Pattern of Response of National Institutes of Health Stroke Scale Components to Early Recanalization in the CLOTBUST Trial

Robert Mikulik, MD, PhD; Ladislav Dusek, PhD; Michael D. Hill, MD; Eva Fulep, MD; James C. Grotta, MD; Marc Ribó, PhD; Carlos Molina, PhD; Andrei V. Alexandrov, MD; for the CLOTBUST Investigators

Background and Purpose—Early recanalization is the likely mechanism by which intravenous thrombolysis improves stroke outcomes. Limited data exist on the patterns of early recovery of various brain functions.

Methods—Data from the Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA (CLOTBUST) trial was used to determine time-related trends in neurological function recovery, as measured by National Institutes of Health Stroke Scale (NIHSS) components at baseline, 30, 60, 90, 120 minutes, and 24 hours. Repeated-measures ANOVA was used to compare patients with complete recanalization versus no or partial recanalization of the middle cerebral artery (MCA) at 120 minutes from tissue plasminogen activator bolus. The correlation structure of the NIHSS was analyzed with multivariable factor analysis. The ability of individual components to diagnose recanalization was assessed with area under the receiver operating characteristic curves.

Results—Altogether, 113 patients from the CLOTBUST trial had complete follow-up NIHSS scores available. All received 0.9 mg/kg IV tissue plasminogen activator within 3 hours of symptom onset (mean age 69±12 years; 58% men; median NIHSS 16; complete MCA recanalization 27%). All NIHSS components attributable to MCA occlusion contributed with varying degrees to the decrease of the total NIHSS score after MCA recanalization. NIHSS components responded in 2 major and mutually independent clusters representing left and right brain functions. The best performing component in diagnosing recanalization was gaze deviation (area under the receiver operating characteristic curve=0.80), but its results were similar to the total NIHSS score (area under the receiver operating characteristic curve=0.75).

Conclusions—All neurological functions, impaired because of MCA occlusion, recovered after recanalization, although not to the same extent. The total NIHSS score is more useful than the individual components in detecting MCA recanalization. (Stroke. 2010;41:466-470.)

Key Words: stroke recovery ■ reperfusion ■ outcomes ■ TCD ■ NIHSS

In acute stroke patients, an improved outcome at 3 months, as measured on the modified Rankin Scale, is associated with early recanalization.1–5 Previous work demonstrated that early recanalization leads to measurable improvements in total National Institutes of Health Stroke Scale (NIHSS) scores within 120 minutes after the start of treatment with intravenous thrombolysis in the Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA (CLOTBUST) trial.3,6

Whether brain reaction to recanalization is global or that some brain functions recover faster than others is unknown. It has been speculated that certain components of the NIHSS score may be more sensitive to arterial recanalization than others; in addition, component scores may show greater sensitivity than the total NIHSS score.7 We sought to determine the pattern of recovery of different brain functions as measured by individual components of the NIHSS score.

Patients and Methods

Data from the CLOTBUST trial3,8 were used to determine the presence of, and time-related trends in, neurological function recovery, as measured by NIHSS component scores, in patients who achieved complete recanalization versus partial or no recanalization at 120 minutes from tissue plasminogen activator (tPA) bolus. The CLOTBUST trial was a phase II, multicenter, randomized clinical trial that determined the safety and signal-of-efficacy of adjuvant therapy with continuous transcranial Doppler (TCD) monitoring

Received September 3, 2009; final revision received November 4, 2009; accepted November 27, 2009.

From the Neurology Department (R.M.), Masaryk University, St. Anne’s Hospital, Brno, Czech Republic; Stroke Program (R.M., E.F., J.C.G., A.V.A.), University of Texas Health Science Center at Houston; Institute of Biostatistics and Analyses (L.D.), Masaryk University, Brno, Czech Republic; Department of Clinical Neurosciences and the Departments of Community Health Science and Medicine (M.D.H.), University of Calgary, Calgary, Canada; Cerebrovascular Unit (M.R., C.M.), Vall d’Hebron Hospital, Barcelona, Spain; and Comprehensive Stroke Center (A.V.A.), University of Alabama, Medical School, Birmingham.

