Computed Tomographic Angiography and Cerebral Blood Volume Can Predict Final Infarct Volume and Outcome After Recanalization

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Background and Purpose—Recanalization rates are higher in acute anterior stroke treated with stent-retrievers when compared with older techniques. However, some still have sizeable infarcts and poor outcome. This may be related to underestimation of core infarct on nonenhanced computed tomography (NECT). CT angiography (CTA) source images (CTASI) and CT perfusion may be more informative. We hypothesize that core infarct estimation with NECT, CTA, and CT perfusion predicts infarct at 24 hours and outcome after fast recanalization.

Methods—Consecutive good recanalization patients with proximal anterior circulation stroke were evaluated. We assessed Alberta Stroke Program Early CT Score (ASPECTs) on NECT for subtle early infarct, hypodensity, loss of gray–white (CTASI), and low cerebral blood volume (CBV; CT perfusion). Sensitivity and specificity for predicting infarct by region were calculated.

Results—Of 46 patients, 36 (78%) had successful thrombectomy. Median ASPECTs was 10 for NECT early infarct and frank hypodensity; for CBV, CTASI-ASPECTs was 8. CTASI had the highest sensitivity of 71% and specificity of 82% for 24 hours NECT infarct. There was moderate correlation and concordance between CBV/24-hour NECT ($R_1=0.51; R_2=0.50$) and CTASI/24-hour NECT ($R_1=0.54; R_2=0.53$). Thirty-four patients (74%) had good outcomes. Median ASPECTS was higher on CTASI (8 versus 5; $P=0.04$) and CBV (9 versus 5; $P=0.03$) for patients with good versus bad outcome. There were better outcomes with increasing CTASI-ASPECTs ($P=0.004$) and CBV-ASPECTs ($P=0.02$).

Conclusions—CTASI and CBV were better at predicting 24-hour infarct and outcome than NECT. Appropriate advanced imaged guided selection may improve outcomes in large-vessel stroke treated with the newest techniques. (Stroke. 2014;45:2683-2688.)

Key Words: biomarkers ■ neuroimaging ■ stroke

The newest generation of stent-retrievers results in higher recanalization rates and faster recanalization times when compared with older generation endovascular therapies for acute stroke.1–3 However, despite good recanalization, outcomes are still poor in 37% to 42% of patients. One reason for this discrepancy may be underestimation of ischemic core on nonenhanced computed tomography (NECT). CT angiography (CTA) source images (CTASI) and CT perfusion may be more informative. We hypothesize that core infarct estimation with NECT, CTA, and CT perfusion predicts infarct at 24 hours and outcome after fast recanalization.

CT angiography (CTA) is routinely performed acutely for patients presenting with suspected large-vessel occlusions. Parenchymal evaluation on CTA source images (CTASI) and collateral analysis on CTA may be superior to NECT in establishing ischemic core and penumbra.4–7 CT perfusion (CTP) is also extensively studied in acute stroke8 although there are limited studies evaluating the use of CTP to direct endovascular therapy.9 Quantitative volumetric analysis of CTASI and CTP in acute stroke is described in the literature; however, the software is not a standard feature on older generation scanners. The Alberta Stroke Program Early CT Score (ASPECTs)10 is a fast, pragmatic semiquantitative method of defining established infarct in the middle cerebral arterial territory. It is useful in predicting outcome and has been applied to CTASI and CTP in a mixed intravenous tissue-type plasminogen activator and endovascular group of patients with middle
cerebral artery occlusions. However, these studies did not account for early recanalization as a result of therapy.

A stroke population treated with the current generation of endovascular devices provides an opportunity to study the pretreatment imaging of patients with large-vessel occlusions. This may enable a better understanding of the relationship between standard NECT and newer biomarkers of ischemic core in a population with known recanalization times. We sought to investigate the sensitivity and specificity of NECT, CTASI, and whole-brain CTP in predicting 24-hour infarct in patients with acute proximal anterior circulation occlusions successfully recanalized with endovascular therapy.

