Endovascular Thrombectomy for Acute Ischemic Stroke in Failed Intravenous Tissue Plasminogen Activator Versus Non–Intravenous Tissue Plasminogen Activator Patients

Revascularization and Outcomes Stratified by the Site of Arterial Occlusions

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Background and Purpose—Intracranial mechanical thrombectomy is a therapeutic option for acute ischemic stroke patients failing intravenous tissue plasminogen activator (IV tPA). We compared patients treated by mechanical embolus removal in cerebral ischemia (MERCI) thrombectomy after failed IV tPA with those treated with thrombectomy alone.

Methods—We pooled MERCI and Multi MERCI study patients, grouped them either as failed IV tPA or non–IV tPA, and assessed revascularization rates, procedural complications, symptomatic hemorrhage rates, clinical outcomes, and mortality. We also evaluated outcomes stratified by the occlusion site and final revascularization.

Results—Among 305 patients, 48 failed, and 257 were ineligible for IV tPA. Nonresponders to IV tPA trended toward a higher revascularization rate (73% versus 63%) and less mortality (27.7% versus 40.1%) and had similar rates of symptomatic hemorrhage and procedural complications. Favorable 90-day outcomes were similar in failed and non–IV tPA patients (38% versus 31%), with no difference according to occlusion site. Among patients failing IV tPA, good outcomes tended to occur more frequently in revascularized patients (47.1% versus 15.4%), although this relationship was attributable solely to middle cerebral artery and not internal carotid artery occlusions, with no difference in mortality. Among IV tPA–ineligible patients, revascularization correlated with good outcome (47.4% versus 4.4%) and less mortality (28.5% versus 59.6%).

Conclusions—The risks of hemorrhage and procedure-related complications after mechanical thrombectomy do not differ with respect to previous IV tPA administration. Thrombectomy after IV tPA achieves similar rates of good outcomes, a tendency toward lower mortality, and similar revascularization rates when stratified by clot location. Good outcomes correlate with successful revascularization except with internal carotid artery occlusions in tPA-nonresponders. (Stroke. 2010;41:1185-1192.)

Key Words: acute stroke ■ endovascular treatment ■ outcome ■ thrombectomy ■ thrombolysis

Revascularization rates in acute ischemic stroke patients with intravenous tissue plasminogen activator (IV tPA) treatment may be as low as 6% for internal carotid artery (ICA) terminus, 30% for middle cerebral artery (MCA) trunk, and 30% for basilar occlusions.1,2 Nonresponse to IV tPA is associated with poor clinical outcomes.3 Although the initial IV tPA trials did not assess revascularization,4–6 failed IV tPA patients have emerged as a subgroup with persistent occlusions,6 confirmed by noninvasive or catheter angiography.7–10 The time window defining failed IV tPA has not been established. Because revascularization after IV tPA is typically confirmed by transcranial Doppler ultrasonography within the first hour,11 this may be an appropriate window within which to consider rescue reperfusion therapies for IV tPA nonresponders.

The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI trials were prospective, multicenter, endovascular mechanical thrombectomy trials for acute ischemic stroke patients treated within 8 hours of symptom onset who were either ineligible for or failed IV tPA therapy, introducing Merci Retriever thrombectomy as an option for acute ischemic stroke patients.12–15 The Multi
MERCI trial also showed that significant hemorrhage from the combined use of IV tPA and thrombectomy (failed IV tPA group) was not significantly higher than with thrombectomy alone (non–IV tPA group). However, it is possible that the effect of nonresponse to IV tPA varies depending on occlusion location and final revascularization. We pooled data from these 2 trials and analyzed outcomes and revascularization rates in patients with failed IV tPA versus non–IV tPA, stratified by vessel occlusion.

Methods
Pooled data from the previously reported MERCI and Multi MERCI trials were analyzed retrospectively in this study. A family of Merci Retrievers (Concentric Medical, Inc.) was used to extract clot from intracranial vessels. The MERCI trial only enrolled patients who were ineligible for IV tPA. In Multi MERCI, patients receiving IV tPA (0.6 mg/kg or 0.9 mg/kg) within 3 hours of stroke onset were included if persistent vessel occlusion was confirmed by angiography. Intra-arterial (IA) tPA was only allowed in cases of thrombectomy failure after 6 passes or to treat distal embolus after successful proximal thrombectomy.

Patients were dichotomized into failed and non–IV tPA groups. Clinical variables, revascularization rates, symptomatic hemorrhage rates, clinical outcomes and mortality at 90 days, and clinically significant procedural complications were compared. Clot locations were confirmed by catheter angiography and were hierarchically categorized based on the most proximal occlusion location: ICA, MCA, or vertebro-basilar. Successful revascularization was defined as achieving thrombolysis in myocardial infarction II or III flow in all treatable vessels (ICA, M1, M2, vertebral, and basilar) documented on final post-thrombectomy angiogram. CT or MRI brain imaging was performed at baseline, 24 hours, and at any time there was a decline in patient neurological status. Symptomatic intracranial hemorrhage was defined as a point increase of ≥4 in the National Institutes of Health Stroke Scale (NIHSS) score within 24 hours with evidence of any blood on 24-hour head CT/MRI scan or any intracranial hemorrhage in which no additional NIHSS scores were available followed by patient death. Intracerebral hemorrhages were further categorized as hemorrhagic infarction type I and II, or parenchymal hematoma types I and II, as described previously. Procedure-related adverse events were adjudicated by an independent data safety monitoring board and were defined as vascular perforation, intramural arterial dissection, or embolization of a previously uninvolved territory, symptomatic hemorrhage, and access site complications requiring surgery or transfusion. Clinically significant procedural complications were defined as a procedure complication with decline in NIHSS score of ≥4 points or death, groin complication requiring surgery, or blood transfusion.

Neurological status was quantified by the NIHSS and modified Rankin Scale (mRS) at 90 days. Good outcome at 90 days was defined as mRS ≤2. Additional comparisons of revascularization, procedural complications, good outcomes, and mortality were stratified by the occlusion site, and outcomes were further stratified by final revascularization.