Correspondence to Robert Mikulik, MD, PhD, Department of Neurology, Masaryk University, St. Anne’s University Hospital, Pekářská 53, 656 91, Brno, Czech Republic. E-mail mikulik@hotmail.com

© 2010 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.109.567263

466
Response of NIHSS Components to Recanalization

versus sham TCD monitoring. All patients had acute middle cerebral artery (MCA) occlusions diagnosed by TCD and were treated with tPA (0.9 mg/kg IV) within a 0- to 3-hour window of symptom onset. Complete recanalization of the MCA was determined by TCD using the previously validated Thrombolysis in Brain Ischemia flow grading system. 1 No angiographic method such as CT or magnetic resonance angiography was used to confirm the artery occlusion. However, TCD accuracy for the detection of complete recanalization versus persisting occlusions of the MCA was >90% compared with digital subtraction angiography in a prospective validation study. 9 Complete recanalization was defined as a Thrombolysis in Brain Ischemia flow grade of 5 in the symptomatic artery. The NIHSS score was determined at the baseline, at 30, 60, and 120 minutes, and 24 hours after the start of treatment by physicians who did not know about the vessel recanalization. Patients with unknown NIHSS scores at 120 minutes (11 patients) were excluded from this analysis.

The NIHSS contains 15 components, which we labeled as follows: 1a, level of consciousness; 1b, questions; 1c, commands; 2, gaze; 3, visual fields; 4, facial palsy; 5a, left motor arm; 5b, right motor arm; 6a, left motor leg; 6b, right motor leg; 7, ataxia; 8, sensory; 9, language; 10, dysarthria; and 11, extinction/neglect.

Statistical Analysis

The response pattern of the NIHSS components to early recanalization was analyzed using recanalization versus no or partial recanalization as the main stratifying factor in 4 ways: (1) analysis of time-related changes of the NIHSS component scores within 24 hours; (2) analysis of the proportion of patients whose NIHSS component scores improved at 120 minutes; (3) analysis of the relationship between early clinical improvement, measured as the number of components that improved at 120 minutes, and recanalization and the 3-month outcome; and (4) analysis of the correlation structure of the NIHSS components.

Repeated-measures ANOVA, based on both a general linear model as well as rank-transformed data, was performed to calculate whether statistical differences in the NIHSS component scores within the first 24 hours existed between patients who achieved complete recanalization versus partial or no recanalization. Based on the results of the nonparametric repeated-measures ANOVA test, we divided the NIHSS components as follows: A, “responding” to recanalization if significant improvement occurred within the first 24 hours on a repeated-measures ANOVA test; B, “partially responding” if no significant improvement occurred but the interaction term time-recanalization was significant; and C, “not responding” if neither was significant.

Fisher exact test was used to analyze differences between categorical data (eg, to compare whether any improvement in the score of each component of the NIHSS [expressed both as improvement by ≥1 point or normalization of score] occurred between patients with recanalization versus partial or no recanalization at 120 minutes). To demonstrate the ability of the best-performing component to diagnose complete recanalization, the area under the receiver operating characteristic curve, a measure of the accuracy of a diagnostic test ranging from 0.5 (no diagnostic ability) to 1.0 (perfect diagnostic ability), was calculated.

Finally, to analyze the correlation structure of the NIHSS, a multivariable factor analysis based on a matrix of Spearman rank correlation coefficients was applied. 10 The aims of factor analysis have been described in previous publications on NIHSS analysis. 11 In brief, factor analysis is a method for reducing the number of parameters in a data set. It can be used to determine whether a larger number of observed variables (eg, 13 components of the NIHSS) can be explained by a smaller number of calculated variables called factors. In our study, the factor analysis was performed to analyze whether there were some simple patterns (factors) by which all NIHSS components responded to recanalization. The factors or patterns of recanalization may be related to biological phenomena, such as right or left brain functions. 11

First, to analyze how many factors (patterns of recanalization) could significantly contribute to the explanation of the changes in all the NIHSS components in response to recanalization, a Scree plot was generated. A Scree plot shows how much variance in all NIHSS components can be explained by each successive factor (see Figure 2).

Second, to demonstrate which NIHSS components responded in mutual association (were correlated) in response to recanalization and how these changes of NIHSS components were related to the factors, a factor loading plot was constructed (see Figure 3).

