Thrombus Branching and Vessel Curvature Are Important Determinants of Middle Cerebral Artery Trunk Recanalization With Merci Thrombectomy Devices

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Background and Purpose—Determinants of successful recanalization likely differ for Merci thrombectomy and intra-arterial pharmacological fibrinolysis interventions. Although the amount of thrombotic material to be digested is an important consideration for chemical lysis, mechanical debulking may be more greatly influenced by other target lesion characteristics.

Methods—in consecutive patients with acute ischemic stroke treated with Merci thrombectomy for middle cerebral artery M1 occlusions, we analyzed the influence on recanalization success and clinical outcome of target thrombus size (length) and shape (curvature and branching) on pretreatment T2* gradient echo MRI. Results—Among 65 patients, pretreatment MRI showed susceptibility vessel signs in 45 (69%). Thrombus length averaged 13.03 mm (range, 5.56–34.91) and irregular shape (curvature or branching) was present in 17 of 45 (38%). Presence and length of susceptibility vessel signs did not predict recanalization or good clinical outcome. Substantial recanalization (Thrombolysis In Cerebral Infarction 2b or 3) and good clinical outcome (modified Rankin Scale score ≤2) were more frequent with regular than irregular susceptibility vessel signs shape (57% versus 18%, P = 0.013; 39% versus 6%, P = 0.017). On multiple regression analysis, the only independent predictor of substantial recanalization was irregular susceptibility vessel signs (OR, 0.16; 95% CI, 0.04–0.69; P = 0.014); and leading predictors of good clinical outcome were baseline National Institutes of Health Stroke Scale (OR, 1.20; 95% CI, 1.03–1.40; P = 0.019) and irregular susceptibility vessel signs (OR, 9.36; 95% CI, 0.98–89.4; P = 0.052).

Conclusions—Extension of thrombus into middle cerebral artery division branches and curving shape of the middle cerebral artery stem, but not thrombus length, decrease technical and clinical success of Merci thrombectomy in M1 occlusions. (Stroke. 2012;43:787-792.)

Key Words: acute ■ endovascular treatment ■ magnetic resonance imaging ■ outcome ■ stroke

Studies of pharmacological intra-arterial fibrinolysis have reported that larger target clot size, measured by thrombus length or volume, is associated with lower rates of recanalization and poor clinical outcome.1–3 However, indirect evidence suggests that thrombus burden may be less important to the success of mechanical recanalization strategies. In clinical trials, intra-arterial fibrinolysis shows a gradient of recanalization efficiency with lower recanalization rates for large thrombus volume sites, like the carotid terminus,4 and higher recanalization rates for low thrombus volume sites, like the middle cerebral artery first segment (M1 MCA).5 In contrast, Merci thrombectomy (MT) showed relatively equal recanalization success rates at carotid terminus and M1 MCA occlusion sites.6

This study investigated the effect on MT success of target thrombus burden and of novel measures of target thrombus and vessel shape. To analyze thrombus morphology, we used the pretreatment MRI susceptibility vessel sign (SVS). The SVS on T2* gradient echo (GRE) MRI is characterized by low-intensity signal conforming to a vessel segment and is generated by deoxyhemoglobin embedded within intraluminal thrombus. The SVS has high sensitivity and specificity for acute large cerebral artery occlusion.7,8 Prior studies have used the SVS to analyze thrombus size but not thrombus shape.9

Materials and Methods

Patient Selection

In a prospectively maintained database, for the period January 2002 to October 2008, consecutive patients were identified who underwent endovascular recanalization therapy for acute cerebral ischemia at an academic medical center. Study entry criteria were: (1) acute cerebral ischemia with last known well time within 8 hours of first
embolectomy pass; (2) treatment with ≥1 Merci Retriever devices; (3) pretreatment MRI protocol including valid GRE sequence; (4) M1 MCA occlusion without internal carotid artery involvement demonstrated on catheter angiography; (5) prestroke modified Rankin Scale score ≤2; and (6) intra-arterial fibrinolysis therapy not administered. Informed consent for embolectomy was obtained in all cases from patients or their legally authorized representatives. Patients treated with intravenous tissue plasminogen activator before embolectomy were included if persistent vessel occlusion was proved by angiography. For each patient, demographics, vascular risk factors, baseline National Institutes of Health Stroke Scale score, and outcome modified Rankin Scale score at 7 days, or discharge if earlier, were analyzed. The study was approved by the hospital Institutional Review Board.