Categorical data were analyzed by the Fisher exact and χ² tests. Continuous data were assessed for normality by the Kolmogorov–Smirnov test; normally distributed continuous data were analyzed by Student t test, and for unevenly distributed continuous data, the Mann–Whitney U test was used. A P value <0.05 was considered statistically significant. No adjustment was made for multiplicity. Statistical analyses were performed using SAS software (version 8.2; SAS Institute Inc).

Results
Demographics
A total of 305 patients were enrolled in the 2 trials: 141 patients in MERCI and 164 patients in Multi MERCI. Forty-eight (15.7%) failed IV tPA, and 257 (84.3%) were not eligible to receive IV tPA before mechanical thrombectomy. In the failed IV tPA group, the mean age was 67.8 ± 12.7 years, and 56.3% (27 of 48) were women. Mean baseline NIHSS score was 19.1 ± 5.5. The mean IV tPA dose was 57 ± 16 mg. In the non–IV tPA group, the mean age was 67.6 ± 16.3 years, and 51.4% (132 of 257) were women. Mean baseline NIHSS score was 19.8 ± 6.7. Baseline characteristics (Table 1) for these 2 populations were similar with the exception of a higher distribution of comorbid dyslipidemia in those failing IV tPA (46.8% versus 31.6%; P=0.05).

Patients with failed IV tPA tended to have a shorter time to intervention and shorter procedure duration (4.0 versus 4.4 hours). Table 1 shows the distribution of occlusion locations, categorized hierarchically by the most proximal occlusion. The distribution of occlusion location was not different between groups, with the MCA being the most common, then the ICA, and then the vertebro-basilar system.

Revascularization Rates
The final revascularization rates were similar between groups (72.9% versus 63.0%), with comparable intergroup IA tPA use. In tPA-nonresponders, revascularization was achieved in 66.7% (12 of 18) of ICA, 74.1% (20 of 27) of MCA, and 100% (3 of 3) of vertebro-basilar occlusions (Table 2). In the non–IV tPA patients, revascularization was achieved in 61.7% (50 of 81), 61.6% (93 of 151), and 76.0% (19 of 25), respectively (Table 3). There was no intergroup difference.

Symptomatic Hemorrhage and Complications
Symptomatic hemorrhage was similar between groups (10.4% versus 8.6%). The 2.1% rate of symptomatic parenchymal hematoma II in patients with failed IV tPA was similar to the 1.9% rate in the non–IV tPA patients. Symptomatic hemorrhage rates by occlusion site were as follows for the failed and non–IV tPA groups, respectively: ICA, 11.1% for both; MCA, 11.1% versus 5.3%; and vertebro-basilar, 0% versus 20.0% (Tables 2 and 3). Symptomatic hemorrhage in ICA occlusions was similar between groups. Although all parenchymal hematoma II hemorrhages occurred with MCA occlusions in the failed IV tPA group, the rates of all symptomatic hemorrhages for both MCA and vertebro-basilar occlusions were similar to the non–IV tPA group.

Hemorrhage by Revascularization Status
In tPA-nonresponders, symptomatic hemorrhage occurred equally by revascularization status (8.6% [3 of 35] versus 15.4% [2 of 13]). In the non–IV tPA group, revascularized patients had less symptomatic hemorrhage (4.3% [7 of 162] versus 15.8% [15 of 95]; P=0.002).

Procedural Adverse Events
Both groups had a similar rate of clinically significant procedural complications (4.2% versus 6.6%). In the failed IV tPA group, procedural complications only occurred with MCA occlusions, at a rate of 7.4%. In the non–IV tPA group, clinically significant complication rates by occlusion site were: ICA, 8.6%; MCA, 4.6%; and vertebro-basilar, 12.0%.
Clinical Outcomes
The rates of good clinical outcomes (mRS, 0 to 2) at 90 days were similar in the failed and non–IV tPA groups (38.3% versus 31.3%). Good outcomes by occlusion site in the failed and non–IV tPA groups were as follows, respectively (Tables 2 and 3): ICA, 29.4% (5 of 17) versus 28.8% (23 of 80); MCA, 40.7% (11 of 27) versus 33.3% (46 of 138); and vertebro-basilar, 66.7% (2 of 3) versus 28.0% (7 of 25). The rate of good outcome at 90 days was similar between groups for each occlusion location.

Outcomes by Postprocedure Revascularization Status
In both groups, good clinical outcomes at 90 days occurred more frequently in subjects for whom revascularization was successful (Figure 1). In the failed IV tPA group, 47.1% (16 of 34) of revascularized patients had a good neurological outcome compared with 15.4% (2 of 13) of nonrevascularized patients ($P=0.09$), powered by MCA (55% versus 0%) but not ICA occlusions (27% versus 33%). In the non–IV tPA group, 47.4% (72 of 152) of revascularized patients had a good neurological outcome compared with 4.4% (4 of 91) of nonrevascularized patients ($P<0.001$). When stratified by occlusion site, a positive relationship existed between revascularization and good outcome, with the exception of ICA occlusions failing IV tPA.

Across cohorts, revascularized patients had a similar rate of good outcomes in both groups (47.1% versus 47.4%), whereas nonrevascularized patients in the failed IV tPA group trended toward better outcome than nonrevascularized patients in the non–IV tPA group (15.4% versus 4.4%;...
\(P=0.16\). Figure 2 shows 90-day good outcomes stratified by revascularization status, IV tPA status, and occlusion location.

Mortality
There was a trend toward less mortality at 90 days in the failed IV tPA group (27.7% [13 of 47] versus 40.1% [101 of 252]; \(P=0.08\)). Mortality rates in patients failing and not receiving IV tPA, by occlusion site, were as follows, respectively (Tables 2 and 3): ICA, 35.3% (6 of 17) versus 50.6% (41 of 81); MCA, 22.2% (6 of 27) versus 33.6% (49 of 146); and vertebro-basilar, 33.3% (1 of 3) versus 44.0% (11 of 25). The rate of 90-day mortality was the same between groups for each occlusion location.

