Clot Burden Score on Admission T2*-MRI Predicts Recanalization in Acute Stroke

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Background and Purpose—To propose a T2*-MR adaptation of the computed tomography angiography-clot burden score (CBS), and assess its value as predictor of 24-hour recanalization and clinical outcome in anterior circulation stroke treated by intravenous thrombolysis ≤4.5 hours from onset.

Methods—Two independent observers retrospectively analyzed pretreatment T2* images for evaluation of clot burden, using a 10-point scale T2*-CBS. Three points are subtracted for susceptibility vessel sign in the supraclinoid internal carotid artery, 2 points each for susceptibility vessel sign in the proximal and distal part of middle cerebral artery, and 1 point each for susceptibility vessel sign in middle cerebral artery branches (with a maximum of 2 points) and for susceptibility vessel sign in anterior cerebral artery. Associations with 24-hour recanalization and favorable outcome (3-month modified Rankin Scale score, ≤2) were assessed in multivariate analyses.

Results—We analyzed 184 consecutive patients (mean age, 67 years) with median (interquartile range) admission National Institutes of Health Stroke Scale score and onset-to-treatment time of 15 (9–19) and 151 (120–185) minutes, respectively. The intraclass correlation for T2*-CBS between observers was 0.97 (95% confidence interval, 0.97–0.98). In multivariate analyses, T2*-CBS ≥6 was significantly associated with 24-hour recanalization (adjusted odds ratio, 5.1 [1.9–13.5]; P=0.001) or with favorable outcome (adjusted odds ratio, 4.2 [1.7–10.8]; P=0.003).

Conclusions—T2*-CBS, a new reproducible semiquantitative score adapted from the computed tomography angiography-CBS, is associated with 24-hour recanalization and 3-month outcome after intravenous thrombolysis. This score needs external validation and could be useful to identify poor responders to intravenous thrombolysis. (Stroke. 2013;44:1878-1884.)

Key Words: infarction ■ MRI ■ outcome ■ thrombolysis ■ thrombus

Recanalization is the strongest predictor of at-risk tissue rescue and clinical impairment reversal, and accordingly is the mainstay of current stroke therapy. Many factors impact the success of recanalization therapy, including clot composition, clot burden, and site of clot impaction. More proximal and longer clots are harder to treat, leading to a worse outcome as compared with shorter and distal clots. Direct imaging of intra-arterial thrombus is made possible with the hyperdense middle cerebral artery sign on computed tomography (CT), and the susceptibility vessel sign (SVS) on T2*-MRI. SVS is related to the presence of deoxyhemoglobin, which causes inhomogeneities in local magnetic field and hence signal loss on T2*sequences. The prognostic value of SVS for arterial recanalization after intravenous thrombolysis and functional outcome remains debated, although some studies demonstrated an association with low recanalization rate, others did not. These discrepancies may be because of the lack of assessment of the amount of clot burden. For this purpose, a CT angiography (CTA)-based scale, denominated clot burden score (CBS), has been proposed. This semiquantitative score allots major anterior circulation arteries 10 points and decreases with the number of segments exhibiting a visible clot (ie, a higher clot burden translates as a lower CBS). CTA-CBS has been shown to be a predictor of recanalization and functional outcome in 2 independent patient cohorts. Whether a CBS, adapted to T2*- data, would predict recanalization after IV thrombolysis better than the presence of any SVS is an intriguing possibility. The primary objective of our study was, therefore, to adapt the CTA-based CBS to T2*-MR and assess its prognostic value on recanalization after IV thrombolysis of anterior circulation stroke. We also tested the prognostic value of T2*-CBS on 3-month functional outcome.

