (0) or minimal (1), partial (2), or complete (3) recanalization.

Results—Incomplete recanalization according to MRI criteria was found in 39 patients (grade 1: n=20; grade 2: n=19), complete recanalization in 10, and persistent occlusion in 33. There was no statistically significant difference in any of the clinical (National Institutes of Health Stroke Scale score) or MRI baseline parameters (DWI lesion, PWI deficit, mismatch volume, mismatch ratio). However, lesion growth was smaller in patients with recanalization (even in patients with only minimal recanalization) and outcome was related to the degree of recanalization (mean modified Rankin score at 90 days: 3.36, 2.70, 1.79, and 1.44 for the groups with no, minimal, partial, and complete recanalization, respectively). Both incomplete and complete recanalization was more frequent in patients receiving thrombolysis.

Conclusions—Incomplete recanalization on day 1 is a frequent MR finding after MCA main stem occlusion, indicating a more favorable clinical course than persistent occlusion. MR indicators of early recanalization could be useful surrogates of efficacy in thrombolytic trials. (Stroke. 2004;35:109-115.)

Key Words: magnetic resonance angiography ■ magnetic resonance imaging ■ stroke, acute ■ thrombolysis
recognized consistently,18,19 which is in line with angiographic and transcranial Doppler (TCD) studies.20,21 As in studies using angiography to determine recanalization status, the Thrombolysis In Myocardial Infarction (TIMI) grading system22 has evolved into the most commonly used system, while other grading systems have been developed for TCD.23 The TIMI grading system was originally developed for thrombolytic trials of myocardial infarction and allows angiographic assessment of coronary perfusion (grade 0 to 3), with incomplete recanalization being graded as either minimal (grade 1) or partial (grade 2).

The aim of this MRI study was to determine the frequency and relevance of incomplete recanalization (TIMI grades 1 and 2) after MCA occlusion in terms of tissue and clinical outcome. The analysis of our patient group (n=82) with MCA main stem occlusion suggests that incomplete recanalization (both minimal and partial) is more beneficial than persistent occlusion.

**Subjects and Methods**

**Patients**

The retrospective analysis was based on data obtained within the Kompetenzzentrum Schlaganfall (study group B5; ongoing study, patients contributing to this analysis were recruited between January 1999 and March 2002). Stroke centers with expertise in stroke MRI from 6 German university hospitals (Berlin, Düsseldorf, Frankfurt, Hamburg, Heidelberg, Mannheim) contributed data to the study population. The common database (in part published previously18) consists of acute stroke patients who received a standardized acute stroke MRI protocol within 6 hours of symptom onset, as well as follow-up MRI at day 1 and 1 week after symptom onset. The National Institutes of Health Stroke Scale (NIHSS) was assessed immediately before the initial MRI and at 1 week after symptom onset. The modified Rankin Scale (mRS) was determined on day 90 after stroke onset to assess disability, either at a follow-up examination or by telephone interview. The mRS scoring was performed without knowledge of recanalization status.

For the present analysis, patients (n=82) were selected if the initial MRA suggested complete MCA main stem occlusion, ie, occlusion of the M1 segment. Patients with both T-occlusions and occlusions distal to the M1 segment were not included in the analysis. By selecting only patients with M1 occlusion, which was the largest subgroup in the database, we focused our analysis on a homogenous patient sample; this facilitated the analysis since we did not have to correct for the influence of occlusion site on follow-up parameters. Patients receiving thrombolytic treatment (n=57; intravenous thrombolysis, n=52; intra-arterial thrombolysis, n=5) were not excluded from the analysis assuming that thrombolysis influences follow-up parameters primarily by influencing recanalization status.

**MRI**

MRI studies were performed on 1.5-T clinical whole-body scanners with echo-planar imaging capabilities (Magnetom Symphony, Siemens: Hamburg, Berlin; Magnetom Vision, Siemens: Düsseldorf, Frankfurt, Mannheim; Marconi EDGE: Heidelberg). The acute stroke MRI protocol included an axial diffusion-weighted imaging (DWI) sequence, bolus-tracking perfusion-weighted imaging (PWI), a conventional T2-weighted sequence, and a time-of-flight MRA of the intracranial arteries. Follow-up studies were performed on day 1 and at 1 week (only DWI, T2-weighted sequence) after symptom onset.