Mortality by Postprocedure Revascularization Status
Nonrevascularized patients had higher rates of mortality in both the failed IV tPA and non–IV tPA groups (Figure 1). Revascularized and nonrevascularized patients in the failed IV tPA groups had similar mortality at 90 days (23.5% versus 38.5%). In contrast, the mortality in the revascularized non–IV tPA group (28.5%) was lower than those not revascularized (59.6%; \(P<0.001\)).

Across cohorts, revascularized patients had a similar rate of mortality in both groups (23.5% versus 28.5%), although among nonrevascularized patients, there was trend toward decreased mortality in the failed IV tPA cohort (38.5% versus 59.6%; \(P=0.23\)). Mortality results, stratified by revascularization status and site of vascular occlusion, are shown in Figure 3.

Discussion
The combination of IV tPA followed by mechanical thrombectomy achieves similar rates of good outcomes compared with thrombectomy alone. Previous IV tPA use does not increase symptomatic hemorrhage risk or procedure-related complications after thrombectomy. Revascularization rates are similar between the failed and non–IV tPA groups when stratified by occlusion location. Revascularized patients have better outcomes regardless of occlusion site.

Results from 2 different IV thrombolysis studies showed that the ICA, MCA, and basilar artery occlusions respond differently to thrombolitics, and revascularization was more frequent in distal occlusions.\(^1\)\(^-\)\(^2\) Revascularization and good outcomes may be improved by a combined multimodal approach.\(^7\)\(^-\)\(^10\)\(^-\)\(^16\)\(^-\)\(^21\) In a series of 69 patients (50 MCA, 18 ICA, and 1 basilar occlusion) treated by IA thrombolysis after nonresponse to IV tPA,\(^9\) the revascularization rate was 72.5%, similar to the 75% rate in another series of 16 patients with MCA and ICA occlusions.\(^8\)

Two studies also demonstrated improved revascularization with mechanical clot disruption after failed IV tPA. In 32 patients with persistent MCA or ICA occlusion after IA or IV

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** Ninety-day (90d) mRS by revascularization status in the cohort of failed IV tPA subjects (A; \(n=47\)) and the cohort that did not receive IV tPA (B; \(n=243\)). Brackets indicate the percentage of subjects achieving a good mRS score of 0 to 2. mRS scores of 3, 4 to 5, and 6 represent intermediate, poor neurological outcome, and death, respectively.

### Table 3. Revascularization Rates and Outcomes by Site of Vascular Occlusion in Non–IV tPA Patients

<table>
<thead>
<tr>
<th></th>
<th>Overall ((n=257))</th>
<th>ICA ((n=81))</th>
<th>MCA ((n=151))</th>
<th>Posterior ((n=25))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final revascularization, n (%)</td>
<td>162 (63.0%)</td>
<td>50 (61.7%)</td>
<td>93 (61.6%)</td>
<td>19 (76.0%)</td>
<td>0.35</td>
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<tr>
<td>Intracranial hemorrhage</td>
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<td>Symptomatic, n (%)</td>
<td>22 (8.6%)</td>
<td>9 (11.1%)</td>
<td>8 (5.3%)</td>
<td>5 (20.0%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Asymptomatic, n (%)</td>
<td>72 (28.0%)</td>
<td>21 (25.9%)</td>
<td>46 (30.5%)</td>
<td>5 (20.0%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Good outcome at 90 days, n (%)</td>
<td>76 of 243 (31.3%)</td>
<td>23 of 80 (28.8%)</td>
<td>46 of 138 (33.3%)</td>
<td>7 (28.0%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Mortality at 90 days, n (%)</td>
<td>101 of 252 (40.1%)</td>
<td>41 (50.6%)</td>
<td>49 of 146 (33.6%)</td>
<td>11 (44.0%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Procedural complication, n (%)</td>
<td>17 (6.6%)</td>
<td>7 (8.6%)</td>
<td>7 (4.6%)</td>
<td>3 (12.0%)</td>
<td>0.28</td>
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\(P\) values are from the likelihood ratio chi-square test.
thrombolysis, aggressive mechanical clot disruption (angioplasty or stenting, catheter or wire clot maceration, and snare device) achieved successful revascularization (thrombolysis in myocardial infarction II/III) in 87.5% of MCA occlusions and 62.5% of ICA occlusions. In 7 patients with basilar occlusions treated by combined IV tPA and mechanical thrombectomy (snares and suction devices) or IA tPA, 87.5% of patients were revascularized.

In our analysis, successful revascularization of ICA, MCA, and basilar artery occlusions was achieved with the Merci device in IV tPA nonresponders, with no difference in complications. Revascularization rates in our cohort of 66.7%, 74.1%, and 100% of ICA, MCA, and basilar occlusions, respectively, were comparable to those of previous combined approach cohorts.

We demonstrate no difference in the rates of symptomatic hemorrhage between patients either failing or ineligible for IV tPA who are subsequently treated with mechanical thrombectomy. The overall 10.4% rate of symptomatic hemorrhage in the combined IV tPA and thrombectomy group is comparable to the 8.2% rate from the pooled data of IV tPA trials. Our observed rate is also lower than the 12.2% rate observed in IA thrombolysis and 20% rate in IA plus IV thrombolysis from one multicenter study but slightly higher than the 6.2% and 5.8% rates from 2 other series of combined IA and IV thrombolysis.

In our study, an 11.1% rate of symptomatic hemorrhage was found in patients with either ICA or MCA occlusions treated with a combined approach, whereas rates of symptomatic hemorrhage after thrombectomy alone were 11.1% in ICA, 5.3% in MCA, and 20% in basilar artery occlusions. Our rates of symptomatic hemorrhage in ICA occlusions in both groups were lower than the 18.8% rate seen in 16 patients treated with mechanical clot disruption after failed IV tPA.

Patients in our study also experienced parenchymal hematoma II hemorrhage less frequently than described in Inter-

Figure 2. Ninety-day good outcomes (mRS ≤2) by revascularization and IV tPA status overall and by occlusion site. BA indicates basilar artery. The number above each bar indicates the number of patients in the cohort.