Materials and Methods

At our institution, all patients presenting with acute stroke undergo an unenhanced CT head and CT angiography of the neck and brain if they have symptom onset <6 hours from presentation or awaken with stroke symptoms. If appropriate, they receive intravenous tissue-type plasminogen activator if onset to ictus is <4.5 hours. Patients are then transferred either to a specialized neurological or to a general intensive care unit.

Our selection criteria for endovascular therapy in patients presenting with acute anterior circulation stroke are the following:

1. CT showing no intracranial hemorrhage and NECT ASPECT score ≥7.
3. CTA demonstrating carotid T, M1, or M2 occlusion.
4. Presenting <6 hours from onset or wake-up strokes with salvageable brain suspected on imaging defined as <1/3 middle cerebral artery territory hypodensity on unenhanced CT or a time-to-peak to cerebral blood volume (CBV) mismatch of >25% on CTP.
5. Endovascular therapy can be initiated within 6 hours of symptom onset. In the case of wake-up strokes, patients with CT ASPECT score >7 are considered candidates regardless of time of onset.

Our exclusion criteria are the known significant renal disease or severe contrast allergy.

The study was approved by our institutional research ethics board. We reviewed consecutive cases of patients presenting with acute anterior circulation stroke treated with recanalization with intra-arterial therapy between Jan 2010 and May 2013. The inclusion criteria were the following:

1. Admission NECT, CTA neck, and Circle-of-Willis. Patients who had technically successful CTP performed were also included. Follow-up 24-hour NECT.
2. Patient had an angiographically documented internal carotid artery, M1, or M2 occlusion.
3. We defined recanalization success as 2thrombolysis in cerebral infarction 2h flow at the end of endovascular treatment.

The primary outcome of our study was to determine the sensitivity and specificity of advanced imaging to determine infarct at 24 hours. The secondary outcome of our study was to correlate advanced imaging to clinical outcome at 30 days.

Evaluation of angiograms and reports to determine recanalization success was performed retrospectively from an interventional neuroradiologist with 2 years experience blinded to outcome. Follow-up modified Rankin Scale data at 1 month was collected for all patients by modified Rankin Scale–trained neurology staff blinded to imaging.

Good clinical outcome was defined as a 30-day modified Rankin Scale ≤2 or a 30-day drop in National Institute of Health Stroke Scale >10.

Imaging Technique

CT Head, Whole-Brain CTA and CTP

From 0730 to 2300 weekdays, stroke code patients are imaged on a 320-slice scanner (Toshiba Medical Systems, Nasu, Japan). We perform an unenhanced CT head, simultaneous whole-brain CTA and CTP, followed by CTA of the neck. CTP was performed using 40 mL of Isovue 370 (Bracco, Princeton, NJ), injected intravenously at 4 mL/s (online-only Data Supplement). Color maps of blood flow, BV, mean transit time, and time to peak were calculated using the singular value decomposition plus deconvolution method. CTA of the neck was acquired from aortic arch to the base of skull, using 120 kV, 300 mA, and 0.5-s. The 0.5-mm source data were reconstructed into 1-mm axial, coronal, and sagittal maximum intensity projection images. A contrast bolus of 40 mL was injected at 5 mL/s followed by a saline flush of 40 mL at 5 mL/s. Timing of the scan was determined by the arrival time of contrast seen on the dynamic volume images of the brain.

CT Head, CTA of the Neck, and Circle-of-Willis

After hours, an unenhanced CT head then CTA of the neck and Circle-of-Willis are performed in the emergency department on a 64-slice scanner (GE Healthcare, Milwaukee, WI). The imaging direction is caudal to cranial using 3.2 mL/s, total of 60 mL of Isovue 370 (Bracco, Princeton, NJ) with 20-mL saline flush at the same 3.2 mL/s.

