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

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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
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 was significant. 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 24: 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 complete recanalization, 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, 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 generated. A Scree plot shows how much variance in all NIHSS components can be explained by each successive factor (see Figure 2).
independent from the reaction of components attributable to left hemisphere stroke (1b + 1c + 5b + 6b + 9).

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 resolu-

Graphical representation of NIHSS component scores across time, showing the patterns of recovery with and without recanalization.
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.

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></td>
<td>R−</td>
<td>R+</td>
</tr>
<tr>
<td>1a. Level of consciousness (LOC)</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>1b. LOC questions</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>1c. LOC commands</td>
<td>15</td>
<td>43</td>
</tr>
<tr>
<td>2. Best gaze</td>
<td>30</td>
<td>57</td>
</tr>
<tr>
<td>3. Visual</td>
<td>18</td>
<td>57</td>
</tr>
<tr>
<td>4. Facial palsy</td>
<td>18</td>
<td>67</td>
</tr>
<tr>
<td>5. Right motor arm</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>6. Left motor arm</td>
<td>16</td>
<td>50</td>
</tr>
<tr>
<td>7. Right motor leg</td>
<td>18</td>
<td>33</td>
</tr>
<tr>
<td>8. Limb ataxia</td>
<td>13</td>
<td>33</td>
</tr>
<tr>
<td>9. Sensory</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td>10. Best language</td>
<td>17</td>
<td>37</td>
</tr>
<tr>
<td>11. Dysarthria</td>
<td>7</td>
<td>43</td>
</tr>
<tr>
<td>12. Extinction/neglect</td>
<td>12</td>
<td>17</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</td>
<td>24</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>2+3</td>
<td>28</td>
<td>43</td>
</tr>
<tr>
<td>4 and more</td>
<td>44</td>
<td>84</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</td>
<td>37</td>
</tr>
<tr>
<td>1</td>
<td>26</td>
<td>50</td>
</tr>
<tr>
<td>2+3</td>
<td>24</td>
<td>63</td>
</tr>
<tr>
<td>4 and more</td>
<td>20</td>
<td>90</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.

Figure 2. The Scree plot shows the eigenvalues plotted over the number of factors (an eigenvalue is the amount of variance explained by one more factor). It is apparent that from the third factor on, the line becomes more flat, which means that each successive factor is accounting for smaller and smaller amounts of the total variance (eg, the first factor accounted for 32% of variance, the second factor for 20%, the third factor for 9%, and the fourth factor for 8% of variance). The plot thus demonstrates that 2 factors accounted for the majority (52%) of variation in the data set.

Figure 3. Factor loadings in plot for 2 factor solutions (therefore it is a 2D plot) demonstrating the correlation structure of changes in the NIHSS components at 120 minutes from baseline in patients with complete recanalization. Dots in the plot represent analyzed parameters (ie, a change in the individual NIHSS component score in response to recanalization). The plot shows how changes in NIHSS scores are related to each other and to the 2 factors. The closer a given parameter is to 0, the smaller its influence in explaining the pattern of reaction to recanalization and vice versa (eg, 5a and 6a have a higher influence because of a better reaction to recanalization than 5b and 6b). Components close to each other (eg, 5a to 6a or 1b to 1c) have similar responses to recanalization and are mutually correlated. Components perpendicular to each other have independent reactions (eg, 5a and 6a are independent of 5b and 6b, which is because of different occlusion sides).
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 (dysarthria) 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.

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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
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