**Postprocessing and Image Analysis**

Postprocessing of the MRI data and determination of lesion volumes were performed off line in each participating center with locally established software as described previously.14 The following primary MRI parameters were determined: acute DWI lesion volume, acute PWI lesion volume, and lesion volume on follow-up T2-weighted images obtained after 1 week (final infarct size). Acute PWI lesion volumes were measured as total perfusion deficit on either time-to-peak (TTP)—or mean transit time (MTT)—maps generated from the perfusion raw data depending on local preferences. The site of the M1 occlusion on MRA was determined as either proximal or distal (beyond the origin of the lenticulostriate arteries).

From these primary parameters, secondary parameters were derived as follows: mismatch volume (acute PWI lesion volume—acute DWI lesion volume), mismatch ratio (acute PWI lesion volume/acute DWI lesion volume), and lesion growth (final infarct size—acute DWI lesion volume).

In addition, recanalization status was assessed on MRI at day 1 after symptom onset using the TIMI score:22 TIMI 0=no recanalization/reperfusion; TIMI 1=minimal recanalization/reperfusion; TIMI 2=partial recanalization/reperfusion; TIMI 3=complete recanalization/reperfusion. Grading was primarily based on the MRA results, but PWI was used in addition in cases of doubt (if available). Whereas assignment of TIMI grades 0 and 3 (based on MRA) is straightforward, differentiation of TIMI grades 1 and 2 is more difficult and somewhat arbitrary. For the purpose of this analysis, TIMI grade 1 was defined as flow signal detectable beyond the area of obstruction, but not in most of the distal vascular bed, corresponding to residual PWI lesions ≥80% of the initial PWI lesion. Incomplete recanalization with filling of most of the vascular bed and a PWI lesion of <80% was classified as TIMI 2 (Figure 1).

**Statistical Analysis**

Patients were divided into 4 groups depending on the TIMI grade (0-3) determined from the day 1 MRI. All data are given as mean±SD unless stated otherwise. In a primary analysis, several acute clinical and imaging parameters (including age, NIHSS, DWI lesion, PWI lesion, mismatch volume, and ratio) were compared with test for baseline differences between the subgroups. Subsequently, comparisons were made for 3 follow-up parameters (mRS 90, final infarct size, lesion growth) using the nonparametric Kruskal-Wallis test.
and Mann-Whitney U tests. Results were considered statistically significant at the 5% level.

Results

The distribution of TIMI grades at day 1 after symptom onset based on MRI criteria was as follows: TIMI 0, n = 33; TIMI 1, n = 20; TIMI 2, n = 19; TIMI 3, n = 10. There was no statistically significant difference concerning any of the analyzed clinical or imaging baseline parameters between the different recanalization groups (Table 1). Possibly as a result of the small sample size, we did not find a difference in recanalization rates between patients with proximal and distal M1 segment occlusion. In addition, no significant difference was found between recanalization grades at 24 hours and the interval between stroke onset and acute MRI (median interval for TIMI 0, 165 minutes; TIMI 1, 150 minutes; TIMI 2, 150 minutes; TIMI 3, 142 minutes).

However, when comparing follow-up parameters between the different groups (Figure 2), there was significantly less lesion growth in the groups with minimal, partial, and complete recanalization (TIMI 1 to 3: 19.6 ± 43, 7.6 ± 28, and 13.0 ± 25 mL, respectively) compared with patients with persistent occlusion (TIMI 0: 57.5 ± 74 mL) and a nonsignificant trend toward smaller final infarcts in the TIMI 1 to 3 groups compared with the TIMI 0 group (TIMI 0 to 3: 95.5 ± 86, 57.1 ± 58, 60.5 ± 52, and 52.7 ± 51 mL, respectively). In addition, follow-up NIHSS at day 7 was significantly lower in the TIMI 1 to 3 groups compared with the TIMI 0 group, while mRS was significantly lower in the TIMI 2 and 3 groups with only a nonsignificant trend in the TIMI 1 group. The percentage of patients achieving an independent state at 90 days (mRS ≤ 2) in the TIMI 0 to 3 groups is given in Table 2.

When analyzing both groups with incomplete recanalization together (TIMI 1 and 2) compared with patients with persistent occlusion, incomplete recanalization was associated with significantly less lesion growth (5 versus 25 mL; \(P \leq 0.01\)) and a more favorable mRS90 (2 versus 4; \(P < 0.05\)), while there was only a trend toward smaller final infarct size (32 versus 63 mL; \(P = 0.08\)). Similar results were obtained when analyzing only the subgroup not receiving thrombolysis, but statistical significance was just missed (\(P = 0.05\) for lesion growth and \(P = 0.07\) for mRS90), probably due to the small sample size (n = 25).

