CT Angiographic Source Images Predict Outcome and Final Infarct Volume Better Than Noncontrast CT in Proximal Vascular Occlusions

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Background and Purpose—Alberta Stroke Programme Early CT Score (ASPECTS) is widely used for assessment of early ischemic changes in acute stroke. We hypothesized that CT angiography source image (CTA-SI) ASPECTS correlates better with baseline National Institutes of Health Stroke Scale score, final ASPECTS and neurological outcomes when compared with noncontrast CT ASPECTS.

Methods—We studied patients presenting with acute ischemic stroke and identified proximal arterial occlusions (internal carotid artery, middle cerebral artery M1, and proximal middle cerebral artery M2) from the Calgary CT Angiography database. CT scans were independently read by 3 observers for baseline noncontrast CT ASPECTS, CT angiography source image ASPECTS, and follow-up ASPECTS. Details of demographics and risk factors were noted. A modified Rankin Scale score ≥2 at 3 months was considered a favorable outcome.

Results—We identified 261 patients with proximal occlusions for analysis. We found a better correlation between CT angiography source image ASPECTS and follow-up ASPECTS (Spearman correlation coefficient $r=0.65$; 95% CI, 0.58 to 0.72; $P<0.001$) than between noncontrast CT ASPECTS and follow-up CT ASPECTS ($r=0.46$; 95% CI, 0.36 to 0.55; $P<0.001$). CT angiography source image ASPECTS correlated better with baseline National Institutes of Health Stroke Scale and 24-hour National Institutes of Health Stroke Scale when compared with noncontrast CT ASPECTS ($P<0.001$). In an adjusted model including both CT angiography source image ASPECTS and noncontrast CT ASPECTS, CT angiography source image ASPECTS was associated with good outcome (OR, 2.30; 95%; CI, 1.16 to 4.53), whereas noncontrast CT ASPECTS was not (OR, 1.54; 95%; CI, 0.84 to 2.82). Among imaging parameters, CT angiography source image ASPECTS was the only independent predictor of good outcome (OR, 2.29; 95%; CI, 1.16 to 4.53).

Conclusions—CT angiography source image ASPECTS correlates better with baseline stroke severity, is a better predictor of final infarct extension, and independently predicts neurological outcome than noncontrast CT ASPECTS. (Stroke. 2011;42:1575-1580.)

Key Words: ASPECTS score ■ CTA-SI ■ infarct ■ ischemic stroke ■ outcome

Early ischemic changes visible on noncontrast CT (NCCT) are felt to represent regions of brain with irreversible ischemic injury. The extent of such changes has aided clinicians in decision-making for intravenous thrombolysis. The Alberta Stroke Programme Early CT Score (ASPECTS) is an alternative approach to semiquantitatively score the extent of early ischemic change within the middle cerebral artery (MCA) territory. ASPECTS has been shown to correlate with outcomes in several clinical trials. The CT angiography (CTA) source images (CTA-SIs) provide another way to evaluate irreversibly injured brain from ischemia. CTA-SI detects regions of brain with hypometabolism due to severe reductions in cerebral blood volume or due to long delays in contrast arriving at the ischemic brain as opposed to cytotoxic edema on NCCT. Visually, the hypometabolism is appreciated as a clearer difference between the...
normal and the abnormal brain (Figure 1; Supplemental Figure I; http://stroke.ahajournals.org). CTA-SI may be able to detect the blood volume abnormalities before the threshold is reached for changes to be appreciated on NCCT. CTA-SI appears to be as sensitive as diffusion-weighted imaging in detecting acute ischemia. We have previously shown that CTA-SI was superior to NCCT for predicting final infarct extent but was unable to show a definitive relationship with clinical outcomes. Similarly, another study of 51 patients confirmed that CTA-SI has higher sensitivity than NCCT for detecting early irreversible ischemia and correlates better with final infarct volume. The present study aimed at studying the correlation of baseline NCCT ASPECTS and CTA-SI ASPECTS with follow-up ASPECTS, National Institutes of Health Stroke Scale (NIHSS), and outcome. We hypothesized that CTA-SI correlates better than NCCT ASPECTS with these parameters.

Methods
This is a retrospective case analysis of a CTA database at a comprehensive stroke center (Foothills Medical Centre, Calgary, Canada). The Calgary CTA database is a Human Research and Ethics Board-approved retrospective study. The patients were categorized into M1-MCA, M2-MCA, and distal internal carotid artery (carotid T, L) occlusions. We excluded patients with distal occlusions beyond the M2 segment. Details of patient demographics and baseline and 24-hour NIHSS were noted. Modified Rankin Scale (mRS) score at 3 months was used for outcome analysis. A mRS score ≤2 was considered a favorable outcome. Where 3-month mRS was not available, we used discharge mRS to impute 3-month outcome.