SVS Analysis
MRI studies were performed on a 1.5-T Siemens Vision scanner (Siemens Medical Solutions) equipped with a standard head coil. GRE sequences were obtained using 7-mm slice thickness, no gap, field of view 220 mm, TR 800 ms, TE 15 ms, and flip angle 30°, matrix 512×512. The GRE SVS was defined as presence of hypointensity in the MCA with diameter exceeding the hypointense signal in the contralateral vessel diameter.7,8 Two experienced stroke physicians, blinded to clinical information, independently assessed the presence and features of SVS on pretreatment GRE scans with rater discrepancies settled by consensus discussion.

SVS was assessed for indices of thrombus burden (length), tortuosity (angle of curvature), and branching, presumed to reflect extension into ≥1 divisions of the MCA (Figures 1 and 2). SVS length was measured using ImageJ (National Institutes of Health, Bethesda, MD). SVS in the M1 MCA were initially independently classified as straight or curved by the 2 readers based on visual inspection and subjective judgment that the vessel segment was essentially straight versus essentially curved. For all curved cases, the subtended angle of curvature of SVS in the M1 MCA was then measured using syngo XWP (VA72B, Siemens AG). One reader (L.Z.) drew a line in the middle of the SVS following whatever curve was present. The software automatically fit a circle segment over the drawn line and calculated the subtended angle of curvature. For comparison, subtended angle curvature was also measured for a random sample of 10 of the cases classified as straight.

The raters also classified SVS shapes as branched or unbranched. Branching was considered present when the axis of a vessel subdivision extended away from the axis of the main trunk at a sudden angle (rather than a gradual curve).

Figure 1. Representative images of susceptibility vessel signs (SVS) on T2* gradient echo imaging (white arrows) in 4 patients. A, A regular SVS that is both unbranched and straight (angle of curvature 6°); B, irregular SVS that is unbranched but is curved (angle of curvature 111°); C, irregular SVS with straight main segment (angle of curvature 8°) but with 2 distal branches; D, irregular SVS that is curved (angle of curvature 211°) and has 1 distal branch.

Figure 2. Classification of susceptibility vessels signs in the study cohort.
Based on these findings, the readers independently classified SVS shapes as regular or irregular with rater discrepancies settled by consensus discussion.

**Thrombectomy Procedure**

All patients underwent conventional cerebral angiography. The thrombectomy procedure has been described previously.\textsuperscript{10} X series devices (X5, X6), L series devices (L4, L5, L6), k\textsubscript{Mini}, and V2.5 Firm were used in thrombectomy. The procedure was stopped if complete recanalization was achieved, if partial recanalization was achieved and the interventionalist felt the risk of further passes outweighed potential benefit, or if the vessel was not opened after 6 device passes. Pretreatment and posttreatment angiograms were scored on the Thrombolyis in Cerebral Ischemia score and the Qureshi scale by an experienced neurointerventionalist blinded to clinical outcome.\textsuperscript{11,12} Any recanalization was defined as a Thrombolyis in Cerebral Ischemia score of 2a, 2b, or 3 and substantial recanalization as Thrombolyis in Cerebral Ischemia 2b to 3. Major device-related complications were defined as device fracture, vessel perforation, arterial dissection, or embolization in a previously uninvolved territory.