Figure 3. Ninety-day mortality by revascularization and IV tPA status overall and by occlusion site. BA indicates basilar artery. The number above each bar indicates the number of patients in the cohort.
Thrombectomy after IV tPA achieves similar rates of good clinical outcomes, a tendency toward lower mortality, and similar revascularization rates when stratified by clot location. Good outcomes, a tendency toward lower mortality, and similar clinical outcomes were similar among the different sites of occlusion, but there was a trend toward lower mortality in patients with MCA occlusions than basilar or ICA occlusions. The only group in this entire cohort with no notable relationship between good outcome and revascularization was in tPA-nonresponders with ICA occlusions. The implications of this finding are unclear at this time, although they may be a result of an uneven distribution of pre-MERCI disability or higher hemorrhage transformation rates after revascularization in this subgroup.

Previous endovascular studies have shown a strong association between successful revascularization and favorable clinical outcomes, and our analysis supports this assertion. In the non–IV tPA group, revascularized patients had a higher proportion of good outcomes and a lower rate of mortality. In addition, patients with revascularized MCA or basilar occlusions had better outcomes and less mortality than the nonrevascularized patients in both treatment groups. With ICA occlusions, good outcome was more frequent in revascularized patients in the non–IV tPA group but not in the failed IV tPA group.

This study has several limitations. Although the MERCI trial did not include failed IV tPA patients (by trial design), they contributed a greater number of non–IV tPA subjects for this analysis, facilitating a more meaningful comparison. Since the MERCI study, there has been progress in the Merci device, operator experience, and case selection, which may favor the failed IV tPA group (all from Multi MERCI). In addition, the failed IV tPA group presented earlier than the non IV tPA group, and since time from symptom onset to tPA bolus has also been shown to affect outcomes in the IV tPA trials, this may have contributed to detected differences.

In conclusion, the risk of symptomatic hemorrhage and procedural complication using the Merci Retriever after failed IV tPA is the same as using thrombectomy alone. Thrombectomy after IV tPA achieves similar rates of good outcomes, a tendency toward lower mortality, and similar revascularization rates when stratified by clot location. Good outcomes correlate with successful revascularization except with ICA occlusions in tPA-nonresponders.

Appendix 1

MERCI Trial Investigators
Wade S. Smith, MD, PhD, University of California, San Francisco was the national principal investigator.

The data safety monitoring board included: chair, Gene Sung, MD, University of Southern California; biostatistician, Phil Horney, MS; members, Tim W. Malisch, MD, University of Illinois at Chicago, Steven L. Giannotta, MD, University of Southern California, Steven Rudolph, MD, Lenox Hill Hospital, and Fady T. Charbel, MD, University of Illinois at Chicago.

The imaging core laboratory consisted of Paul Kim, MD, University of Southern California.

The writing committee included: Ronald Budzik, MD; Y. Pierre Gobin, MD; Thomas Grobelny, MD; Randall T. Higashida, MD; Chelsea Kidwell, MD; Helmi L. Lutsep, MD; Michael Marks, MD; Gary Nesbit, MD; Marilynn M. Rymer, MD; Jeffrey Saver, MD; Isaac E. Schlaug, MD; Wade S. Smith, MD; Sidney Starkman, MD; and Gene Sung, MD. The site principal investigators, coinvestigators, and study coordinators in order of enrollment are as follows. University of California at Los Angeles Medical Center (22): Sidney Starkman, MD; Gary Duckwiler, MD; Megan Leary, MD; Chelsea Kidwell, MD; Jeffrey Saver, MD; Fernando Vinuela, MD; Reza Jahan, MD; Y. Pierre Gobin, MD; and Judy Guzy, RN, Oregon Health Science University (22): Helmi Lutsep, MD; Stanley Barnwell, MD; Wayne Clark, MD; Ted Lowenkopf, MD; Elizabeth North, MD; Joseph Quinn, MD; Robert Egan, MD; Todd Kuethe, MD; John Roll, MD; George Luh, MD; Gary Nesbit, MD; and Barbara Dugan, RN, Saint Luke’s Hospital (21): Thomas Grobelny, MD; Naveed Akhtar, MD; Steven Arkin, MD; Irene Bettinger, MD; Marilyn Rymer, MD; Charles Weinstein, MD; Michael Schwartzman, MD; Christine Boutwell, MD; and Barbara Gruenenfelder, RN, Massachusetts General Hospital (11): Walter Koroshetz, MD; Johnny Pryor, MD; Neeraj Badjatia, MD; Ferdinando Buonanno, MD; Lawrence Conrad, MD; David Greer, MD; Kaul Nogueira, MD; James Rabinov, MD; Guy Rordorf, MD; Jonathan Rosand, MD; Lee Schwamm, MD; John Sims, MD; Eric Smith, MD; Brian Hoh, MD; Joshua Hirsch, MD; Cent Ayata, MD; Leigh Hochberg, MD; and Joanie Cacciola, RN, NY Presbyterian Hospital—Columbia (11): John Pile-Spellman, MD; Sean Lavine, MD; Sundeep Mangla, MD; Philip Meyers, MD; and Leslie Schmidt, MD, The Stroke Center at Hartford Hospital (11): Isaac Silverman, MD; Stephen Ohki, MD; Gary Speigel, MD; Martha Ahlquist, MD; Philip Meyers, MD; and Leslie Schmidt, NP, The Stroke Center at Hartford Hospital (11): Isaac Silverman, MD; Stephen Ohki, MD; Gary Speigel, MD; Martha Ahlquist, MD; Philip Meyers, MD; and Leslie Schmidt, NP. The Stroke Center at Hartford Hospital (11): Isaac Silverman, MD; Stephen Ohki, MD; Gary Speigel, MD; Martha Ahlquist, MD; Philip Meyers, MD; and Leslie Schmidt, NP. The Stroke Center at Hartford Hospital (11): Isaac Silverman, MD; Stephen Ohki, MD; Gary Speigel, MD; Martha Ahlquist, MD; Philip Meyers, MD; and Leslie Schmidt, NP.