Image Acquisition
NCCT and CTA were acquired using a standardized protocol. Standard nonhelical NCCT was performed on a multislice CT scanner (GE Medical Systems or Siemens) using 120 kV, 170 mAs with 5-mm slice thickness. Continuous axial slices parallel to the orbitomeatal line were obtained from the skull base to vertex. NCCT was followed by CTA with a helical scan technique. Acquisitions were obtained after single bolus intravenous contrast injection of 90 to 120 mL nonionic contrast media into an antecubital vein at 3 to 5 mL/s. Imaging was autotriggered by the appearance of contrast media in the ascending aorta. Standard coverage included area from the arch to the vertex. Source images were reconstructed at 1.25-, 2.5-, or 4.0-mm thickness in axial planes at half-thickness intervals. NCCT completed between 1 and 7 days after the stroke onset was used for follow-up ASPECTS interpretation.

Image Analysis
Images were viewed on a wide-screen high-resolution monitor with adequate window and level settings to maximize the contrast produced by small attenuation difference between the normal and ischemic tissue. NCCT brain was evaluated for focal parenchymal hypodensity, loss of gray–white differentiation, and scored as per ASPECTS scoring. The method of ASPECTS scoring has been further clarified to require evaluation of all axial cuts within the MCA territory and exclude isolated cortical swelling (see Puetz et al for details). CTA-SI was viewed at the window and levels where maximum contrast between normal and ischemic tissue can be obtained. Both the baseline NCCT and CTA were evaluated independently by 3 readers. A good interrater agreement has been previously shown from our institute. The readers were blinded to the entire clinical data and outcome except the side of involvement. The reading of NCCT ASPECTS and CTA-SI ASPECTS was spaced adequately over days to keep the assessment blinded as much possible.

Statistical Analysis
ASPECTS scores are displayed as medians with interquartile ranges. Correlations between ASPECTS scores are by Spearman correlation coefficient with confidence limits calculated using Fisher z transformation. Correlations are graphically displayed as bubble plots, where the area of the bubble is proportional to the number of observations at each point. Univariate associations with good outcome, defined as mRS scores 0 to 2, are determined by Fisher exact test, t test, or Wilcoxon rank sum test as appropriate. For analyses of good outcome, we excluded data of 10 patients who had mRS ≥2 at baseline. A “good scan” was defined as a priori as ASPECTS score 8 to 10 based on previous observations. The χ statistic was used to quantify the agreement between NCCT and CTA-SI regarding the presence or absence of a good scan. A multivariable logistic regression model was constructed to determine the independent predictors of good outcome (defined as mRS ≤2). Candidate variables were all those associated with good outcome with P<0.15 in univariate analysis. Nonsignificant variables (P>0.05) were removed by stepwise backward elimination. To test whether CTA-SI ASPECTS scores conferred independent predictive information regarding good outcome, both CTA-SI and NCCT ASPECTS scores were forced into the final model.

Results
Of a database containing 1341 patients, we identified 261 patients with proximal occlusions for analysis. There were 133 males (50.96%) and 128 females (49.04%) with a mean age of 67±15 years. The baseline variables are outlined in Table 1. The different occlusions observed were (no., %): distal internal carotid artery (34, 13%), MCA-M1 (143, 54.76%), and MCA-M2 (84, 32.18%).

The baseline median (interquartile range) NCCT ASPECTS score was 8 (6 to 9), CTA-SI ASPECTS was 6 (5 to 8), and final ASPECTS score was 6 (3 to 8). There was a better correlation between CTA-SI ASPECTS and follow-up ASPECTS (r=0.65; 95% CI, 0.58 to 0.72) than between NCCT ASPECTS and follow-up ASPECTS (r=0.46; 95% CI, 0.36 to 0.55; Figure 2A–B; P<0.001 for comparison of the 2 coefficients). We
also observed a better correlation between CTA-SI and baseline NIHSS scores (r = 0.40; 95% CI, 0.30 to 0.50) than between NCCT ASPECTS and baseline NIHSS scores (r = 0.25; 95% CI, −0.13 to 0.36; Table 2; P < 0.001 for comparison of the 2 coefficients). Furthermore, 24-hour NIHSS score was also better correlated with baseline CTA-SI (r = 0.43; 95% CI, 0.33 to 0.53) than NCCT ASPECTS (r = 0.25; 95% CI, −0.13 to 0.36; P < 0.001 for comparison of the 2 coefficients).