**Measurement of Outcome**

The primary clinical outcome was death or dependency at Day 7 or discharge, whichever came first, as indexed by modified Rankin Scale scores 3 to 6 (poor clinical outcome) versus 0 to 2 (good clinical outcome). To assess hemorrhagic transformation, control scans, either CT or MRI including GRE sequences, was performed at 24 hours in all patients. Additional MRI or CT scans were obtained in any case of neurological deterioration. Hemorrhages were adjudicated as subarachnoid hemorrhage, remote (extraanispheric) cerebral hematoma,\textsuperscript{13} or as European Cooperative Acute Stroke Study hemorrhagic infarction Type 1 or 2 or parenchymal hematoma Type 1 or 2.\textsuperscript{14} Symptomatic intracranial hemorrhage was defined as any intracranial hemorrhage associated with a \( \geq 4 \)-point increase in National Institutes of Health Stroke Scale score.

**Statistical Analysis**

Categorical variables were analyzed by \( \chi^2 \) or Fisher exact test, as appropriate. Continuous variables were compared with an independent-sample \( t \) test or Mann-Whitney \( U \) test, as appropriate. Interobserver agreement was calculated by \( k \)-statistics. Stepwise multiple regression analysis with a backward selection process (exit criterion of \( P > 0.1 \)) was used to choose predictor variables for substantial recanalization and poor clinical outcome, respectively. Because of modest sample size, to reduce variables for the multiple regression analysis, a composite vascular risk factor variable was also used, reflecting presence of \( \geq 1 \) of hypertension, diabetes, hyperlipidemia, atrial fibrillation, or prior stroke. Tobacco and alcohol were not included in the composite variable because of low frequencies in the study population. For all statistical analyses, the level for a significant difference was set at \( P \leq 0.05 \) and for a trend toward significance at \( P \leq 0.1 \).

**Results**

During the study period, 110 patients within 8 hours of stroke onset were treated with MT and underwent pretreatment MRI. Among these, 40 were excluded because the target thrombus was outside the M1 MCA segment, including the internal carotid artery (26), tandem occlusion (5), and M2 MCA segment (9). In addition, 5 patients were excluded for receiving intra-arterial fibrinolysis after unsuccessful MT.

A total of 65 patients fully met study entry criteria. Mean age was 65±20 years (mean±SD) and 42 were female (65%). Median baseline National Institutes of Health Stroke Scale score was 18 (range, 5–24). Ten received intravenous tissue plasminogen activator before embolectomy. Mean time from onset to pretreatment MRI was 232.2±101.8 minutes (range, 33–432 minutes). Mean time from onset to endovascular treatment was 325.5±95.3 minutes (range, 91–468 minutes). Among the 65 patients, 112 devices were used, including 1 device alone in 34 patients, 2 devices in 21, 3 devices in 7, and 4, 5, and 6 devices each in 1 patient. Device categories deployed included: X series alone in 22 patients, L series alone in 29, L5+X series in 5, k\textsubscript{Mini} alone in 1, L5+K\textsubscript{Mini} in 6, V2.5 Firm alone in 1, and L5+V2.5 Firm in 1. Forty-five of 65 patients (69%) had a SVS present. Interobserver agreement for the presence of SVS was very good (\( k = 0.84 \)). In all cases, SVS was ipsilateral to the clinically affected hemisphere. Any recanalization was achieved in 72% of patients and substantial recanalization in 40%. Sixty-two patients underwent control MRI at 24 hours, whereas 3 patients with unstable vital signs underwent CT. Major device-related complications occurred in 5 of 65 patients (7%), including 2 vessel perforations with subarachnoid hemorrhage, 2 arterial dissections, and 1 embolization in a previously uninvolved anterior cerebral artery territory. Baseline characteristics, recanalization rates, device-related complications, radiological hemorrhagic transformation, symptomatic intracranial hemorrhage, and good clinical outcome did not differ among those with and without a SVS (Table 1).