In the subgroup of patients treated with intravenous thrombolysis, the percentage with both incomplete and complete recanalization was greater than in the subgroup of patients not receiving intravenous thrombolysis (Table 3).

TABLE 1. Baseline Parameters

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>NIHSS Acute</th>
<th>DWI Acute, mL</th>
<th>PWI Acute, mL</th>
<th>Mismatch Volume, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI 0 (n = 33)</td>
<td>61 (20–89)</td>
<td>13.0 (3–23)</td>
<td>18 (2–118)</td>
<td>151 (18–252)</td>
<td>97 (4–226)</td>
</tr>
<tr>
<td>TIMI 1 (n = 20)</td>
<td>66 (46–89)</td>
<td>12.5 (5–26)</td>
<td>22 (1–187)</td>
<td>131 (14–224)</td>
<td>91 (0–189)</td>
</tr>
<tr>
<td>TIMI 2 (n = 19)</td>
<td>64 (37–87)</td>
<td>14.0 (4–20)</td>
<td>28 (3–181)</td>
<td>162 (60–246)</td>
<td>115 (1–202)</td>
</tr>
<tr>
<td>TIMI 3 (n = 10)</td>
<td>56 (45–80)</td>
<td>14.5 (8–21)</td>
<td>24 (14–103)</td>
<td>129 (47–193)</td>
<td>86 (16–171)</td>
</tr>
<tr>
<td>All</td>
<td>62.5 (20–89)</td>
<td>13 (3–26)</td>
<td>22 (1–187)</td>
<td>146 (14–252)</td>
<td>100 (0–226)</td>
</tr>
</tbody>
</table>

All values are given as median (range).

Interestingly, none of the patients not receiving thrombolysis were classified as complete recanalization.

Discussion

This MRI study shows that incomplete recanalization/reperfusion (as determined 1 day after symptom onset) occurs frequently after acute MCA occlusion, particularly after thrombolysis. Both minimal and partial as well as complete recanalization/reperfusion resulted in limited lesion growth compared with persistent occlusion, and a graded response in regard to clinical outcome was seen depending on completeness of recanalization.

Only a few studies reported detailed data on the recanalization status after MCA occlusion using the TIMI scale to differentiate between different degrees of reperfusion. Angiographic data are available from 2 early studies on intravenous...
thrombolysis, which used angiography to document treatment effects. Partial recanalization (TIMI 2) was noted in both series, but TIMI grades 0 and 1 were pooled, not allowing a separate analysis. Similarly, in both the PROACT I and II studies, recanalization was assessed at the end of the 2-hour intraarterial period with prourokinase (r-proUK), differentiating between complete (TIMI 3) and partial (TIMI 2) recanalization, but not between no and minimal reperfusion (TIMI 0 or 1). In these angiographic studies, recanalization was assumed in TIMI 2+3 patients, but the influence of different TIMI grades on outcome was not analyzed in detail.

When applying the TIMI system (which was developed for coronary angiography) to MRI, technical differences between MRA and angiography need to be considered. With time-of-flight (TOF) MRA, it is intravascular flow that is encoded to generate an image of the intracranial circulation—rather than filling of the vessel bed with a contrast agent as in angiography. It is unclear whether this technical difference between angiography and MRA is important in the assessment of recanalization in acute stroke patients. In patients with carotid artery or MCA stenosis, it is well known that time-of-flight MRA may overestimate the degree of stenosis in comparison to angiography. In acute stroke patients, on the other hand, it is conceivable that very low flow may not be detectable with TOF MRA despite an open vessel. This may theoretically lead to an underestimation of TIMI flow grades obtained with TOF MRA compared with angiography. In particular, a certain proportion of MRI TIMI 1 patients may correspond to TIMI 2 patients with angiography. However, this hypothesis remains speculative as no direct comparison between TIMI flow grades obtained with MRI and angiography is currently available.