Next, we defined a “good scan” as an ASPECT score 8 to 10 based on a prespecified previously published cut point (see statistics section for details). The proportion of patients with a good NCCT scan at baseline was higher (132 of 261 [51%]) compared with a good CTA-SI (90 of 261 [35%]; P < 0.001). There was only moderate agreement between the 2 measures of a good scan (κ = 0.40; 95% CI, 0.30 to 0.51). The proportion with a good scan on the final NCCT was only 69 of 261 (26%). There was moderate agreement between the baseline CTA-SI and final ASPECTS (κ = 0.50; 95% CI, 0.39 to 0.61) but weak agreement between baseline ASPECTS and final ASPECTS (κ = 0.26; 95% CI, 0.15 to 0.36). We did not find an interaction between CTA-SI ASPECTS and time of acquisition with regard to the relationship with good outcome after controlling for other factors.

Three-month mRS scores correlated better with baseline CTA-SI ASPECTS (r = −0.32; 95% CI, −0.21 to −0.43) than the NCCT ASPECTS (r = −0.18; 95% CI, −0.06 to −0.29; P < 0.001 for comparison of the 2 coefficients; Figure 2C–D; Table 2). Factors predicting good outcome (mRS ≤ 2) on univariate analysis were lower age, lower NIHSS scores, higher ASPECTS scores (as measured by either NCCT or on CTA-SI), current smoking, and lower mRS scores at baseline (Table 3). Multivariable-adjusted analysis showed that CTA-SI ASPECTS was a better predictor of functional outcome than NCCT ASPECTS (Table 4). When controlling for CTA-SI ASPECTS, the relationship between NCCT ASPECTS and functional outcome was no longer significant.

**Discussion**

CTA complements NCCT head in acute stroke by allowing localization of vessel occlusion as well as providing informa-
tion on tissue-level perfusion using the early contrast enhanced source images of the whole brain created on the CTA (CTA-SI).5,14 Compared with quantitative perfusion CT, which delineates mean transit time, cerebral blood volume (CBV), and cerebral blood flow well, CTA-SI delineates mean transit time, cerebral blood volume (CBV), and cerebral blood flow, but can be a crude measure of perfusion at the tissue level. The present study shows that CTA-SI ASPECTS is strongly associated with baseline clinical stroke severity, final infarct extent, and 90-day outcome. Studying a large patient population, we are now able to show for the first time that a "good scan" on CTA-SI ASPECTS (defined as ASPECTS score >7) was an independent predictor of good outcome, even after controlling for ASPECTS measured on the noncontrast scan and baseline stroke severity (as measured by NIHSS). Furthermore, CTA-SI ASPECTS was superior to NCCT ASPECTS at predicting initial clinical stroke severity, final stroke extent, and 90-day outcome.

Table 3. Univariate Analysis of Predictors of a Good Outcome*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Good CTA-SI ASPECTS (8–10)</th>
<th>Good NCCT ASPECTS (8–10)</th>
<th>NIHSS per point</th>
<th>Age, y</th>
<th>NCCT ASPECTS</th>
<th>CTA-SI ASPECTS</th>
<th>Baseline NIHSS score</th>
<th>Onset to CTA, min</th>
<th>Onset to admission, min</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.29 (1.16–4.53)</td>
<td>1.54 (0.84–2.82)</td>
<td>0.95 (0.90–0.98)</td>
<td>0.137</td>
<td>0.25</td>
<td>0.40</td>
<td>0.25</td>
<td>0.40</td>
<td>0.25</td>
<td>0.001†</td>
</tr>
</tbody>
</table>
| NIHSS indicates modified Rankin Scale; CTA, noncontrast CT; ASPECTS, Alberta Stroke Programme Early CT Score; CTA-SI, CT angiography source image; NCCT, noncontrast CT; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

Previous studies have shown strong relationships among CTA-SI hypotauation, infarct volumes, and perfusion abnormalities, but have not demonstrated strong relationships with 90-day outcomes because of small sample sizes or lack of postdischarge or long-term disability data.10,16,17 In our previous study of 39 patients, we showed only an unadjusted nonsignificant trend toward an association between CTA-SI ASPECTS and 90-day outcome.9 Another study of 37 patients showed a relationship between CTA-SI ASPECTS and good outcome in univariate analysis but not in multivariable-adjusted analysis controlling for age and NIHSS.15 The same observation held true in the group with major reperfusion but not among patients without reperfusion. In a comparative study among NCCT, CTA-SI, and diffusion-weighted imaging, lesion volumes on CTA-SI correlated well with baseline diffusion-weighted imaging and there was an increased infarct growth and a poorer outcome in patients with poor collaterals, although a direct correlation between baseline CTA-SI ASPECTS and outcome was not studied.14 By contrast, in our larger study, we are able to show for the first time that CTA-SI ASPECTS information is associated with clinically relevant stroke disability outcomes. Additionally, we showed that CTA-SI ASPECTS is more informative than NCCT ASPECTS in predicting outcome, because in the model containing both CTA-SI and NCCT ASPECTS, the former model term remained significant, whereas the latter did not. Therefore, our data suggest that review of CTA-SI ASPECTS provides information not available from NCCT alone that is useful in predicting clinical outcome from stroke.