Statistical Analysis

We performed analyses using MedCalc Software version 12.1.4.0 (Mariakerke, Belgium). We dichotomized patients into good versus poor outcomes, based on a modified Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE)-2 criteria (30-day modified Rankin Scale ≤2 or a decrease in National Institute of Health Stroke Scale, >10). We grouped patients with CTASI and CTP into low, medium, and high baseline ASPECTS. Differences between groups were evaluated by χ2; Fisher exact tests for proportional data, or Mann–Whitney U tests for comparisons of group medians. Continuous variables were summarized as mean (±1 SD) or medians (interquartile range or range) as appropriate. We calculated the accuracy, sensitivity, and specificity of each imaging modality by constructing 2x2 contingency tables using the 24-hour CT as the reference standard. Correlation (R) and concordance coefficients (R) were calculated to determine the degree of covariance and agreement between noncontrast CT, CTA source images, CTP-CBV-ASPECTS, and the 24-hour NECT. A weighted κ score was calculated to assess interobserver agreement for NECT, CTASI, CBV, and 24-hour CT on a region-by-region basis, with a κ value of 0 to 20 indicating poor agreement; 20 to 40 fair agreement; 40 to 60 moderate agreement; 60 to 80 substantial agreement; and 80 to 98 almost perfect agreement.

We calculated intraclass correlation to assess agreement between observers for collateral score. An intraclass correlation coefficient of <0.40 is poor, 0.40 to 0.59 is fair, 0.60 to 0.74 is good, and ≥0.74...
Results

In the study period, there were 69 consecutive patients who underwent intra-arterial therapy. There were 47 patients (68% good recanalizations) that met the inclusion criteria. One patient had large chronic infarcts on baseline NECT and was excluded. The remaining 46 patients formed the study group.

Of the patients with good recanalization, 36 (78%) were treated with stent-retrievers, 5 had thromboaspiration (Penumbra, Alameda, CA), 3 intra-arterial tissue-type plasminogen activator, 1 MERCI (Concentric Medical, Mountain View, CA), 1 Penumbra and angioplasty, and 1 angioplasty alone. Twenty-three patients underwent whole-brain CTP. Median National Institute of Health Stroke Scale was 17. The median recanalization time was 56 minutes. There were 3 (6.5%) symptomatic hemorrhages. Thirty-four (74%) patients had good outcomes. Median ASPECTS (95% confidence interval [CI]) was highest for NECT early infarct changes of 10 (9–10) and NECT frank hypodensity changes of 10 (10–10). The median CBV-ASPECTS was 8 (5.7–9) and the median CTASI-ASPECTS was also 8 (7–9).

CTASI-ASPECTS had the highest sensitivity at 71% and specificity of 82%. In the subset of 23 patients who had CTP, CBV-ASPECTS had a sensitivity of 54% and specificity of 84% with a CTASI-ASPECTS sensitivity and specificity of 64% and 81%, respectively. Early infarct changes on NECT had a sensitivity of 20% and specificity of 97%. Frank hypodensity changes on NECT had a sensitivity of 20% and specificity of 97%. Linear regression showed moderate correlation (τ) and concordance (κ) between CBV and infarct on the 24-hour CT scan (τ = 0.51 and κ = 0.50; 95% CI, 0.12–0.75) and CTASI and 24-hour CT (τ = 0.54 and κ = 0.53; 95% CI, 0.29–0.71) for individual ASPECTS regions and total ASPECTS scores, respectively (Table 1; Figure 1). There was no significant correlation with NECT early infarct or NECT frank hypodensity and 24-hour CT.

We dichotomized patients into good versus bad outcomes (Table 2). There were significant differences in median CTASI scores for patients with good versus bad outcomes (8 versus 5; P<0.04). Similar findings were also found for CBV (9 versus 5; P<0.03). There was no significant difference in baseline NECT between the 2 groups. As expected, patients with worse outcomes had significantly lower 24-hour NECT scores (P<0.0001).

Weighted κ was fair (κ = 0.353; 95% CI, 0.169–0.533) for frank hypodensity changes on plain CT, moderate for NECT (κ = 0.494; 95% CI, 0.213–0.774), and poor for CBV (κ = 0.400; 95% CI, 0.136–0.664). As expected, patients with worse outcomes had significantly lower 24-hour NECT scores (P<0.0001).