A value of P < 0.05 was considered statistically significant, and all tests were 2-tailed. Analyses were performed using Statistica 8, SPSS 16.0, and R-project 2.8.0.

Results

A total of 113 patients in CLOTBUST had complete follow-up NIHSS scores available (mean age 69 ± 12 years; 58% men; median NIHSS score 16 [range 4 to 34]; and complete MCA cerebral artery recanalization 27%).

There were no statistical differences (Mann–Whitney U test) in the baseline scores of any NIHSS component (data not shown). The recovery patterns of the NIHSS components are shown in Figure 1 and were as follows: responding items, 1b (questions); 1c (commands); 2 (gaze); 3 (visual fields); 4 (facial palsy); 5a (left motor arm); 6a (left motor leg); 6b (right motor leg); 7 (ataxia); 8 (sensory); 9 (language); 10 (dysarthria); and 11 (extinction/neglect); and nonresponding items, 1a (level of consciousness); and 7 (ataxia).

The proportion of patients who achieved improvements by ≥1 point or complete recovery of NIHSS component scores at 120 minutes is provided in Table 1. As shown, one of the best-responding components to recanalization was 2: best gaze, 50% of patients completely recover their impaired gaze at 120 minutes if they achieved recanalization compared with 13% if they achieved partial or no recanalization (P = 0.002). The area under the receiver operating characteristic curve to diagnose complete recanalization was 0.80 (95% CI, 0.58 to 0.91) for 2 (best gaze), which was similar to the performance of the total NIHSS score (area under the receiver operating characteristic curve = 0.75 [95% CI, 0.57 to 0.86]).

Table 2 shows how early improvement, measured as the number of NIHSS components that improved, was related to early recanalization and the 3-month outcome. From the table, it is evident that the more NIHSS component scores improved by ≥1 point or normalized at 120 minutes, the higher the rate of recanalization at 120 minutes (P < 0.01) and modified Rankin Scale score 0 to 1 at 3 months (P < 0.01). For example, of the patients for whom no component improved by ≥1 point at 120 minutes, 24% had recanalization at 120 minutes and 19% had a modified Rankin Scale score of 0 or 1 at 3 months. Of the patients for whom 2 or 3 components improved by ≥1 point, 43% had recanalization at 120 minutes, and 36% had a modified Rankin scale score of 0 or 1 at 3 months.

A factor analysis to analyze the correlation structure of the NIHSS yielded a Scree plot (Figure 2) that demonstrates that 2 factors accounted for a large amount (52%) of variation in the data set. Using 2 factor solutions, Figure 3 demonstrates the overall correlation structure of the changes of the NIHSS component scores, with a 2D plot of factor loadings. Figure 3 demonstrates that except for 1a (level of consciousness) and 7 (ataxia), all other components were at least partially intercorrelated in response to recanalization. The reaction of the components attributable to right hemisphere stroke (5a + 6a + 11) was
Discussion
In our study, we found that overall, nearly all NIHSS component scores contributed to the decrease of the total NIHSS score after early recanalization. This finding supports the criterion validity of the NIHSS as the measure of recanalization. However, some components, such as language (aphasia), right motor symptoms, and neglect, responded less well than others. Our data support previous work showing that the speed of recovery was variable for different neurological deficits. However, the spectrum of nonresponding deficits somewhat differs in our study because according to previously published data, the deficits not responding to tPA infusion were aphasia, facial palsy, and dysarthria.

In our study, the best single responding component was 2 (best gaze). The difference in the score for best gaze between groups with and without recanalization was evident 30 minutes after the start of tPA treatment and increased with time. This finding is concordant with a previous study in which complete recovery of gaze deviation was also the very first neurological deficit that recovered after tPA treatment. We infer that different volumes of brain tissue are necessary for the manifestation of neurological deficits attributable to ischemia and its recovery as a result of recanalization. Thus, early recovery of forced gaze deviation after recanalization implies that a large region of ischemic dysfunction is needed for this phenomenon to occur; recovery of even some brain tissue results in the resolution of this physical finding. However, in our study, we cannot directly confirm this conclusion because we did not use any tissue blood flow imaging methods to document what regions of the brain were affected by ischemia.