In the 45 patients with a SVS, SVS length was 13.03±6.88 mm (range, 5.56–34.91 mm). An irregular SVS morphology was present in 17, including 5 with both curvature and branching, 6 with curvature without branching, and 6 with branching without curvature (Figure 2). Among the 11 patients with curved thrombus shape, the mean angle of curvature was 113\textdegree\textpm42 SD; range, 53\textdegree–211\textdegree. Among 10 randomly selected patients with straight thrombus shape, the mean angle of curvature was 18\textdegree\textpm6 SD; range, 13\textdegree–34\textdegree. Branching was noted in 11 patients, including 5 single branches into 1 M2 division and 6 with double branches into 2 M2 divisions. Interobserver agreement for the shapes of SVS was very good with \( \kappa \) values of 0.88 for curve versus straight and 0.94 for unbranched versus branched. Baseline characteristics, device-related complications, radiological hemorrhagic transformation, symptomatic intracranial hemorrhage, and rate of any recanalization did not differ with statistical significance among the irregular and the regular groups (Table 2). The substantial recanalization rate was higher for the regular than the irregular groups (57% versus 18%; OR, 6.22; 95% CI, 1.45–26.62; \( P = 0.013 \)). Poor clinical outcome was less frequent in patients with regular than irregular SVS (61% versus 94%; OR, 0.10; 95% CI, 0.01–0.84; \( P = 0.017 \)). Length of SVS was longer for the irregular than the regular morphologies (16.89±7.80 mm versus 10.68±5.09 mm, \( P = 0.002 \)). Length of SVS was longer for curved than for straight shape (17.05±6.87 mm versus 11.73±6.45 mm, \( P = 0.024 \)). However, length of SVS did not differ among those with any recanalization versus no recanalization (13.31±6.94 mm versus 12.26±6.94 mm, \( P = 0.657 \)) or among those with substantial recanalization versus no substantial recanalization (11.65±5.97 mm versus 14.03±7.42 mm, \( P = 0.256 \)). Point estimates were lower for SVS length among those with versus without good clinical
Table 1. Clinical Features of Patients With and Without a Susceptibility Vessel Sign

<table>
<thead>
<tr>
<th>MCA Susceptibility Vessel Sign</th>
<th>Absent</th>
<th>Present</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>20 (31%)</td>
<td>45 (69%)</td>
<td>0.555</td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>62.7±23.6</td>
<td>67.0±19.1</td>
<td>0.400</td>
</tr>
<tr>
<td>Female (%)</td>
<td>11 (55%)</td>
<td>31 (68%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Median NIHSS score (IQR)</td>
<td>16.5 (18.8–10.3)</td>
<td>18.0 (22.5–15.0)</td>
<td>0.062</td>
</tr>
<tr>
<td>Pretreatment Qureshi scale, 3A/3B</td>
<td>17/3</td>
<td>39/6</td>
<td>0.568</td>
</tr>
<tr>
<td>Time from onset to MRI, min</td>
<td>243±108</td>
<td>228±100</td>
<td>0.782</td>
</tr>
<tr>
<td>Time form onset to thrombectomy, min</td>
<td>333±100</td>
<td>323±94</td>
<td>0.893</td>
</tr>
</tbody>
</table>

Vascular risk factors

- Hypertension: 11 (55%) vs 24 (53%) (P = 1.000)
- Diabetes: 5 (25%) vs 11 (24%) (P = 1.000)
- Coronary artery disease: 3 (15%) vs 11 (24%) (P = 0.521)
- Hyperlipidemia: 8 (40%) vs 13 (29%) (P = 0.402)
- Atrial fibrillation: 6 (30%) vs 20 (44%) (P = 0.411)
- Prior stroke: 1 (5%) vs 3 (7%) (P = 1.000)
- Tobacco: 2 (10%) vs 4 (9%) (P = 1.000)
- Alcohol: 2 (10%) vs 1 (2%) (P = 0.222)
- Any recanalization: 14 (70%) vs 33 (73%) (P = 0.773)
- Substantial recanalization: 7 (35%) vs 19 (42%) (P = 0.784)
- Device-related complications: 1 (5%) vs 4 (9%) (P = 0.392)
- Any intracranial hemorrhagic transformation: 9 (45%) vs 25 (56%) (P = 0.591)
- Symptomatic intracranial hemorrhagic transformation: 4 (20%) vs 9 (20%) (P = 1.000)
- Good clinical outcome, mRS score ≤2: 4 (20%) vs 12 (27%) (P = 0.757)

MCA indicates middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; mRS, modified Rankin Scale.