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Appendix 2

Multi MERCI Trial Investigators
Wade S. Smith, MD, PhD, University of California, San Francisco, was the international principal investigator.

The data safety monitoring board included: chair, Gene Sung, MD, MPH, University of Southern California; biostatistician, Phil Hormel, MS; and members, Tim W. Malisch, MD, Alexian Brothers Medical Center; Steven Rudolph, MD, Maimonides Medical Center; and Arun Amar, MD, Stanford University.

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Disclosures

Gary R. Duckwiler is a scientific advisor and stockholder in Concentric Medical, Inc. Gary Walker is an employee of Concentric Medical, Inc.

References


Endovascular Thrombectomy for Acute Ischemic Stroke in Failed Intravenous Tissue Plasminogen Activator Versus Non–Intravenous Tissue Plasminogen Activator Patients: Revascularization and Outcomes Stratified by the Site of Arterial Occlusions
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for the MERCI and Multi MERCI Investigators

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The article, “Endovascular Thrombectomy for Acute Ischemic Stroke in Failed Intravenous Tissue Plasminogen Activator Versus Non–Intravenous Tissue Plasminogen Activator Patients: Revascularization and Outcomes Stratified by the Site of Arterial Occlusions” by Shi et al (Stroke. 2010;41:1185–1192) included an error in Appendix 2. Dr Fawaz Al-hussain’s name and affiliation were incorrect. The correct information appears below as well as in the current online version.

The investigator’s name should appear as Fawaz Al-hussain, MD, King Saud University.
大脑中动脉主干闭塞与第二段闭塞机械取栓术的临床结局：
脑缺血机械取栓（MERCI）和多中心MERCI试验的汇总分析

Clinical Outcomes in Middle Cerebral Artery Trunk Occlusions Versus Secondary Division Occlusions After Mechanical Thrombectomy: Pooled Analysis of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI Trials

Zhong-Song Shi, MD; Yince Loh, MD; Gary Walker, PhD; Gary R. Duckwiler, MD; for the MERCI and Multi-MERCI Investigators

背景和目的: 血管内血管再通术对急性缺血性卒中患者有益,但其益处是否在大脑中动脉(MCA)第二段(M2)闭塞与MCA主干(M1)闭塞存在差异尚不清楚。本文对由血管造影术确定的MCA M1闭塞患者与单独M2闭塞患者,用Merci Retriever装置进行机械取栓后的血管再通状态和临床结局进行了比较。

方法: 回顾性分析了脑缺血机械取栓(MERCI)和多中心MERCI试验中MCA卒中的汇总数据。患者分成两组: MCA M1闭塞和单独M2闭塞,评价了两组的基线特征、血管再通率、出血率、并发症、结局和死亡率。

结果: MERCI和多中心MERCI试验中的178例MCA闭塞患者,84.3%为M1闭塞,15.7%为单独M2闭塞。单独M2闭塞患者与M1闭塞患者相比有更高的血管再通率,更少的平均机械疏通次数,且具有更短平均操作时间的趋势。尽管在所有患者中,M2的结局从数字上看是优于M1,但M2与M1组之间在症状性出血、有临床意义的操作不良反应、90天良好结局或90天的死亡率等方面无统计学差异。在多因素分析中,最终的血管再通是90天良好结局最强的预测因素。

结论: MCA M1闭塞和单独M2闭塞的患者在接受机械取栓后可以达到相对高的血管再通率和良好的临床结局。而事实上,与M1闭塞的患者相比,单独M2闭塞患者具有更高的血管再通率,需要更少的机械疏通次数且没有增加并发症。

关键词: 急性脑卒中 血管内治疗 大脑中动脉 结局 取栓术

(Stroke.2010;41:953-960. 林森 译 曾进胜 校)
栓 (MERCI) 和多中心 MERCI 第一部分试验的汇总分析已经证明，颈内动脉闭塞的患者可以达到相对较高的血管再通率 [17]。然而，它并没有评估 MCA M2 闭塞与 MCA M1 闭塞的机械性血管再通的结局差异。本研究的目的是评价经过血管造影确定的 MCA M1 闭塞与单独 M2 闭塞的急性缺血性卒中患者使用 Merci Retriever 装置进行机械取栓术是否会影响其血管再通状态。同时本研究也旨在通过血管再通状态比较不同组 (M1 vs. M2) 中所有 MCA 闭塞患者使用机械取栓术的安全性和有效性。

方法
MERCI 与多中心 MERCI 试验的汇总数据对确定的急性 MCA 闭塞中进行了回顾分析。汇总数据包括总共 305 例缺血性卒中患者，其中 141 例来自于 MERCI 试验，164 例来自于多中心 MERCI 试验。这两个试验的详细计划书在之前的研究所已经作了描述 [13-17]。简单来说，纳入试验的患者不是不适合进行 IV tPA 治疗，就是经过导管法血管造影确认接受 IV tPA 治疗后闭塞的血管未再通。试验使用一类 X 系列和 L5 Merci Retriever 装置 (Concentric Medical, Inc, Mountain View, Calif) 从管腔中取出血栓试图来使闭塞的颅内血管再通。第一代装置 (X4、X5 和 X6 Retriever) 在两个试验都有应用，而第二代装置 (L5 Retriever 装置) 只用在多中心 MERCI 试验中。IA tPA 被允许在治疗中装置 6 次疏通依然失败或成功施行近端血栓去除术后，溶解装置无法靠近的远端血栓时应用。两个研究方案中，任何部位的闭塞都不允许使用血管成形术或支架。

