Importance of Early Ischemic Computed Tomography Changes Using ASPECTS in NINDS rtPA Stroke Study

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Background and Purpose—The importance of early ischemic change (EIC) on baseline computed tomography (CT) in the decision to thrombolyze the patient with acute ischemic stroke has been controversial. ASPECTS is a semiquantitative scale that scores the extent of EIC within the middle cerebral artery territory. We examined whether ASPECTS could be a treatment modifier by systematically reviewing the CT scans in the NINDS rtPA Stroke Study.

Methods—Six hundred eight of the 624 CT scans were available and of sufficient quality. One of 2 teams (n=3 each) of expert ASPECTS readers evaluated each scan for an ASPECTS value using a consensus score approach. Each team was blind to all clinical information except symptom side and blind to follow-up imaging and outcome information. ASPECTS values were stratified before analysis. Multivariable logistic regression was used to determine if an ASPECTS by treatment interaction existed on treatment response, outcome, and intracerebral hemorrhage risk.

Results—A total of 57.2% (348 of 608) of scans showed EIC with an ASPECTS <10. ASPECTS dichotomized into 8 to 10 and <8 did not have a treatment-modifying effect on good outcome but showed a trend to lower mortality at 90 days with tPA (relative risk 0.67, 95% confidence interval 0.41 to 1.06, P=0.10). ASPECTS 8 to 10 were associated with a trend to larger benefit of tPA with a number needed to treat (NNT) of 5 versus ASPECTS 3 to 7 with a NNT of 8.

Conclusion—There was no evidence of treatment effect modification by the baseline ASPECTS value in the NINDS rtPA Stroke Study. Therefore, exclusion of patients for thrombolysis within 3 hours of symptom onset based on EIC is not supported by our data. There is a trend to reduced mortality and increased benefit to rtPA if the baseline CT scan is favorable (ASPECTS >7). (Stroke. 2005;36:2110-2115.)

Key Words: computed tomography ■ diagnostic imaging ■ ischemia ■ thrombolytic therapy ■ stroke, acute

The efficacy of tissue plasminogen activator (rtPA) for acute ischemic stroke within 3 hours of symptom onset was demonstrated in the NINDS rtPA Stroke Study. Among multiple baseline clinical factors, only early time to treatment predicted a better outcome with treatment. Computed tomography (CT) was used to exclude intracranial hemorrhage (ICH) before the allocated treatment was administered. The extent of early ischemic change (EIC) on the baseline CT did not influence patient eligibility in the trial. Patients benefited independent of stroke severity. However, a small proportion of patients developed symptomatic intracerebral hemorrhage (ICH).

There is accumulating evidence suggesting that EIC on CT before the administration of acute stroke therapies can predict both functional outcome and the risk of ICH. However, in patients solely treated within 3 hours of symptom onset, the NINDS investigators showed a 31% EIC prevalence and EIC was not a modifier of the treatment effect. The detection of EIC was low when compared with other studies, although this may be the result of earlier CT scanning in the 0- to 3-hour window trial compared with the other 0- to 6-hour trials.

Furthermore, the concept that the risk of ICH after thrombolysis is related to the degree of EIC has been recently challenged. We hypothesized that: (1) the use of Alberta Stroke Programme Early CT Scale (ASPECTS) on the baseline CT scan from The NINDS rtPA Stroke Study would increase the detection rate of EIC; and (2) a differential treatment effect with rtPA could be detected dependent on the extent of EIC in the middle cerebral artery (MCA) territory as quantified by ASPECTS.

Methods

The NINDS rtPA Stroke Study was a multicenter, prospective, double-blind, placebo-controlled, randomized trial of intravenous rtPA for acute ischemic stroke performed from January 1991 through October 1994. Methodology of the trial has been previously published.

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A noncontrast CT scan of the brain was mandatory before enrollment in the study to rule out ICH. All CT scans were performed on third- or fourth-generation CT scanners. All the baseline CT scans were obtained with 10-mm slice thickness and consisted of the following technical factors: 120kV, 170mA, matrix size 512×512.3 second scanning time for posterior fossa, and 2-second scanning time for supratentorial compartment. Window levels and window width were optimized for gray/white matter distinction. (S. Patel, personal communication, 2003)

For this study, all baseline CT scans were reevaluated retrospectively by two of 3 groups of 3 expert CT readers using ASPECTS. Follow-up CT scans were not reevaluated. Hemorrhage detection9 and infarct volume measurement (methodology described in Appendix 2 of reference 10)10 were already available from previous review of follow-up CT scans. This studies’ readers were kept blind from this and all other follow-up CT information, however. ASPECTS was assessed by systematically scoring each of 10 regions on the scan and assigning a score of one for a normal and 0 for a region showing signs of ischemia. Signs of ischemia are defined as x-ray hypoattenuation, loss of the gray–white boundary (which is the result of x-ray hypoattenuation of the gray matter), and/or effacement of cortical sulci. ASPECTS is only scored for acute changes. The regions are subdivided into 2 levels, which involve the basal ganglionic axial cuts and supraganglionic cuts. All axial cuts are used to examine individual regions. The individual regions include subcortical structures (lentiform nucleus, caudate nucleus, and posterior limb of internal capsule) and cortical structures (insula, M1 thalamus, M6; see Figure 1 in reference 5).5 The only clinical information given to reviewers of the scans was symptom-side. Symptom-side information was derived from the baseline NIHSS score based on side of predominant motor weakness, aphasia, or hemispatial neglect. Readers remained blinded to treatment assignment.