In our previous analysis on the same data set, we demonstrated that an NIHSS score reduction of ≥40% at 120 minutes, compared with baseline, had a sensitivity of 74%
Table 1. Percentage of Patients Achieving Improvement by ≥1 Point or Normalization of the Score for Every NIHSS Component at 120 Minutes Compared With Baseline, Stratified by Recanalization

<table>
<thead>
<tr>
<th>NIHSS Components</th>
<th>Percentage of Patients Who Improved Score by ≥1 Point at 120 Minutes</th>
<th>Percentage of Patients Who Normalized* Status at 120 Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a. Level of consciousness (LOC)</td>
<td>8 13 0.479</td>
<td>7 13 0.452</td>
</tr>
<tr>
<td>1b. LOC questions</td>
<td>10 37 0.002</td>
<td>7 20 0.079</td>
</tr>
<tr>
<td>1c. LOC commands</td>
<td>15 43 0.002</td>
<td>11 30 0.020</td>
</tr>
<tr>
<td>2. Best gaze</td>
<td>30 57 0.015</td>
<td>13 50 0.002</td>
</tr>
<tr>
<td>3. Visual</td>
<td>18 57 0.002</td>
<td>13 33 0.026</td>
</tr>
<tr>
<td>4. Facial palsy</td>
<td>18 67 0.001</td>
<td>6 20 0.065</td>
</tr>
<tr>
<td>5. Right motor arm</td>
<td>18 27 0.427</td>
<td>8 30 0.011</td>
</tr>
<tr>
<td>5. Left motor arm</td>
<td>16 50 0.001</td>
<td>5 17 0.054</td>
</tr>
<tr>
<td>6. Right motor leg</td>
<td>18 33 0.122</td>
<td>8 20 0.103</td>
</tr>
<tr>
<td>6. Left motor leg</td>
<td>13 33 0.042</td>
<td>6 17 0.127</td>
</tr>
<tr>
<td>7. Limb ataxia</td>
<td>1 3 0.462</td>
<td>1 3 0.462</td>
</tr>
<tr>
<td>8. Sensory</td>
<td>21 27 0.608</td>
<td>13 27 0.151</td>
</tr>
<tr>
<td>9. Best language</td>
<td>17 37 0.039</td>
<td>4 3 0.998</td>
</tr>
<tr>
<td>10. Dysarthria</td>
<td>7 43 0.001</td>
<td>4 23 0.003</td>
</tr>
<tr>
<td>11. Extinction/neglect</td>
<td>12 17 0.538</td>
<td>6 13 0.243</td>
</tr>
</tbody>
</table>

R− indicates patients without complete recanalization at 120 minutes; R+, patients with complete recanalization at 120 minutes.

*Patients who had positive score at baseline for NIHSS component and who completely recovered on this component at 120 minutes.

Table 2. Percentage of Patients Who Achieved Complete Recanalization at 120 Minutes or a mRS Score of 0 to 1 at 3 Months as a Function of the No. of NIHSS Components That Improved by ≥1 Point or Normalized at 120 Minutes

<table>
<thead>
<tr>
<th>No. of components that improved by ≥1 point at 120 minutes</th>
<th>Complete Recanalization, %</th>
<th>mRS Score 0 to 1, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>21 24 19</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>20 40 25</td>
<td></td>
</tr>
<tr>
<td>2+3</td>
<td>28 43 36</td>
<td></td>
</tr>
<tr>
<td>4 and more</td>
<td>44 84 55</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of components that normalized at 120 minutes</th>
<th>Complete Recanalization, %</th>
<th>mRS Score 0 to 1, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>43 37 26</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>26 50 27</td>
<td></td>
</tr>
<tr>
<td>2+3</td>
<td>24 63 50</td>
<td></td>
</tr>
<tr>
<td>4 and more</td>
<td>20 90 65</td>
<td></td>
</tr>
</tbody>
</table>

n indicates No. of patients who achieved improvement of 0, 1, 2+3, and 4 or more components; mRS, modified Rankin Scale.

and a specificity of 80% for identifying complete recanalization. Based on the current analysis, no single component performed better than the total NIHSS score. Scoring best gaze had a diagnostic ability similar to that of the total NIHSS score in diagnosing complete recanalization, but it cannot be used in diagnosis if gaze deviation is absent before treatment. Our data further demonstrate that patients with a higher number of improved or normalized components at 120 minutes had both a higher rate of recanalization and a better outcome at 3 months.