Both recanalization and time to recanalization are likely to strongly influence final infarct volume and will thus decrease the sensitivity of both CTA-SI and CBV to predict infarct progression. Wang and colleagues recently observed that in the group without reperfusion, ASPECTS on both CT perfusion (CTP)–SI and CTA-SI could effectively predict final infarct core, but in the group with reperfusion, CTP-SI had a

Table 4. Independent Predictors of a Good Outcome*

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥80 y</td>
<td>0.25</td>
<td>0.137–0.555</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>NIHSS per point</td>
<td>0.954</td>
<td>0.90–0.989</td>
<td>0.04†</td>
</tr>
<tr>
<td>Good NCCT ASPECTS</td>
<td>1.540</td>
<td>0.84–2.82</td>
<td>0.16</td>
</tr>
<tr>
<td>Good CTA-SI ASPECTS</td>
<td>2.29</td>
<td>1.16–4.53</td>
<td>0.01†</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; CTA, noncontrast CT; ASPECTS, Alberta Stroke Programme Early CT Score; CTA-SI, CT angiography source image; mRS, modified Rankin Scale.

*Excluding 10 patients with baseline mRS score >2.
†Significant.
potential advantage over CTA-SI in predicting final infarct core.\(^19\) Among 22 patients of MCA occlusion treated with intra-arterial thrombolysis, recanalization was associated with a similar final infarct size as the initial CTP and increased growth among nonrecanalized patients. The initial infarct volume on CTP also correlated with outcome.\(^20\) Recanalization was not measured in our study to confirm that our CTA-SI predicts infarct core. Infarct growth into the penumbra is highly likely if recanalization does not occur thereby impacting the predictive ability of CTA-SI.\(^21\) In a recent observation comparing ASPECTS on arterial and venous phase CTP-SI with ASPECTS on cerebral blood flow and CBV, the authors observed that the penumbra region could be characterized by a mismatch between the ASPECTS on arterial phase CTP-SI and the venous phase CTP-SI.\(^22\) This mismatch model in acute ischemic stroke could possibly determine penumbra and infarct core.\(^23\)

Baseline NIHSS is well known to predict stroke severity but may not correlate to CT findings. The concept of clinical–CT mismatch as well as outcomes with large infarcts may be variable.\(^23\) In both situations, the outcomes may differ in a given patient. We found a higher correlation of CTA-SI ASPECTS with baseline NIHSS and 24-hour NIHSS. Changes on NCCT ASPECTS may not necessarily represent true core, which CTA-SI ASPECTS may do, although the NIHSS is likely to be determined by both core and penumbra. Therefore, a clinical–CT correlation with CTA-SI may reflect more sensitive detection of ischemic regions compared with the NCCT ASPECTS, especially because the final ASPECTS correlated better with baseline CTA-SI. Treatment decisions may thus be more reliably based on CTA-SI ASPECTS than NCCT ASPECTS. Because recanalization is a critical determinant of outcome, treatment decisions should not be biased until a definitive imaging marker can identify patients who will not benefit with recanalization.

Despite potential advantages, CTP technology is still limited by brain coverage issues with most CT systems, which limits widespread applicability. New-generation 320-slice scanners enable rapid assessment of whole brain perfusion and give additional information on time course of vascular enhancement at the expense of higher radiation dosage. Each imaging modality and parameter has limitations. Our CTA protocol involves imaging of the aortic arch, neck arteries, and brain arteries on the same contrast bolus. Therefore, our brain source images are sufficiently delayed that contrast has already entered the venous-weighted phase of the “perfusion curve.” Abnormalities detected on our CTA source images likely reflect major cerebral blood volume abnormalities in most cases. Other CT scanners only perform head CTA, which if the scanners are fast enough may result in arterielly weighted images in which imaging is getting ahead of the contrast due to transit time delays. Such arterielly-weighted CTA source images may better reflect penumbral tissue than infarct core. A recent observation by Sharma and colleagues also suggests that the hypoattenuation volumes on CTA-SI more closely correlate with perfusion CT- measured cerebral blood flow rather than with CBV volume.\(^24\) They caution that the interpretation of CTA-SI as a dominant reflection of CBV and infarct core may not be correct with modern-day scanners. This may lead to overestimation of the infarct core by CTA-SI.