Weighted κ was fair (κ = 0.353; 95% CI, 0.169–0.533) for frank hypodensity changes on plain CT, moderate for NECT (κ = 0.494; 95% CI, 0.213–0.774), and poor for CBV (κ = 0.400; 95% CI, 0.136–0.664). As expected, patients with worse outcomes had significantly lower 24-hour NECT scores (P<0.0001).

We dichotomized baseline ASPECTS scores on advanced imaging and compared them with outcome (Figure 2). There was significant difference in the proportion of good outcomes among CTASI-ASPECTS levels (P=0.014) and CBV-ASPECTS levels (P=0.03) and a greater proportion of good outcomes with increasing CTASI-ASPECTS (low to high; P=0.004) and CBV-ASPECTS (P=0.02), respectively. Significant differences were found between proportion of good outcomes comparing low with high CTASI scores (37.5% versus 90.4%; P=0.008) and between mid and high CBV-ASPECTS (28.5% versus 84.6%; P=0.022). There was no significant difference in good outcomes between low to mid (37.5% versus 70.6%; P=0.19) and mid to high (70.6% versus 90.4%; P=0.207) CTASI-ASPECTS or low to mid (33.5% versus 18.5%; P=1.0) and low to high (33.3% versus 84.6%; P=0.136) CBV-ASPECTS.

One patient with low CBV=3 and good outcome was found on MRI to have cortical infarction with underlying

Table 1. Concordance Between Baseline Imaging and 24-Hour CT

<table>
<thead>
<tr>
<th>Imaging (n)</th>
<th>Concorance With Final</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>NECT (46)</td>
<td>0.00</td>
<td>(−0.13 to 0.12)</td>
</tr>
<tr>
<td>NECT-hypodensity (46)</td>
<td>0.00</td>
<td>(−0.05 to 0.05)</td>
</tr>
<tr>
<td>CTA source images (46)</td>
<td>0.53</td>
<td>(0.29 to 0.71)</td>
</tr>
<tr>
<td>CT perfusion CBV (23)</td>
<td>0.50</td>
<td>(0.12 to 0.75)</td>
</tr>
</tbody>
</table>

ASPECTS indicates Alberta Stroke Program Early CT Score; CT, computed tomography; CTA, CT angiography; and NECT, nonenhanced CT.
preservation of white matter in the same areas demonstrating low CBV. Of the 3 patients with low CTASI (0–3) who eventually had a good outcome, 2 of the 3 had follow-up MRIs that demonstrated infarcts in the same areas of abnormal CTASI; the third patient did not have an MRI but had patchy nonconfluent low CBV changes in areas of abnormal CTASI.

Discussion
We studied the relationship between NECT and advanced imaging in a group of highly select patients with acute stroke presenting with good baseline CTs and proximal large-vessel occlusions, who underwent successful recanalization, predominantly with stent-retrievers. The results of our primary outcome indicate that in spite of good, prompt recanalization, some patients with a good baseline NECT scans still have sizeable infarct on 24-hour CT (Figure 3). Although we cannot entirely exclude progression to infarct during the intervention but before recanalization, ischemic core evident on advanced imaging may have been missed on baseline NECT. This is similar to other studies where advanced CT imaging correlated well with acute diffusion-weighted imaging (DWI).

We also found that advanced imaging with CTASI and CBV had similar performance with both having higher sensitivity than plain CT for 24-hour infarct. Similarly, in our study, we found significant correlation among CTASI, CBV, and 24-hour CT. In contrast to some recent studies evaluating CTP in acute stroke in which recanalization status is uncertain, our study population was unique in that we evaluated a relatively homogenous cohort where recanalization was achieved with endovascular means and confirmed angiographically.

Our secondary analysis showed that even with good recanalization, a proportion of patients will still have poor clinical outcomes. The finding of significantly lower CTASI and CBV-ASPECTS in patients with poor outcomes emphasizes the importance of careful evaluation of these advanced imaging modalities for prognostication and supports the theory of smaller ischemic core predicting better outcome. As expected, patients with poor outcomes had lower 24-hour CT ASPECTS.