Review occurred over a 2-day period with all scans randomly assigned to each group of 3 readers. One member from each group switched teams the second day to ensure uniform rating between groups. Three raters agreed on a consensus ASPECTS value after discussing each scan. All members of ASPECTS review had experience using the ASPECTS methodology with a detailed tutorial performed before initiating reading.

Favorable outcome was defined as a modified Rankin scale of 0 to one at 3 months, Barthel index ≥95, and NIHSS ≤1. Symptomatic ICH was defined as neurologic deterioration within 24 hours of treatment associated with ICH.

### Statistical Analysis

The primary outcomes were excellent functional outcome defined as a 90-day modified Rankin scale score less than 2, the occurrence of symptomatic ICH, and death. Secondary outcomes were excellent neurologic outcome defined as a 90-day NIHSS score less than 2 and good functional activity recovery defined as a 90-day Barthel Index score of 95 or greater. ASPECTS was dichotomized at less than or equal to 7 or greater than 7, and trichotomized into greater than 7, 3 to 7, and less than 3. The primary hypothesis was that a differential treatment effect on the primary outcome existed according to whether the baseline ASPECTS was greater than, less than, or equal to 7. The power to detect an interaction, estimated as described by Hsieh,11 with an odds ratio for the interaction term greater than or equal to 1.25 was low at 21%. Secondary analyses considered alternate outcomes using the ASPECTS dichotomy (≥7/≤7) as well as the ASPECTS trichotomy (>7/3 to 7/1≤3). Trichotomizing the ASPECTS allowed for more detailed understanding of the ASPECTS ≤7 group. Trends in outcomes were assessed using Cuzick nonparametric test for trend across ordered groups. We used derived additive interaction terms as described by Rothman12 to help explain the relationship between ASPECTS and treatment as predictors of outcome and mortality. The use of such terms arguably makes the analysis more directly clinically relevant.

The data are described with standard descriptive statistics and stratified analysis. Logistic regression was used to assess whether an ASPECTS by treatment interaction was present for the primary outcomes using a likelihood ratio test. One-way analysis of variance was used to assess the relationship among lesion volume by ASPECTS categories. The number-needed-to-treat and the number-needed-to-harm were calculated as the inverse of the absolute risk difference accordingly, and 95% confidence intervals for each are reported.13

### Results

Of the 624 patients enrolled in the trial, 620 CT scans were available for interpretation and 608 CT scans were deemed of sufficient quality to allow for reasonable interpretation of EIC. There were 308 patients treated with placebo and 300 patients treated with rtPA. No differences in baseline characteristics or outcome were detected between 16 patients excluded and 608 included in this study.

The distribution of ASPECTS values were skewed. In 43.9% (n=267) of baseline CT scans, ASPECTS values were 10 (no evidence of EIC in MCA territory). Seven of these patients had an ASPECTS value of 10 and either evidence of a new posterior cerebral artery territory (n=5) or a new brain stem stroke (n=2). Therefore, 57.2% of patients (n=348) showed evidence of EIC. The median ASPECTS value was 9 (interquartile range 7 to 10) and was the same value in both the 0 to 90 and 91 to 180 cohorts (P=0.892). The median ASPECTS value in the patients showing ischemia in greater than one third of the MCA territory was 5 (interquartile range 3 to 8) compared with 9 (interquartile range 7 to 10) in patients with ischemia in less than one third of the MCA territory (P<0.001). A weak negative correlation (P=−0.31) between ASPECTS and stroke severity (baseline NIHSS) was observed. Age and baseline serum glucose were not correlated with ASPECTS.

In the primary analysis, there was no evidence of a multiplicative interaction between the ASPECTS value and rtPA treatment in a simple logistic regression model when ASPECTS was dichotomized at ≤7 versus >7. There was no evidence for masking confounding by the baseline NIHSS score, age, baseline glucose, or stroke onset to treatment time. This lack of multiplicative interaction was also true for additional outcomes of NIHSS 0 to one, Barthel Index >95, and occurrence of symptomatic ICH. However, the risk of death with rtPA treatment compared with placebo tended to be lower in the ASPECTS 8 to 10 group (12% vs 18%; relative risk [RR]=0.67, 95% confidence interval 0.41 to 1.06; P=0.10). No mortality benefit was observed in the rtPA arm with ASPECTS 0 to 7 group (RR=1).