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Methods

Patients

This retrospective analysis was based on a prospectively collected registry of consecutive patients treated by IV thrombolysis for ischemic stroke between January 2006 and November 2011, in 1 center. Since 2006, 1.5 Tesla MR imaging (Signa EchoSpeed, GE Healthcare) is systematically implemented in our center as first-line diagnostic workup in candidates for thrombolysis. The standard MR protocol includes fluid-attenuated inversion recovery, diffusion-weighted imaging (DWI), T2*-weighted gradient echo imaging, intracranial 3D time-of-flight MR angiography (MRA), and perfusion-weighted imaging (PWI) whenever feasible with no delay. DWI–PWI patterns, hypoperfusion, or DWI lesion volumes were not a basis for clinical decision making except in borderline cases. The total acquisition time for MR was <10 minutes. A follow-up MR was scheduled at 24 hours after treatment and included the same set of sequences as the admission MR imaging except PWI. Patients included in the present study were those treated by IV tissue-type plasminogen activator (0.9 mg/kg) within 3 hours after stroke onset until November 2008, and within 4.5 hours thereafter, and who had both pretreatment and follow-up MR imaging. Patients with severe artifacts on T2*, DWI, or MRA, posterior circulation stroke, or treated with endovascular treatment were excluded. Age, sex, hypertension, diabetes mellitus, hyperlipidemia, smoking, arterial blood pressure, and serum glucose level at admission, National Institutes of Health Stroke Scale (NIHSS) score before and 24 hours after treatment (with early neurological improvement defined as a ≥2 NIHSS score reduction within the first 24 hours, or NIHSS score ≤2 at 24 hours) were collected. Outcome at 3 months was assessed using the modified Rankin Scale score and dichotomized into favorable (≤2) or unfavorable. Stroke pathogenesis was assessed using Trial of Org 10172 in Acute Stroke Treatment classification. This study was approved by the local Ethics Committee.

Image Analysis

The acquisition parameters of the T2*-weighted gradient-echo sequence were as follows: repetition time/echo time 460/13 ms, flip angle 25°, 24×18 cm² field of view, 256×224 matrix, 1 excitation, 24 slices, 6-mm contiguous slice thickness, duration 1 minute 21 seconds. Two radiologists (4 and 20 years of experience) independently reviewed all T2* images on a dedicated workstation for T2*-CBS quotation. They had access to DWI images, but were blinded to MRA and clinical data. They searched for SVS, that is, a hypointense CBS quotation. They had access to DWI images, but were blinded to MRA and clinical data. They searched for SVS, that is, a hypointense signal on T2* within a vascular cistern, exceeding the size of the homologous contralateral arterial diameter. To assess the clot burden, the original CTA-CBS was adapted to MRI and termed T2*-CBS. As shown in Figure 1, T2*-CBS is a 10-point scoring system to define the extent of thrombus in the anterior circulation. Because susceptibility artifact at the skull base prevents evaluation of the infradural internal carotid artery, this segment was not analyzed and 3 points were assigned to the supraclival internal carotid artery level, for consistency with the CTA-CBS. A score of 10 implies clot absence. A score of 0 implies complete multivessel segment occlusion. T2*-CBS was subsequently dichotomized using a >6-point cut-off, according to and for comparison with CTA-CBS studies. Discordances between observers were resolved by consensus. One reader qualified T2*-images quality as either good without motion artifacts or diagnostic quality, despite artifacts. Pretreatment occlusion was assessed on MRA or, for questionable distal occlusions, on the presence of fluid-attenuated inversion recovery hyperintense vessel and maximum of the tissue residue function (Tmax) perfusion maps. It was categorized as proximal (internal carotid artery and M1) or distal (M2 or beyond). Recanalization was assessed on MRA and categorized as complete (ie, normal anterior circulation on MRA) versus incomplete or absent. Pretreatment and follow-up DWI lesions were segmented to compute initial and final DWI volumes as detailed elsewhere. Critically hypoperfused tissue, on the basis of a Tmax >6 seconds, was segmented from PWI maps (BrainStat AIF, READY View software). The PWI–DWI mismatch profile was considered present when Volume_{hypoperfusion} >1.8×Volume_{DWI}.

Statistical Analysis

Statistical analysis was performed using IBM SPSS 19.0 for Windows software. Continuous variables were compared with Student t test or a Mann–Whitney test, as appropriate. Categorical variables were compared using χ² or Fisher exact test, as appropriate. Intraclass correlation and κ statistics were used to assess interobserver agreement for T2*-CBS considered as a continuous variable and further dichotomized using a >6 threshold. Given that the T2*-CBS is an adaptation of the CTA-CBS, we used the >6 threshold previously identified on CTA. However, because the T2*-CBS slightly differs from the original CTA-CBS, we checked that this was the best threshold to identify 24-hour recanalizers using a receiver operating characteristic curve. We also performed an internal crossvalidation on the basis of 1000 bootstrap replicates; 95% confidence intervals (CI) for median sensitivity and specificity of each T2*-CBS cut-off were estimated using the bias correction and acceleration method (SAS version 9.3, SAS Institute, Inc, Cary, NC). We compared pretreatment characteristics in univariate analyses between patients with T2*-CBS ≤6 and >6 and between patients with and without 24-hour complete recanalization, when assessable. Two backward stepwise multivariate binary logistic regression analyses were then done with 24-hour recanalization or 3-month favorable outcome as the dependent variable. Variables were selected for entry into the model on the basis of results of the univariate analysis (P<0.20), and further excluded from the model when P>0.10. The odds ratio (OR) and 95% CI were obtained. A 2-tailed P value of <0.05 was considered significant.