Table 2. Clinical Features of Patients With Regular and Irregular Target Thrombus Shape

<table>
<thead>
<tr>
<th>MCA Susceptibility Vessel Sign</th>
<th>Regular</th>
<th>Irregular</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>28 (62%)</td>
<td>17 (38%)</td>
<td>0.393</td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>64.6±21.2</td>
<td>71.1±14.8</td>
<td>0.326</td>
</tr>
<tr>
<td>Female (%)</td>
<td>21 (75%)</td>
<td>10 (59%)</td>
<td>0.043</td>
</tr>
<tr>
<td>Median NIHSS score (IQR)</td>
<td>18 (22.8–12.3)</td>
<td>18 (22.5–18.0)</td>
<td>0.436</td>
</tr>
<tr>
<td>Pretreatment Qureshi scale, 3A/3B</td>
<td>25/3</td>
<td>14/3</td>
<td>0.658</td>
</tr>
<tr>
<td>Time from onset to MRI, min</td>
<td>209±94</td>
<td>259±103</td>
<td>0.087</td>
</tr>
<tr>
<td>Time form onset to thrombectomy, min</td>
<td>309±84</td>
<td>347±108</td>
<td>0.094</td>
</tr>
<tr>
<td>Length of susceptibility vessel sign, mm</td>
<td>10.7±5.1</td>
<td>16.9±7.8</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Vascular risk factors

- Hypertension: 15 (54%) vs 9 (53%) (P = 1.000)
- Diabetes: 7 (25%) vs 4 (24%) (P = 1.000)
- Coronary artery disease: 7 (25%) vs 4 (24%) (P = 1.000)
- Hyperlipidemia: 11 (39%) vs 2 (12%) (P = 0.088)
- Atrial fibrillation: 14 (50%) vs 6 (35%) (P = 0.372)
- Prior stroke: 2 (7%) vs 1 (6%) (P = 1.000)
- Tobacco: 4 (14%) vs 0 (0%) (P = 0.281)
- Alcohol: 0 (0%) vs 1 (6%) (P = 0.378)
- Any recanalization: 21 (75%) vs 12 (71%) (P = 0.743)
- Substantial recanalization: 16 (57%) vs 3 (18%) (P = 0.013)
- Device-related complications: 2 (7%) vs 2 (12%) (P = 0.626)
- Any intracranial hemorrhagic transformation: 18 (64%) vs 7 (41%) (P = 0.216)
- Symptomatic intracranial hemorrhagic transformation: 6 (21%) vs 3 (18%) (P = 1.000)
- Poor clinical outcome, mRS score ≥3: 17 (61%) vs 16 (94%) (P = 0.017)

MCA indicates middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; mRS, modified Rankin Scale.

We found that, in contrast to intra-arterial fibrinolysis, the recanalization success of MT was not strongly determined by the size of the target thrombus. This finding accords with the observation in multicenter trials that MT is equally efficacious for thrombi located in large proximal arterial segments as for thrombi located in smaller, distal arterial segments. This finding also is consonant with the known physiological mechanisms of differing recanalization therapies. Pharmacological fibrinolysis requires enzymatic digestion by plasmin of fibrin strands in target thrombi. The speed of enzymatic reactions is typically proportional to the amount of substrate to be processed. In narrow cerebral arteries, larger clot volume results in a smaller surface area-to-volume ratio, further decreasing the effectiveness of fibrinolysis. Moreover, the local supply of plasminogen that can be converted to active plasmin may be completely exhausted during attempts to enzymatically clear large clot burdens. In contrast, in
mechanical retrieval therapy, nitinol helical loops and arcing filaments capture the distal portion of the thrombus and then extract the entire thrombus, including all clot portions proximal to the distal most entrapped segment. The success of the mechanical strategy is consequently less dependent on the volume of clot to be extracted.