Therefore, a complete neurological examination and a total NIHSS score is the universal and best guide for physicians to clinically assess whether recanalization has been achieved.

A factor analysis of the baseline NIHSS score in the National Institute of Neurological Disorders and Stroke (NINDS) trial and the Clomethiazol for Acute Stroke Study-Ischemic (CLASS-I) trial.
showed that ataxia and consciousness contributed little to the total NIHSS score.11,13 Our data similarly showed that neither level of consciousness nor ataxia were useful measures of recanalization. However, our finding may be because of the population studied; all patients had MCA occlusion, which generally does not lead to ataxia and is less likely to lead to a disturbed level of consciousness than posterior circulation ischemia. Therefore, the nature of our data does not allow us to conclude whether ataxia and consciousness are responding to recanalization. For the same reason, our data cannot be used to support the exclusion of some components from the NIHSS, as was suggested in previous articles.14–16

Another finding of the factor analysis of NINDS and CLASS-I studies data was that there were 2 factors underlying the NIHSS, representing left and right brain function.11,13,17 Our data (Figure 2, Scree plot) also showed that 2 factors accounted for the majority (52%) of the total variance in our data set. Adding a third factor would explain only 9% more of the variance. Therefore, we used a 2-factor solution and constructed factor loadings in the plot to show how the changes of NIHSS components were related to each other and to the factors (Figure 3). Figure 3 demonstrates that NIHSS components responded to recanalization in 2 major and mutually independent clusters (5a+6a+10+11 and 1b+1c+5b+6b+9), representing left and right brain functions. The improvement of component 10 (dysphonia) correlated with dominant hemisphere strokes because its testing is affected by aphasia. From Figure 3, it is also evident that motor (5a+6a and 5b+6b) and cortical (10+11 and 1b+1c+5+9) responses on both sides of the brain responded closely together. Our data simply reflect the simultaneous recovery of brain functions that are anatomically proximate and affected by one occluded artery and its recanalization.

A limitation of our study is that the population included only patients with MCA occlusions, and therefore, our results may not apply to patients with small vessel strokes or posterior circulation strokes. Conversely, we used a homogenous patient population to study those brain areas affected by MCA occlusion. Although impairment of these brain areas is not reflected in some NIHSS components, such as ataxia, the response of the majority of the NIHSS components can be well studied in our patient population. The other advantage is that the data on recanalization by TCD were blinded to clinical examination in the CLOTBUST trial.

In conclusion, we showed that all NIHSS components affected by MCA occlusion are responsive to recanalization within 120 minutes from the start of the treatment. The components not affected by MCA occlusion were ataxia and level of consciousness. The best response was gaze deviation, but it did not perform better than the total NIHSS in diagnosing complete recanalization. Therefore, a total NIHSS score is the best guide for physicians to clinically assess whether recanalization has been achieved. Our data validate the NIHSS as a measure of recanalization in acute stroke. Ultimately, our study improved our understanding of the reaction of brain to recanalization.

Acknowledgments
We thank Anne Johnson for her editorial assistance.

Sources of Funding
This study was supported by a grant from IGA MH CR NS10106-3/2008.

Disclosures
A.V.A. served as principal investigator of the CLOTBUST trial and received funding from NINDS and Genentech, Inc. for this study. He is also on the Genentech, Inc. speakers bureau.

References
Pattern of Response of National Institutes of Health Stroke Scale Components to Early Recanalization in the CLOTBUST Trial

Robert Mikulik, Ladislav Dusek, Michael D. Hill, Eva Fulep, James C. Grotta, Marc Ribo, Carlos Molina and Andrei V. Alexandrov
for the CLOTBUST Investigators

Stroke. 2010;41:466-470; originally published online February 4, 2010;
doi: 10.1161/STROKEAHA.109.567263

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/41/3/466

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/