There are few studies with a limited number of patients reporting CTASI and CTP in acute stroke. Lin et al found CBV was better than CTASI in predicting follow-up infarct on DWI in a patient population who underwent heterogeneous treatments with either intravenous tissue-type plasminogen activator or endovascular therapy. However, in their study, recanalization status was assessed at a mean of 30 hours with MRA in comparison with our study with known recanalization time. A recent study reported their results using CTP but not using CTASI in patients treated with thromboaspiration.

Table 2. Dichotomized Baseline, Procedural, and Imaging Data

<table>
<thead>
<tr>
<th></th>
<th>30-D mRS&lt;3 or Decrease in NIH</th>
<th>Bad Outcome</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>34</td>
<td>12</td>
<td>...</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>4</td>
<td>3</td>
<td>0.36</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>21</td>
<td>7</td>
<td>1.00</td>
</tr>
<tr>
<td>Hyperlipidemia*</td>
<td>21</td>
<td>6</td>
<td>0.51</td>
</tr>
<tr>
<td>Atrial fibrillation*</td>
<td>11</td>
<td>7</td>
<td>0.17</td>
</tr>
<tr>
<td>Baseline NIHSS†</td>
<td>16.5 (12–20)</td>
<td>17.5 (16–20)</td>
<td>0.35</td>
</tr>
<tr>
<td>Median puncture to recan, min†</td>
<td>56 (39–69)</td>
<td>66 (49–98)</td>
<td>0.17</td>
</tr>
<tr>
<td>IV tPA*</td>
<td>26</td>
<td>9</td>
<td>1.00</td>
</tr>
<tr>
<td>Stent-retriever*</td>
<td>28</td>
<td>7</td>
<td>0.12</td>
</tr>
<tr>
<td>Discharge mRS†</td>
<td>2 (1–3)</td>
<td>5 (4–6)</td>
<td>...</td>
</tr>
<tr>
<td>NECT-ASPECTS†</td>
<td>9 (9–10)</td>
<td>10 (9–10)</td>
<td>0.37</td>
</tr>
<tr>
<td>NECT-hyp-ASPECTS†</td>
<td>10 (10–10)</td>
<td>10 (10–10)</td>
<td>0.81</td>
</tr>
<tr>
<td>CTASI-ASPECTS†</td>
<td>8 (6–9)</td>
<td>5 (3–7)</td>
<td>0.04</td>
</tr>
<tr>
<td>CTP-ASPECTS‡</td>
<td>9 (8–9)</td>
<td>5 (4–7)</td>
<td>0.029</td>
</tr>
<tr>
<td>FINAL-NECT-ASPECTS†</td>
<td>8.5 (7–9)</td>
<td>4 (2–6)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CTASI-ASPECTS indicates CT angiographic source image-Alberta Stroke Program Early CT score; CTP, computed tomographic perfusion; IV tPA, intravenous tissue-type plasminogen activator; mRS, modified Rankin score; NECT, nonenhanced CT; NECT-hyp, NECT-hypodensity; NIH, National Institute of Health; and NIHSS, National Institute of Health Stroke scale.

*Comparison of proportions (Fisher exact test).
†Comparison of medians (Mann–Whitney U test).
‡n=46.

Figure 2. A, Chart demonstrating proportion of good outcomes by trichotomized computed tomographic angiographic source image (CTASI)-Alberta Stroke Program Early CT Score (ASPECTS). B, Chart demonstrating proportion of good outcomes by trichotomized cerebral blood volume (CBV)-ASPECTS.
Successful recanalization was reported in 31 of 51 (61%) patients. Our study had successful recanalization in 46 patients, intentionally focusing advanced imaging on a select good recanalization cohort. Similar to our study (median 9 versus 5; \(P=0.029\)), they found a significant difference in CBV-ASPECTS (median 8 versus 6; \(P=0.0007\)) in patients who had good outcomes versus poor outcomes. However, their study did not evaluate CTASI, which is readily available and used in some centers where CTP may not always be accessible. Interestingly, our study also demonstrated a significant difference in median CTASI-ASPECTS (8 versus 5; \(P=0.04\)) in patients with good outcomes, suggesting a possible close relationship between baseline CBV and CTASI for estimating ischemic core.