The relatively low partial and complete recanalization rate following intravenous thrombolysis in our open study (TIMI 2+3: 38.5% versus 24% in patients without intravenous thrombolysis) is in line with data from previous angiographic case series. For patients with M1 occlusion, Del Zoppo et al reported recanalization in 12 of 34 (35%) patients 1 hour after intravenous treatment with duteplase; von Kummer et al reported recanalization in 10 of 37 (27%) patients within 8 hours and in 14 of 37 (38%) patients after 24 hours of symptom onset following thrombolysis (mostly intravenous recombinant tPA [rtPA]); and Ernst et al reported recanalization in 4 of 7 (57%) patients with acute M1 occlusion after combined intravenous-intraarterial thrombolysis. Higher recanalization rates have been found in PROACT II for intraarterial thrombolysis (66%) and in recent large case series of intraarterial thrombolysis (79%, 30% 60%). Similarly, high recanalization rates have been found in transcranial Doppler and duplex studies (up to 78%) for patients treated with intravenous thrombolysis. The reason for these apparently different recanalization rates is not entirely clear but may be related to differences in the grading systems, diagnostic inaccuracies, or facilitation of clot lysis with TCD. Independent of these methodological discrepancies, our MRI study suggests that at least some TIMI 1 patients benefit from (minimal) recanalization in addition to TIMI 2/3 patients who are commonly regarded as treatment responders.

Why should minimal recanalization be beneficial from a pathophysiological perspective? The significant reduction of lesion growth in the TIMI 1 group compared with the group with persistent occlusion suggests that even minimal recanalization is sufficient to increase perfusion in the periphery of ischemic regions from a critical level to oligemia, leading to an improvement in collateral supply to this region. This shift from critical ischemia to oligemia appears to occur early enough for long-term tissue salvage. Possibly, early minimal recanalization is sufficient to keep the tissue viable, before more complete recanalization occurs, which would be in line with the observation that recanalization rates increase up to 1 week after symptom onset. In addition, incomplete clot lysis may lead to recanalization of the proximal M1 segment with reperfusion of the basal ganglia and may save this region from inclusion into the final infarct.

Despite the significant reduction of lesion growth and better NIHSS scores at 7 days in the TIMI 1 group compared with the group with persistent occlusion, there was only a trend toward better clinical outcome at 90 days. It is currently unclear whether the sample size was simply too small to reach significance or whether there is a pathophysiological reason for this finding. One may speculate that factors other than recanalization (such as plasticity, compensation, etc) become more important for functional recovery with increasing time from symptom onset leading to a less prominent difference at 90 days compared with 7 days. However, when analyzing both groups with incomplete (minimal and partial) recanalization together, there was a clear clinical and imaging benefit associated with incomplete recanalization, even at 90 days. Separate analysis of the subgroup not receiving thrombolysis indicated that this effect is independent of thrombolytic treatment.

### TABLE 2. Clinical Follow-Up Parameters

<table>
<thead>
<tr>
<th>Treatment</th>
<th>NIHSS Acute</th>
<th>NIHSS 7 Days</th>
<th>mRS 90 Days</th>
<th>mRS ≤2 90 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI 0</td>
<td>13.0 (3–23)</td>
<td>12.5 (1–42)</td>
<td>4 (0–6)</td>
<td>36%</td>
</tr>
<tr>
<td>TIMI 1</td>
<td>12.5 (5–26)</td>
<td>7.5 (1–25)</td>
<td>3 (0–6)</td>
<td>45%</td>
</tr>
<tr>
<td>TIMI 2</td>
<td>14.0 (4–20)</td>
<td>3.0 (0–25)</td>
<td>1 (0–5)</td>
<td>63%</td>
</tr>
<tr>
<td>TIMI 3</td>
<td>14.5 (5–21)</td>
<td>2.5 (0–12)</td>
<td>1 (0–6)</td>
<td>60%</td>
</tr>
<tr>
<td>All</td>
<td>13.0 (3–26)</td>
<td>8.0 (0–42)</td>
<td>3 (0–6)</td>
<td>48%</td>
</tr>
</tbody>
</table>

All values are given as median unless stated otherwise.

### TABLE 3. Recanalization Status in Patients With and Without Thrombolysis

<table>
<thead>
<tr>
<th></th>
<th>No Thrombolysis</th>
<th>Intravenous Thrombolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>TIMI 0</td>
<td>17</td>
<td>68.0</td>
</tr>
<tr>
<td>TIMI 1</td>
<td>2</td>
<td>8.0</td>
</tr>
<tr>
<td>TIMI 2</td>
<td>6</td>
<td>24.0</td>
</tr>
<tr>
<td>TIMI 3</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Σ</td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