Our study has limitations. It is a retrospectively analyzed data. We do not have recanalization data, which may have influenced the results. Also, there was some variability in time from onset to image acquisition time across patients. Because we are studying 2 imaging parameters, the change would be expected to influence both. However, we could not find any statistical difference between onset to CTA time and outcomes. We, however, found a statistical relationship between onset time and outcome. In 10 patients, we had to impute discharge mRS. However, in view of a larger data set, this may not have influenced the results. This method of imputation is supported by a recent article showing a high correlation between early functional activity at Day 7 to 10 or Day 30 mRS and 90-day mRS.\(^25,26\)

Conclusions

Our study suggests that CTA-SI ASPECTS can predict final ASPECTS, 24-hour NIHSS scores, and clinical outcomes better than NCCT ASPECTS. However, the effect of recanalization on these observations needs to be determined.

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Figure showing NCCT, CTA-SI and Final Infarct on NCCT head.
67 yrs old male presenting with right upper limb and lower limb weakness and aphasia, within 60 minutes of symptom onset. Baseline NCCT brain (A) shows early ischemic changes in the region of left lentiform nucleus (arrow). CTA-SI image (B) reveals hypoattenuation in the region of left MCA territory (arrows) which corresponds to the follow up CT(C) showing well evolved left MCA infarct (arrows).
Abstract

静脉注射重组组织型纤溶酶原激活物治疗缺血性卒中
急性血管再通率低
——真实临床经验呼唤进一步行动

Low Rates of Acute Recanalization With Intravenous Recombinant Tissue Plasminogen Activator in Ischemic Stroke
Real-World Experience and a Call for Action

Rohit Bhatia, MD, DM, DNB; Michael D. Hill, MD, FRCPC; Nandavar Shobha, DNB, DM; Bijoy Menon, MD, DM; Simerpreet Bal, MD, DM; Puneet Kochar, MD; Tim Watson, MD, FRCPC; Mayank Goyal, MD, FRCPC; Andrew M. Demchuk, MD, FRCPC

背景和目的：给予脑梗死患者注射重组组织型纤溶酶原激活物 (rt-PA) 后的血管急性再通率，保守经典的评价方法是通过经颅多普勒 (TCD) 评价近端闭塞血管情况。我们试图通过研究对于 CT 血管成像 (CTA) 方法证实近端血管 ( 颈内动脉、大脑中动脉 M1 段、M2 段和基底动脉 ) 闭塞的患者，经静脉内注射 rt-PA 治疗后，急性血管再通率的情况以评价血管闭塞情况及疗效。

材料和方法：回顾 2002 至 2009 年卡尔加里 (Calgary) 卒中研究项目中患者的 CTA 资料，入组病例为所有近端动脉闭塞且接受静脉注射 rt-PA 治疗的患者，通过 TCD 或血管成像 ( 急性血管内治疗 ) 评价血管情况。通过观察 TCD/第一轮血管成像、血管内治疗后血管成像来了解并记录急性血管再通率。3 个月后改良的 Rankin 量表评分≤2 被认为疗效好。

结果：本研究的 1314 名患者的 CTA 结果显示，388 例证实为近端血管闭塞，其中 216 名患者接受静脉注射 rt-PA 治疗，127 名患者接受进一步影像检查以评价血管再通情况。TCD/血管成像来评估血管情况 (46 名应用 TCD，106 名应用血管成像)，仅有 21.25%(27/127) 被证实有急性血管再通。按照闭塞血管亚型，急性血管再通率情况如下：远端颈内动脉 ( 包括 / 不包括颈内动脉颈段的阻塞或狭窄 )4.4%(1/24)，大脑中动脉 M1 段 ( 包括 / 不包括颈内动脉颈段的阻塞或狭窄 )32.3%(21/65)，M2 段 30.8%(4/13) 和基底动脉 4%(1/25)，同时对于血管再通和没有再通患者使用 rt-PA 的时间也进行了比较。血管再通情况 (P<0.0001；危险比 =2.7；95% 可信区间，1.5-4.6) 对于预后 ( 统计时根据年龄和 NIHSS 评分进行调整 ) 判断有着强烈的提示意义。

结论：观察到基线 CTA 证实为近端血管闭塞的患者静脉注射 rt-PA 后的血管急性再通率低，而血管再通对于预后良好判断具有强烈提示意义。

关键词：颅内血管闭塞，缺血性卒中，血管再通，溶栓

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