Our median time from groin puncture to recanalization for patients experiencing good versus bad outcomes was 56 and 66 minutes, respectively (Table 1). This is <80-minute median puncture to recanalization time in Interventional Management of Stroke (IMS) III. It suggests that prompt recanalization is less of an issue now compared with the past because many centers are now capable of consistently faster recanalization. With higher recanalization rates approaching 70% in ours and other studies compared with 40% in published series, the challenge now lies in better image-based patient selection.

We were concerned about the recent literature, suggesting that CTASI overestimates ischemic core. We do not typically perform MRI in acute stroke and we did not, therefore, directly correlate CTASI or CTP with DWI on every patient. We had 3 of 8 patients who had low (0–3) baseline CTASI scores and ultimately good outcomes with recanalization. Interestingly, 2 of these 3 patients on MRI showed DWI restriction in the same regions predicted by CTASI and CBV map. Similarly, we had 1 of our patients with a low CBV score of 0 to 3 having a good outcome. This was 1 of 3 patients with low CTASI-ASPECTS and follow-up DWI, which showed cortical infarcts sparing the underlying white matter. The preservation of white matter may partially explain the good outcome in this patient. An alternative explanation may be that infarct location is fundamentally linked to neurological deficits and that the location of the infarcts in our patient was relatively noneloquent stroke. Psychogios et al also reported a minority of patients with low (0–4) or mid (5–7) CBV-ASPECTS scores who experienced a good outcome after recanalization. These findings suggest that although CTASI and CBV can reliably identify ischemic core, the core will not always predict poor outcome.

Our study has important limitations. A 320-slice CT scanner capable of simultaneous CTA and CTP is not readily available without postprocessing in all centers and may affect reproducibility of our results. We did not perform CTP on all patients because of the restricted availability between 2300 and 0730 hours. We cannot be certain that the patient population presenting during these hours are the same as those presenting when CTP was available. We evaluated static images for assessment of CTA collaterals and, therefore, we cannot assess the extent of any delayed filling of collaterals. Similar to other studies, we used the 24-hour CT scan as the reference standard for infarct rather than DWI. DWI has been shown to be more accurate than CT scan for determination of infarcts, but it is not a standard part of our poststroke imaging protocol. We also cannot exclude the possibility of infarct progression between the time of imaging and recanalization. However this, as well as our choice to use semiquantitative ASPECTS rather than volumetric analysis, are pragmatic limitations reflective of acute care.
Conclusions
We evaluated a highly select group of patients with acute anterior circulation stroke presenting with good baseline CTs undergoing successful, confirmed endovascular recanalization. CTASI and perfusion CBV maps were better at predicting 24-hour infarct and clinical outcomes than NECT and thus may represent ischemic core. Our study is an important contribution to improve the validation of CTASI and CTP as an imaging biomarker of cerebrovascular disease. Given the high recanalization rates with the newest generation of endovascular tools, a better understanding of how advanced imaging can direct appropriate selection of patients with small ischemic core may improve outcome in acute proximal vessel occlusions.

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References
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SUPPLEMENTAL MATERIAL

We acquire 19 volumes covering the whole brain consisting of 320 images, 0.5 mm thickness, covering 16 cm in the z direction. The first volume was acquired with a 7 s injection delay. The acquisition parameters for the first volume were 80 kVp and 300 mA. Next, 13 volumes were acquired starting at 11 s at a sampling interval of every 2 s during the arterial and capillary phases. Then, 5 total volumes were acquired every 5 s at 80 kVp and 100 mA. The total scan duration was 60 s. Post-processing was performed on a VitreaFx, version 1.0, workstation (Vital Images Inc., MN) using the delay-insensitive singular-value decomposition (SVD) plus nonparametric deconvolution method. The supraclinoid segment of the internal carotid artery was the reference arterial input function to avoid any volume averaging. The posterior portion of the superior sagittal sinus was selected for the venous output function.