Patients with local thrombolysis (n=5) not included.
Our study has several limitations: (1) Imaging was performed on different MRI systems, and postprocessing as well as image analysis was done in the 6 local centers participating in the study; this may have led to a greater degree of variability in the assessment of lesion volumes and recanalization status as compared with studies using a central image analysis facility. However, all participating centers have substantial expertise in stroke MRI, which should minimize variability due to inexperience. (2) Although all participating centers aimed at using MRI in all patients presenting within 6 hours of symptom onset (after exclusion of MRI contraindications), an unknown number of patients did not receive acute MRI for reasons such as lack of MRI scanner availability, technical difficulties, medical instability, and refused consent. In addition, it is likely that some patients were not included in the database due to neurological or medical deterioration prior to the follow-up examinations, making repeated MRI impractical. Assuming that this was the case in more patients with persistent occlusion as compared with patients with recanalization, we may have underestimated the proportion of patients with persistent occlusion. (3) The TIMI system has clear limitations when used for assessing recanalization in the intracranial circulation. In particular, the frequent finding of an apparent local fragmentation followed by distal embolization resulting in 1 or multiple branch occlusions may not be adequately captured. (4) Ongoing testing of patients with persistent occlusion as compared with patients with recanalization, we may have underestimated the proportion of patients with persistent occlusion as compared with patients with recanalization. (5) The TIMI system has clear limitations when used for assessing recanalization in the intracranial circulation. In particular, the frequent finding of an apparent local fragmentation followed by distal embolization resulting in 1 or multiple branch occlusions may not be adequately represented in a system that primarily assesses local recanalization.

In summary, incomplete recanalization on day 1 is a frequent MR finding after MCA main stem occlusion and is predictive of a favorable clinical course. Even a TIMI 1 flow grade on MRI 24 hours after symptom onset was found to be associated with less lesion growth (P?<0.05) than persistent occlusion. MR indicators of early recanalization could be useful surrogates of efficacy in acute stroke studies.

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**References**


Degree of Arterial Recanalization: An End Point For Efficacy in Future Intravenous Thrombolytic Trials

From a pathophysiologic viewpoint, acute stroke is, in most cases, the consequence of an arterial occlusion, and the primary mechanism of action of thrombolysis is clot lysis, resulting in recanalization and reestablishment of cerebral blood flow. The National Institutes of Neurological Disorders and Stroke (NINDS) trial\(^1\) clearly demonstrated a beneficial effect of intravenous recombinant tissue plasminogen activator (rtPA) when given <3 hours after symptom onset. However, the NINDS trial, like other clinical trials of intravenous thrombolysis, did not monitor presence and location of arterial occlusion and recanalization at different times after stroke. Criticism of the widespread use of tPA was based on the lack of vascular imaging in the standard emergent evaluation of acute stroke for a rational selection of patients who will obtain more benefit from thrombolysis. In the last few years, however, a tremendous progress and widespread implementation of noninvasive neurovascular techniques including transcranial Doppler (TCD), computed tomography angiography (CTA), and magnetic resonance angiography (MRA) have been achieved. These imaging modalities are being increasingly performed in the acute stroke setting without substantial delay in a large number of centers worldwide. Previous TCD and MRI studies have shown that early recanalization strongly associated with early neurological improvement, reduced infarct size, and favorable prognosis.\(^2\)\(^-\)\(^4\) However, the term recanalization involves various grades of success with differential effects on ischemic tissue evolution, clinical course, and outcome.

In the accompanying article, Neumann-Haefelin and colleagues\(^5\) studied 82 highly selected and homogeneous stroke patients with middle cerebral artery (MCA) main stem occlusions. All patients underwent a multiparametric MRI protocol including diffusion- and perfusion-weighted imaging (DWI, PWI) and MRA within 6 hours of stroke onset. The same protocol was repeated at 24 hours and 1 week. The authors applied the Thrombolysis In Myocardial Infarction (TIMI) score to assess the degree of arterial recanalization on 24-hour MRA. Using this angiographic grading system, patients were grouped into those with persistent occlusion (TIMI 0), minimal (TIMI 1), partial (TIMI 2), or complete (TIMI 3) recanalization. Patients who achieved TIMI 1 and 2 were pooled and regarded as incomplete recanalization. After adjustment for baseline stroke severity, initial DWI lesion, and PWI/DWI mismatch volume, the authors found that both complete and complete recanalization associated with a reduced DWI lesion growth compared with persisted occlusion. Moreover, a graded response in long-term outcome was seen in relation to the completeness of recanalization. These findings are in consonance with previous TCD and MRI studies,\(^2\)\(^-\)\(^4\)\(^,\)\(^6\) indicating that the amount of early recanalization represents one of the major determinants of stroke outcome. The present study highlights that even minimal recanalization may contribute to rescue penumbra tissue from infarction. Moreover, the authors confirm previous observations indicating that persistent MCA occlusion during the first 24 hours of onset represents one of the worst possible scenarios in terms of tissue damage enlargement and outcome. A previous MRI study\(^7\) showed a significant increase in DWI lesion at day 5 in patients without recanalization at 48 hours, which indicates further infarct dynamics and progressive infarct growth even after several days in patients with persistent occlusion. Nevertheless, the observations of Neumann-Haefelin et al also reveal a crude reality, that minimal recanalization, although better than persistent occlusion, leads to an unacceptable high rate (55%) of poor outcome and dependency at 3 months compared with partial and complete recanalization. Therefore, in the context of patients with proximal MCA occlusion, minimal recanalization is simply “better than nothing.”