本研究纳入经数字减影血管造影确定的单独 MCA M1 和 / 或 M2 闭塞的患者。分析中排除了那些 ICA/MCA 串联闭塞或 ICA-T 闭塞的患者。患者分为 MCA M1 闭塞组和单独 MCA M2 闭塞组。成功的血管再通定义为经数字减影血管造影所确认的所有的应治疗的血管行治疗后达到心肌梗塞溶栓 (TIMI) 血流分级的 II 级或 III 级。CT 或 MRI 扫描在基线、24 小时以及患者神经状态下降的任何时候进行。根据 ECASS 试验的分类，大脑内出血分为出血性梗死 I 和 II 型或脑实质血肿 I 和 II 型。症状性出血是指 24 小时内 NIHSS 分数增加 ≥ 4 分，且 24 小时内头部 CT/MRI 扫描发现有出血的证据，或在除和之外无更多合适的 NIHSS 分数提示基线时没变化，但患者死亡于某的任何颅内出血。操作相关的不良事件由独立的数据安全与监督委员会裁定，且被定义为血管穿孔、动脉壁内夹层、或之前未受累区域栓塞、症状性出血，以及需要外科手术或输血处理的操作区并发症。临床上操作相关的严重并发症是指 NIHSS 降低 ≥ 4 分的手术并发症或死亡、需要外科手术或输血处理的腹股沟区并发症。

神经状态由 NIHSS 和 30 及 90 天的改良 Rankin 评分 (mRS) 来评定。各闭塞组患者的评估内容包括血管再通率、出血转化率、临床上严重的操作相关并发症、90 天临床结局及死亡率。90 天良好的结局被定义为 mRS ≤ 2。由于单独 M2 闭塞样本较小，M1 和 M2 闭塞的数据被汇总起来并进行多元 logistic 回归分析以此来确定 90 天良好结局的独立预测变量。对血管再通状态分层后进行临床特点、并发症和结局的比较。组与组之间差异的比较采用 95% CI。如果这个区间不包含 0，则组之间的差异在 P = 0.05 时被认为是有意义的。虽然这是一个回顾性的亚组分析，但所考虑的两个组的样本大小应该是在两组间结局比较上至少具有 80% 的效能检出 28% 的绝对差异和 50% 的效能检出 20% 的绝对差异。单因素分析确定 90 天的良好结局的独立预测变量，其中所有 Wald χ² P < 0.2 变量都将纳入多元 logistic 回归模型去确定 90 天良好结局的预测变量。该模型按前进 / 后退逐步回归的方法来建立，且基于 χ² 的统计值，变量为 0.05 时进入模型而在 0.10 时离开该模型。在主要效应的模型建立后，任何有意义的双向交互条件存在的假设用似然比 χ² (G2) 统计进行检测。最终的模型由 Hosmer 和 Lemeshow 检验进行拟合度的检测。P < 0.05 认为有统计学意义。本文中的统计分析是使用 SAS 软件来完成的。(8.2 版本 ; SAS 公司)

结果
MCA 卒中患者的人口学特征
在 MERCI 和多中心 MERCI 试验中，对 178 例经血管造影确定为 MCA 闭塞的患者进行了治疗。其中 80 例患者来自 MERCI 试验，98 例来自多中心 MERCI 试验。平均年龄 69.0 岁 (SD 15.7)，103(57.9%) 为女性患者。平均基线 NIHSS 分数是 18.8 分 (SD 5.8)，范围为 9 至 40 分。队列中 27(15.2%) 例患者接受了 IV tPA 治疗并在进行机械取栓前均未再通；剩余的 151 例患者则不适合接受 IV tPA 治疗。患者从卒中起病至器械进入动脉的平均时间为 4.3 小时 (SD 1.6)，范围为 0.7 至 10.8 小时。

178 例患者中，84.3%(n=150) 表现为单独 MCA M1 闭塞或 M1/M2 合并的闭塞，15.7%(n=28) 表现为单独 MCA M2 闭塞。在 150 例 MCA M1 闭塞患者中，73 例来自 MERCI 试验，77 例来自多中心 MERCI 试验。在 28 例 MCA M2 闭塞患者中，7 例来自 MERCI 试验，21 例来自多中心 MERCI 试验。
有统计学差异。MCA M1 闭塞患者可能更易患冠状动脉病, 且凝血酶原时间更短, 收缩压更低 (表1)。在M1组中, 血红蛋白 Hb 和 M2 血管治疗组中使用较少。在M2组中, 最常用的是 L5 装置 (53.6%)，紧接着是 X6(28.6%)，之后是 X5(25.0%)，未使用 X4。两组中，7% 的患者在评定其基线 NIHSS 分数时应用了镇静剂。尽管与 M1 组 (52.5%) 相比，M2 组 (73.1%) 患者存在明显较高的比例的严重或完全性失语，但两组中 NIHSS 的运动评分部分无统计学差异。

血管再通率

经 Merci 治疗后的即时血管再通率 (TIMI II/III 血流分级 ) 在 MCA M1 组与单独 M2 组中分别为 46.0% 和 71.4%(表 2)。包括接受联合治疗的患者在内，单独 MCA M2 组的最终血管再通率高于 MCA M1 组 (82.1% vs. 60.0%)。另外，相对于 MCA M1 闭塞，单独 MCA M2 闭塞所需的疏通次数更少 (2.1 vs. 3.1) 并具有平均操作时间更短的趋势 (1.6 vs. 1.8 小时)。

良好结局和死亡率

尽管单独 MCA M2 闭塞组的良好结局率与 MCA M1 闭塞组相比，从数字上看具有较高的比例 (40.7% vs. 33.3%)，但两组 90 天良好临床结局 (mRS ≤ 2) 并无统计学差异 (表 2)。一般来说，远端动脉闭塞预后有较好的结局，但在本系列中，左侧 M2 闭塞占 67.9%，而左侧的 M1 闭塞只有 47.3% (有认为左侧大脑半球梗死患者长期预后差，而本组 M2 闭塞左侧更多)。

两组 90 天的死亡率也无统计学差异，然而，从数字上看，单独 MCA M2 闭塞组比 MCA M1 闭塞组低 (25.9% vs. 32.9%；表 2)。

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出血并发症

两组颅内出血率无统计学差异 (M1 组 36.7% vs. M2 组 42.9%)。同样，两组的显著性出血率也无统计学差异 (M2 组 3.6% vs. M1 组 6.7%)。从数字上看，M2 闭塞患者的有临床不良操作相关不良反应比 M1 闭塞更低 (3.6% vs. 5.3%)。