Results

General Population

During the study period, 272 patients underwent recanalization therapy; 88 were excluded because of a time-to-treatment >4.5 hours (n=22), absence of initial MR imaging (n=19), severe artifacts on initial MR imaging (n=5), absence of follow-up MR imaging (n=14), posterior circulation strokes (n=17), or endovascular treatment (n=11). Eligible patients did not differ from noneligible patients in age, sex, or baseline NIHSS score (data not shown). A total of 184 patients met the eligibility criteria, including 105 men, with a median (interquartile range) age and admission NIHSS score of 69 (57–78) and 15 (9–19) years, respectively. Occlusion was proximal in 114 patients. Median time-to-treatment was 151 min (120–185) and <3 hours in 124 patients. Follow-up MRI was acquired at a median delay of 26 hours (22–31) from stroke onset. Recanalization was not assessable in 21 patients, who were excluded from the recanalization analysis.

T2*-Clot Burden Score

On the T2* sequence, a SVS was visible in ≥1 arterial segment (T2*-CBS <10) in 144 patients (77%). There was no association between T2*-images quality and the identification of SVS (P=0.69). There was an almost perfect interobserver agreement for T2*-CBS considered as a continuous variable (intraclass correlation, 0.97; 95% CI, 0.97–0.98). The interobserver agreement for distinguishing patients with T2*-CBS ≤6 from those with T2*-CBS >6 reached κ=0.90. Median (interquartile range) T2*-CBS was 8 (6–9). The receiver operating characteristic analysis (Figure I in the online-only Data Supplement) demonstrated an area under the curve of 0.65 (95% CI, 0.57–0.73; P=0.002) for the whole T2*-CBS to predict 24-hour recanalization, and confirmed that T2*-CBS...
>6 was the cut-off point that maximized the sum of sensitivity (89.7% [82.5–96.9]) and specificity (45.2% [35.3–55.3]). The median sensitivity and specificity of each T2*-CBS cut-off based on 1000 bootstrap replicates were very close to the original results, and >6 T2*-CBS cut-off still maximized the sum of sensitivity (median 89.9% [79.4–95.4]) and specificity (median 44.7% [35.9–55.7]).

T2*-CBS was ≤6 (ie, high clot burden) in 51 patients (28%; illustrative example on Figure 1). All patients with distal occlusion (Figure 2) and 63 (55%) with proximal occlusion (Figure 3) had T2*-CBS >6. Table 1 provides univariate comparisons between patients with high (T2*-CBS ≤6) or low clot burden (T2*-CBS >6). Patients with T2*-CBS ≤6 had significantly higher baseline NIHSS score,
larger initial DWI volume, and larger PWI-DWI mismatch volume, as well as more proximal occlusion than patients with T2*-CBS >6.

Recanalization and 3-Month Outcome
Among the 163 patients with available data on recanalization, complete recanalization was observed in 68 patients (42%). Twenty-four-hour recanalizers had significantly higher T2*-CBS (ie, smaller clot burden), more distal occlusion and lower baseline NIHSS scores (Table 2). Of note, the presence of any SVS (ie, T2*-CBS <10) did not significantly differ between patients who did and did not recanalize. When T2*-CBS was split into tertiles, recanalization occurred in 14% of 50 patients with T2*-CBS (0–6), 55% of 58 patients with T2*-CBS (7–8), and 53% of 55 patients with T2*-CBS (9–10).

In multivariate analysis, T2*-CBS >6 was significantly associated with 24-hour recanalization (OR, 5.1; 95% CI, 1.9–13.5; P=0.001) after adjustment for distal occlusion (OR, 2.7; 95% CI, 1.2–6.1; P=0.02), cardioembolic stroke (OR, 2.2; 95% CI, 1.1–4.6; P=0.03), diabetes mellitus (OR, 2.4; 95% CI, 1.1–4.6; P=0.01), and diastolic blood pressure (OR, 1.0; 95% CI, 0.99–1.04; P=0.09). Smoking, sex, and initial NIHSS score were sequentially removed from the initial model by backward logistic regression. The above associations remained significant in alternative (sensitivity) multivariate logistic regression models adjusted for initial NIHSS score (data not shown). When this analysis was restricted to proximal occlusions (n=114), T2*-CBS >6 and cardioembolic stroke remained significantly associated with 24-hour complete recanalization (OR, 5.2; 95% CI, 1.9–13.9; P=0.001 and OR, 2.7; 95% CI, 1.1–6.6; P=0.03, respectively).