Although target clot burden did not affect embolectomy success, target clot morphology exerted a substantial influence. Clots that were straight and unbranched were recanalized 3 times as often as clots that were curved and/or branched. This observation accords with the mechanism of action of retrieval embolectomy. Thrombus fills the lumen of occluded arteries so that clot shape is an internal cast of the occluded arterial segment. A curved shape indicates the clot was molded by a more tortuous M1 MCA segment, in which some of the mechanical force applied during retriever pull-back will be dispersed radially, whereas a straight shape indicates a straight M1 MCA segment in which the mechanical forces can be exerted on the target thrombus with less impedance. A branched shape indicates thrombus entering arterial branch segments off the MCA trunk so that the distal most thrombus is (1) in a smaller artery less easily accessed by the device; (2) oriented at an angle to the MCA trunk segment, dispersing retrieval forces applied across along the line of the main trunk; (3) potentially more strongly packed into the recipient vasculature and resistant to extraction; and (4) may require multiple successful retriever passes to extract different thrombus projections from different terminal division branches. Because of the importance of recanalization to clinical outcome, regular target clot shape not only determined frequency of revascularization success, but also frequency of good functional outcome at discharge.

Although our study is the first to exploit the susceptibility vessel sign as a source of information regarding clot shape and size before mechanical recanalization therapy, prior studies have investigated the relation between the presence or absence of the SVS and fibrinolytic recanalization and clinical outcome. In 1 study, presence of a SVS arising from an occluded vessel did not predict recanalization response to intravenous tissue plasminogen activator, whereas in an occluded vessel did not predict recanalization response to outcome. In 1 study, presence of an SVS arising from an occluded vessel sign as a source of information regarding clot size and frequency of good functional outcome at discharge.

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In this study of M1 MCA occlusions, we found that the T2* susceptibility sign had a sensitivity of 69% in identifying occlusions confirmed at angiography within 8 hours of onset. This rate is congruent with prior studies evaluating the sensitivity of the SVS in proximal cerebral occlusion, which have reported sensitivity rates of 50% to 97% within 6 hours of symptom onset.

Our study has limitations. Early patients in the series were treated only with the first generation design of the Merci Retriever device, whereas for later patients, the interventionalist selected devices from among several available Merci Retriever options. However, recanalization rates have not been reported to substantially differ by generation of retriever device. Clinical outcome was evaluated with the modified Rankin Scale assessed at Day 7 or at discharge if earlier than Day 7, not the final 3-month clinical state. However, studies have demonstrated that Day 7 modified Rankin Scale score powerfully predicts the final 3-month clinical outcome. The cohort was recruited over an extended length of time and different generations of devices were used by progressively more experienced operators. However, recanalization rates did not differ substantially in earlier versus later time periods. GRE is very sensitive to motion artifact and noise, which could suggest curvature or branching where none was present. The high interrater reliability and the correlation with clinical outcomes suggest such effects were modest. The study sample size was modest and not based on a formal power analysis, limiting power to detect differences between groups, and was performed at a single center. Confirmation and extension in larger and multicenter cohorts is needed.

We conclude that irregular clot morphology on GRE MRI decreases the technical and clinical success of mechanical retrieval thrombectomy in M1 MCA occlusions. In contrast, retrieval intervention success is not strongly influenced by the size or deoxyhemoglobin content of the clot to be cleared. Irregular SVS morphology indicates the presence of anatomic factors that will make retrieval more difficult. Excessive artery tortuosity and involvement of distal branches may constrain effective delivery of the embolectomy device and its exertion of retraction force. These findings reinforce the perspective that mechanical thrombectomy and pharmacological fibrinolysis are complementary and potentially synergistic treatment strategies. The results also suggest that treatment strategies may usefully be informed by analysis of thrombus shape, size, and composition on pretreatment MRI or CT in addition to thrombus location and parenchymal tissue state. Features of target thrombus shape are important predictor variables to collect and analyze in the design of future clinical trials of endovascular therapy for acute ischemic stroke.

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References

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