多元 Logistic 回归分析

与先前的 MERCI 试验分析相似，年龄、基线 NIHSS 和操作后的血管再通状态均为 90 天良好临床结局的预测因素。具体结果见表 3。最终的血管再通状态是良好结局最强的独立预测因素 (OR 为 30.91)。
血管再通与血管未再通患者的比较

在所有 MCA 闭塞的患者中，血管再通的比未再通的患者具有更高比例的 90 天良好结局、更低的死亡率和短期性出血、疏通次数更多和操作时间更短（表 4）。年龄、NIHSS 分数、危险因素和入院时实验室检查结果等基线特征在最终血管再通与未再通患者之间是相似的。

讨论

本研究结果表明应用 Merci 装置进行机械取栓后，MCA M1 闭塞或单独 M2 闭塞患者能达到较高的血管再通率和良好的临床结局。单独 M2 闭塞患者的血管再通率更高，并具有平均操作时间更短的趋势。

越来越多的证据显示血管再通率和良好临床结局受血管闭塞位置的显著影响。IV 和 IA 溶栓的研究发现，溶栓治疗对 MCA 闭塞比对 ICA 和基底动脉闭塞更有效果 [9,14]。与先前的 MERCI 和多中心 PROACT II 研究分析中 MCA M1 闭塞的血管再通率相似，低至基底动脉闭塞的 8% 的血管再通率 [17,18]。而单独 MCA M2 闭塞 82% 的血管再通率则明显高于其他位置的闭塞。

本研究中机械取栓治疗 MCA 闭塞后，63.5% 的血管再通率高于其他实验中只用 IV 溶栓治疗的患者。有研究报告，起病 6 小时内 18% 的 MCA 闭塞性栓塞患者可能出现由经颅多普勒超声确定的自发再通 [19]。在 PROACT II 研究中，卒中起病后 6 到 8 小时，大约 18% 的接受静脉肝素治疗后的急性 MCA 闭塞患者可能会出现经颅多普勒超声确定的自发再通 [5]。另一项基于 82 例 MCA 主干闭塞患者的研究，采用 TIMI 血流分级和 MR 血管造影确定自发再通，结果显示起病后 24 小时，IV 溶栓组比未溶栓者具有更高的自发血管再通率 [20]。IV 溶栓组和未溶栓组的局部和全部血管再通率（TIMI II/III）分别为 38.5% 和 24% [20]。

尽管已发表的 IV 溶栓试验中，MCA M1 与单独 M2 闭塞的血管再通状态差异未有报道，但本研究中单独 MCA M2 闭塞的血管再通优于 M1 闭塞，与最近两篇 IV 溶栓研究一致 [8,19]。根据经颅多普勒超声标准，MCA M2 与 M1 闭塞患者接受 IV tPA 治疗后，2 小时的完全再通率分别为 44.2% (50/113) 和 30% (49/163) [19]。另一项采用 CT 血管造影和/或经颅多普勒超声监测的研究，IV tPA 24 小时后 53% 的 M1 闭塞患者 (n=32) 和 68% 的 M2 闭塞患者 (n=19) 达到完全再通 [19]。对 IV tPA 后进行取栓治疗与只进行取栓治疗的血管再通率比较超出了我们目前研究的范围。取栓前的 IV tPA 治疗会软化凝块，促进 Merci 装置穿透凝块和取回。对不同位置动脉闭塞采用 IV tPA 后再行机械取栓治疗，这种疗法产生的潜在血管再通的益处在以后的研究中进行探讨。

与 PROACT II 研究中接受治疗的 121 例患者相比，本研究的中位基线 NIHSS 和平均年龄均高于 PROACT II (基线 NIHSS：18 vs. 17；年龄：69 岁 vs. 64 岁)，本组患者与其有相似的血管再通率 (MERCII 多中心 MERCII 63.5% vs. PROACT II 66%)。90 天良好结局 (34.5% vs. 40%) 和死亡率 (31.8% vs. 25%)，以及更低的症状性出血 (6.2% vs. 10.0%) [9]。最近的一项研究全面比较了 MERCII 多中心 MERCII
和 PROACT 的数据。在对 MCA 闭塞患者使用尿激酶 IA 溶栓治疗的研究中，血管造影显示有 57 例患者为 MCA M1 闭塞，21 例为 M2 闭塞，22 例为 M3 或 M4 闭塞。与我们的研究相比，该研究报告了更高的血管再通率（76%），更好的 90 天良好结局（68%），更低的死亡率（10%）以及相似的症状性出血（7%）。该研究还显示良好的结局与入院时低的卒中评分（中位基线 NIHSS，14）和更小的年龄（平均年龄，61 岁）相关。

IA 溶栓研究中，MCA 闭塞患者血管再通情况由血管造影记录；然而，MCA M1 闭塞对单独 M2 闭塞分层的血管再通状态和临床结局并未在这些随机临床试验中报告。在一个对卒中患者使用尿激酶 IA 溶栓治疗的研究中，147 例 MCA M1 闭塞和 57 例 M2 闭塞患者的血管再通率 (TIMI II 级和 III 级) 分别为 77.6% 和 63.2%。在该研究中，单独 M2 闭塞与 M1 闭塞相比，具有更低的血管再通率，这与我们研究的结果不同。目前尚不清楚这个差异是否与 IA 溶栓和机械取栓不同的血管内治疗方式相关。