To better understand this trend to lower mortality, we trichotomized the ASPECTS score into 3 groups based on extent of early change (ASPECTS >7, 3 to 7, <3). Prognostically, across the 3 groups, a lower ASPECTS category predicted poorer outcome (mRS 2 to 6) (P=0.015), increased mortality (P=0.002), but not increased symptomatic ICH (P=0.15). When death or symptomatic ICH were considered as a composite outcome, poorer outcome with lower ASPECTS category remained significant (P=0.003). In every case, rtPA treatment improved the proportion of patients achieving an excellent functional outcome. In the ASPECTS >7 group, a mortality benefit is seen with rtPA treatment and in the ASPECTS <3 group, mortality was increased with rtPA compared with placebo (Figure 1).
Examination of the absolute risk differences (Figure 1) among patients with baseline ASPECTS >7 showed improved outcomes (48% vs 29%; 3 month mRS ≤1) with rtPA when compared with placebo. Among patients with more extensive EIC (ASPECTS 3 to 7), improved outcome was observed (36% vs 23%; 3 month mRS ≤1). When the baseline CT scan revealed very extensive EIC (ASPECTS ≤3), no benefit from rtPA could be demonstrated (Table 1). Two of the 5 deaths in the treated group with ASPECTS ≤3 were associated with symptomatic ICH compared with none in the placebo group (Table 2).

An exploratory analysis using the most powerful measures of effectiveness (NIHSS ≤2 at 24 hours or NIHSS 15-point improvement from baseline to 24 hours) of rtPA in the NINDS rtPA Stroke Study revealed no evidence of a multiplicative treatment by baseline CT ASPECTS interaction when the baseline CT ASPECTS was dichotomized at ≤7/7.

There was a negative but nonlinear correlation between baseline ASPECTS and final infarct volume in both the placebo and rtPA groups. Final infarct volumes were different across the 3 categories of ASPECTS (P=0.002) but not according to treatment assignment (Table 3).

**Discussion**

The results from the present study do not support the concept that quantifying EIC using a standardized validated scoring system on the baseline noncontrast CT scan are critical to intravenous thrombolysis decision-making in the first 3 hours from acute stroke symptom onset. The thrombolytic treatment effect is robust. In this regard, our study is consistent with the recently published reevaluation of the NINDS rtPA Stroke Study for EIC on CT scans using the one third MCA rule, which found benefit from tPA even if one third MCA territory is involved.

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**TABLE 1. Outcome Analysis Based on ASPECTS Dichotomy and Trichotomy—Absolute Risk Reduction (ARR) and Number Needed to Treat (NNT) Calculated by 1/ARR With Confidence Intervals**

<table>
<thead>
<tr>
<th>ASPECTS</th>
<th>ARR (%)</th>
<th>NNT for mRS 0–1 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8–10</td>
<td>19.5 (10.2–28.8)</td>
<td>5 (3–10)</td>
</tr>
<tr>
<td>0–7</td>
<td>12.0 (–0.002–24.2)</td>
<td>8 (440 NNH to 8 to 8 NNT)</td>
</tr>
<tr>
<td>3–7</td>
<td>13.3 (0.3–26.3)</td>
<td>8 (4–356)</td>
</tr>
<tr>
<td>0–2</td>
<td>10.0 (–0.09–28.6)</td>
<td>10 (11 NNH to 8 to 3 NNT)</td>
</tr>
</tbody>
</table>

*This NNT analysis based on mRS 0–1 at 3 months. Confidence interval notation is based on the method suggested by Altman. The interpretation of the ASPECTS 0–2 cohort is that the range of benefit is as few as 3 to an infinite number of patients need to be treated to benefit one but as few as 11 to an infinite number needed to be treated to result in net harm. CI indicates confidence interval.

**TABLE 2. Risk of Symptomatic ICH Based on Baseline ASPECTS Value Dichotomized and Trichotomized**

<table>
<thead>
<tr>
<th>ASPECTS</th>
<th>rtPA Symptomatic ICH Rate, 95% CI (%)</th>
<th>Placebo Symptomatic ICH Rate, 95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8–10</td>
<td>5.0 (2.4–9.0)</td>
<td>1.0 (0.1–3.5)</td>
</tr>
<tr>
<td>0–7</td>
<td>6.1 (2.2–12.7)</td>
<td>0</td>
</tr>
<tr>
<td>3–7</td>
<td>4.5 (1.2–11.1)</td>
<td>0</td>
</tr>
<tr>
<td>0–2</td>
<td>20.0 (1.6–38.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