The mechanism of neurological improvement and reduced lesion growth in some patients with proximal MCA occlusion...
who achieve minimal recanalization is related to an increased perfusion as a result of distal displacement of the offending clot into the MCA main stem. Minimal clot migration or partial clot dissolution may restore collateral flow, when the most proximal aspect of the M1 MCA thrombus was partially obstructing collateral channels through the cortex, particularly via the anterior cerebral artery (ACA). The release of collaterals may lead to reperfusion of the ACA/MCA borderzone and cortical periphery of the ischemic penumbra. On the other hand, the proximal MCA thrombus may involve the lenticulostrate arteries supplying the ganglia basal and internal capsule. Minimal recanalization with distal clot migration may be enough to restore flow and function to the posterior limb of the internal capsule, where the motor fibers are represented, leading to an improvement of motor function. This may explain the beneficial effect of minimal recanalization on long-term outcome, since recovery of motor function may play an important role in the degree of independence for daily living activities in stroke survivors.

Although several case series have consistently demonstrated that early recanalization represents one of the powerful predictors of good long outcome after thrombolysis, some stroke patients experience little or no improvement and remain disabled despite tPA-induced recanalization. Other factors in addition to recanalization—including stroke severity, older age, systolic hypertension, location of arterial occlusion, collateral blood supply, and time from stroke onset to treatment—may play an important role in determining clinical outcome in patients treated with tPA. The beneficial effect of early restoration of cerebral blood flow on stroke outcome may be hampered in part by factors such as extent of irreversible brain injury before recanalization, excessive glucose burden at the time of reperfusion, and blood pressure changes during thrombolysis.

The TIMI score is an angiography-based grading system, which was originally developed and used to describe flow in the coronary arteries. Its clinical use has been extended to cerebral circulation. However, the TIMI grading system had certain limitations when applied to assess recanalization of intracranial arteries. The TIMI system evaluates local recanalization and, therefore, it does not accurately reflect the dynamic nature of the recanalization process during stroke thrombolysis. For instance, the phenomenon of proximal clot fragmentation followed by downstream embolization occluding smaller arteries cannot be adequately represented by the TIMI system. Moreover, TIMI flow grades obtained with time-of-flight MRA may be underestimated in comparison to angiography, making it sometimes difficult to differentiate between TIMI 1 and 2. This limitation has been solved, at least in part, by Neumann-Haefelin et al evaluating the extent of residual PWI lesion to better discriminate between TIMI 1 and TIMI 2.

Selection of a study end point for phase I and II trials depends mainly on the expected mechanism and effect of the given drug. The study of Neumann-Haefelin et al adds to the cumulative evidence suggesting that the noninvasive assessment of the degree of arterial recanalization, as an indicator of biologic activity of a thrombolytic drug, should be used as an end point for efficacy in future intravenous thrombolytic trials. New thrombolytic agents or approaches to enhance the efficacy of tPA such as combination with glycoprotein IIb-IIIa inhibitors or ultrasounds need to be properly tested, establishing their ability to achieve early recanalization. CLOTBUST is a multicenter randomized phase II trial that uses recanalization on TCD at 120 minutes of tPA bolus as primary efficacy end point. The feasibility to assess arterial occlusion and recanalization in stroke thrombolysis is supported by the increasing distribution and around-the-clock availability of noninvasive neurovascular techniques. Further studies are required to identify the time point of recanalization that better reflect the maximum thrombolytic effect (60 minutes, 120 minutes, or 24 hours) and to evaluate whether the combination of imaging protocols (ie, TCD monitoring plus MRI) adds to the knowledge of the effects of the speed and degree of clot dissolution after thrombolysis on ischemic tissue evolution and outcome.

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References
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