<table>
<thead>
<tr>
<th>年龄中位数，年 (IQR)</th>
<th>血管再通 (n=113)</th>
<th>血管未再通 (n=65)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>女性</td>
<td>54.9%(62/113)</td>
<td>63.1%(41/65)</td>
<td>0.34</td>
</tr>
<tr>
<td>高血压</td>
<td>75.2%(85/113)</td>
<td>81.5%(53/65)</td>
<td>0.36</td>
</tr>
<tr>
<td>糖尿病</td>
<td>28.6%(32/112)</td>
<td>18.5%(12/65)</td>
<td>0.15</td>
</tr>
<tr>
<td>血管偏斜</td>
<td>34.6%(37/107)</td>
<td>35.1%(20/57)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>冠状动脉病变</td>
<td>45.5%(51/112)</td>
<td>29.0%(18/62)</td>
<td>0.04</td>
</tr>
<tr>
<td>充血性心力衰竭</td>
<td>21.6%(24/111)</td>
<td>21.5%(14/65)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>吸烟</td>
<td>17.9%(19/106)</td>
<td>19.3%(11/57)</td>
<td>0.84</td>
</tr>
<tr>
<td>频率</td>
<td>40.7%(46/113)</td>
<td>50.0%(32/64)</td>
<td>0.27</td>
</tr>
<tr>
<td>血液系统疾病</td>
<td>6.4%(7/110)</td>
<td>6.3%(4/64)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>周围血管疾病</td>
<td>11.8%(13/110)</td>
<td>12.7%(8/63)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>血糖中位数，mg/dL(IQR)</td>
<td>119.0(105-146)(113)</td>
<td>118.0(103-143)(63)</td>
<td>0.56</td>
</tr>
<tr>
<td>收缩压中位数，mmHg(IQR)</td>
<td>143.0(130-166)(112)</td>
<td>152.5(138-164)(64)</td>
<td>0.21</td>
</tr>
<tr>
<td>舒张压中位数, mmHg(IQR)</td>
<td>74.0(63-82)(112)</td>
<td>77.0(65-89)(64)</td>
<td>0.23</td>
</tr>
<tr>
<td>基线 NIHSS 中位数 (IQR)</td>
<td>17.0(14-22)(113)</td>
<td>19.0(15-23)(65)</td>
<td>0.18</td>
</tr>
<tr>
<td>左侧 MCA 闭塞</td>
<td>52.2%(59/113)</td>
<td>47.7%(31/65)</td>
<td>0.64</td>
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<tr>
<td>起病至股动脉穿刺时间中位数，小时 (IQR)</td>
<td>4.1(3.1-5.3)</td>
<td>4.5(3.5-5.6)</td>
<td>0.19</td>
</tr>
<tr>
<td>Merci 前静脉 tPA 失败</td>
<td>17.7%(20/113)</td>
<td>10.8%(7/65)</td>
<td>0.28</td>
</tr>
<tr>
<td>动脉溶栓治疗</td>
<td>37.2%(42/113)</td>
<td>23.1%(15/65)</td>
<td>0.07</td>
</tr>
<tr>
<td>静脉动脉溶栓治疗</td>
<td>46.9%(53/113)</td>
<td>32.3%(21/65)</td>
<td>0.06</td>
</tr>
<tr>
<td>自身血症</td>
<td>8.5%(9/107)</td>
<td>8.3%(1/64)</td>
<td>0.67</td>
</tr>
<tr>
<td>血糖中位数，mg/dL(IQR)</td>
<td>116.0(105-146)(113)</td>
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在 M1 闭塞和单独 M2 闭塞中，成功的血管再通与更高的效益风险比相关。单独 M2 闭塞患者比 M1 闭塞患者更有利的临床结局倾向。单独 M2 闭塞的这些有益作用也被一项 IV tPA 溶栓治疗患者的多普勒超声研究证实。卒中介入治疗试验 I 和 II 的汇总数据显示单独 M2 闭塞患者其良好的临床结局独立于血管再通状态之外，因为尽管存在不完全的再通和再灌注，部分 M2 闭塞患者的仍获得良好的临床结局。尚不清楚单独 M2 闭塞患者其良好的临床结局倾向是否与更高的血管再通率或更小的缺血区域相关联。可以推测 M2 与 M1 闭塞中，更多的侧支循环是某一既定病人达到良好临床结局的可能潜在因素。尽管 M2 组相比 M1 组，存在具有更好结局的倾向，但这个差异可能因更高的左侧 M2 闭塞频率而抵消（67.9% vs. 47.3%）。研究的纳入标准要求必须具有高的基线 NIHSS 分数，因此优势半球的 M2 闭塞更可能入组。
近，另一个可从缺血性卒中患者颅内动脉中移出凝块的治疗工具 -Penumbra 系统，已经获美国食品药品监督管理局批准通过[26]。这个血管内的血管再通治疗也对卒中患者有益，但是它对于单独 M2 卒中及 M1 卒中的效果还未明确报道。另外，颅内放置自胀式支架是对急性 MCA M1 闭塞的血管再通所做的替代选择，但其在单独 MCA M2 卒中中的应用却很有限[27]。

本研究存在一些局限。回顾性收集两个无对照试验的研究数据并由此进行事后分析。纳入两个试验的 M2 闭塞患者的样本量小于 M1 闭塞患者。由于大部分 M2 闭塞患者来自于多中心 MERCI 试验，因此 M2 闭塞组更好的结局可能是因为操作者从不断增加的经验中所得知识的以及多中心 MERCI 中应用的新一代 Merci Retriever 装置的合并的结果。病例的选择可能存在偏差。两组基线卒中的严重度是相似的，这表明只有严重神经功能缺陷的 MCA M2 闭塞患者才能被纳入这两个试验。MCA M2 闭塞组可能纳入的患者多；基线时即有大面积缺血性病灶的患者；已接受 IV tPA 治疗或伴无效再灌注自发诱导再通的早期 MCA M1 或曾有过 ICA/MCA 串联状或 ICA 终端闭塞的患者。这可能解释了类似的 3 月临床结局而不只是组与组之间卒中的不平衡。最后，不能从 MERCI 或多中心 MERCI 中获取基线抗血栓的应有分布，也不能进行比较。

总之，MERCI 和多中心 MERCI 试验的汇总数据回顾分析结果显示，单独 MCA M2 闭塞患者与 MCA M1 闭塞患者相比，可以从更高的血管再通率中获益，而且对 Merci Retriever 装置进行再通要求更少的疏通次数。此外，基于 MCA 闭塞患者汇总数据的多变量分析，证明了最终的血管再通是操作后 90 天良好结局最强的预测因素。

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