*The high risk of hemorrhage occurs in the ASPECTS 0–2 group.
However, this study did reveal value in EIC detection because careful evaluation of the CT scan has useful in predicting likelihood of benefit. Those patients with ASPECTS 8 to 10 had 12% mortality in the rtPA arm and 18% in the placebo arm, suggesting a subgroup of patients with a trend to reduced mortality if rtPA administered. No mortality reduction was seen in the tPA-treated patients in the ASPECTS 3 to 7 subgroup (Figure 1). The extent of ischemic change (ASPECTS score) also predicts the likelihood of benefit with a trend to lower number needed to treat with ASPECTS >7 (ARR 19%, NNT=5) than ASPECTS 3 to 7 (ARR 13%, NNT=8). Patients with a baseline CT ASPECTS <3 had a nonsignificantly higher rate of mortality and symptomatic ICH with rtPA. This observation must be tempered by the small numbers (3% of patients enrolled in the trial), which had such extensive EIC. This study does not provide sufficient evidence to recommend that patients be excluded from rtPA on the basis of extensive EIC (ASPECTS <3).

The European Co-operative Acute Stroke Study (ECASS-1) trial first identified the possible importance of EIC. They identified a trend to increased mortality with tPA treatment of patients with EIC visible in greater than one third of the MCA territory in patients treated up to 6 hours after symptom onset. This led to an assumption of a qualitative interaction between treatment effect and EIC and the recommendation that patients should not receive thrombolysis if CT scan patients may not be ideal targets for thrombolysis, whereas EIC manifested as cortical sulcal effacement or very subtle hypoattenuation as a result of thrombolysis when intracranial occlusion absent (no penumbra). In PROACT-2, all high ASPECTS value patients (small regions of core) had such MCA occlusion (large penumbral areas), thus explaining the robust effect of intraarterial prourokinase at high ASPECTS values.

Another very plausible explanation for the lack of effect modification in the current study is that EIC may be a less critical factor for treatment decisions in the early stages of ischemia when time is the most critical factor influencing benefit from rtPA. In PROACT-2, patients were treated 3 hours later than NINDS rtPA at a time when EIC may represent a more irreversible injury.

The relative importance of the individual characteristics of EIC (sulcal effacement, parenchymal hypoattenuation, and distortion of gray white differentiation) on CT is not known. The frequently seen subtle signs of ischemia on CT scan may not always represent irreversible injury. Regions of ischemic brain showing definite hypoattenuation as a manifestation of tissue edema are likely but not always irreversibly damaged (core of ischemia and therefore not salvageable with thrombolysis), whereas EIC manifested as cortical sulcal effacement or very subtle hypoattenuation as a result of hypocperfusion on baseline CT scan more likely can reverse. Recent work has suggested that sulcal effacement without hypodensity is the result of increased cerebral blood volume and reperfused areas of brain. These areas have not consistently resulted in infarction on follow-up imaging. Modification of ASPECTS methodology may be required to ignore the potentially reversible EIC finding of sulcal effacement. CT technology and CT imaging techniques used at the time in the NINDS rtPA Stroke Study may have limited our observations. We have previously suggested 5-mm axial cuts should be used for acute stroke CT imaging to allow visualization of all ASPECTS regions on more than one slice.
NINDS rtPA Stroke Study used 10-mm axial cuts at baseline to shorten CT imaging time, which in the early 1990s was relatively slow compared with current high-speed CT scanners (S. Patel, personal communication). Despite this limitation, the ASPECTS readers considered most available scans to be of good to excellent quality. Adequate scanning power, good window width, and window leveling for filming were used in a majority of scans.

Poor outcome still occurred in some patients despite a high ASPECTS score. In some cases, this may be because ASPECTS does not address ischemic change in other vascular territories such as the anterior cerebral artery, posterior cerebral artery, or vertebrobasilar system. Alternately, ASPECTS may not fully reflect the core of ischemia. Newer contrast-enhanced CT techniques such as blood-pool analysis from CT angiography source images or CT perfusion studies are now available using multislice CT scanners and may more accurately identify “core” and “penumbra” than conventional CT and provide better identification of salvageable ischemic brain. Similarly, multimodal magnetic resonance imaging techniques are also available as alternatives for thrombolysis decision-making.

The results of the current study suggest that EIC evaluation by ASPECTS improves early ischemic change detection. Higher ASPECTS values are associated with a greater magnitude of benefit from rtPA and a trend to reduced mortality. ASPECTS does not, however, identify patients who should or should not receive thrombolytics. CT ischemic change may be more relevant for thrombolytic decision-making in the 3- to 6-hour time window after stroke onset given the results of the ECASS-I trial and PROACT-2 ASPECTS analysis. Regions of CT ischemic change may become irreversibly damaged if treatment is delayed. Early treatment appears more critical to thrombolysis and overwhelms the significance of early CT changes.

References

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