At 3 months, 100 (56%) of 177 patients (7 patients were lost to follow-up) had favorable outcome. In multivariate analysis, T2*-CBS >6 was significantly associated with favorable outcome (OR, 4.2; 95% CI, 1.7–10.8; P=0.003) after adjustment for age (OR, 0.92; 95% CI, 0.89–0.96; P<0.001), NIHSS score at admission (OR, 0.89; 95% CI, 0.82–0.99; P=0.002), and initial infarct volume on DWI (OR, 0.98; 95% CI, 0.96–0.99; P=0.001). Delay from onset-to-treatment, serum glucose level, distal occlusion, and pretreatment systolic blood pressure were sequentially removed from the initial model by backward logistic regression. When this analysis was restricted to proximal occlusions, T2*-CBS >6, age, NIHSS score at admission and initial infarct volume on DWI remained significantly associated with favorable outcome (OR, 5.8; 95% CI, 2.0–17.2; P=0.002; OR, 0.93; 95% CI, 0.89–0.97; P=0.001; OR, 0.84; 95% CI, 0.76–0.94; P=0.001, and OR, 0.98; 95% CI, 0.96–0.99; P=0.002, respectively).

Discussion
Our data show that as assessed on T2*-MR, the clot burden but not the presence of any SVS was associated with 24-hour recanalization in a cohort of patients with acute anterior circulation stroke treated with IV thrombolysis. We also found that

Figure 3. Illustrative example of proximal occlusion with T2*-CBS=8 (susceptibility vessel sign in distal part of right M1). A through C, axial T2*-weighted sequence. D, Three-dimensional time-of-flight MR angiography. CBS indicates clot burden score.
patients with less thrombus burden were more likely to have favorable functional 3-month outcome. T2*-CBS is based on the detection of SVS in the anterior circulation. Similar to the hyperdense middle cerebral artery sign on nonenhanced CT, the SVS has raised expectations for predicting response to various revascularization strategies. Two prior studies found the presence of susceptibility sign to be an independent predictor of recanalization,9,13 but 2 others found it had no prognostic value,7,15 and 2 recent studies found that when located in the M1 segment, it was clearly associated with poor response to IV thrombolysis.11,12 Using a 24-hour recanalization end point, we found that the presence of any SVS (ie, T2*-CBS <10) had neither good nor poor predictive value on 24-hour recanalization. However, contrary to the presence of any SVS, a high clot burden, as defined a priori by a 6-point cut-off on the T2*-CBS, was significantly associated with poor 24-hour recanalization. Consistent with established knowledge,3,23 proximal occlusions were less prone to recanalization. Our results strengthen the idea that not only occlusion site, but also the resulting amount of thrombus burden is an important determinant of recanalization after IV thrombolysis in anterior circulation stroke.17,24 Importantly, patients with higher CBS were also less likely to have favorable outcomes at 3 months.

Our results based on MR closely match those from the original CTA-CBS, showing that patients with higher thrombus burden have higher baseline NIHSS scores,16–18 larger infarctions,16,17 larger hypoperfused areas,17,18 and more importantly, lower 24-hour recanalization rates17 and poorer outcome at 3 months.16–18 Interestingly, we found the CBS interobserver ratings on T2* sequences to be extremely reliable, in line with CTA-CBS findings.16,17 Taken together, our findings and these earlier reports suggest that the CBS, originally designed for CTA, can be adapted to MR to help predict the response to IV thrombolysis in acute ischemic stroke. Although our scoring applies only to centers that use MRI as first-line imaging workup in acute stroke, and as such has limited applicability, large centers are increasingly implementing acute stroke MRI, given its acknowledged safety and clinical utility. Readily available and reproducible scoring systems, such as T2*-CBS and CTA-CBS, could be applied to candidates for thrombolysis regardless of the screening imaging modality. Applying CBS may be important in choosing the optimal treatment for individual patients on the basis of amount of clot burden. In future interventional stroke trials, CBS could help select homogenous group of patients with high clot burden who might benefit from more aggressive recanalization strategies.

Table 1. Univariate Comparisons Between Patients According to T2*-CBS

<table>
<thead>
<tr>
<th>Demographics/risk factors</th>
<th>T2*-CBS &gt;6 (n=133)</th>
<th>T2*-CBS ≤6 (n=51)</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68±14</td>
<td>66±15</td>
<td>0.52</td>
</tr>
<tr>
<td>Male</td>
<td>77 (58%)</td>
<td>28 (55%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Hypertension</td>
<td>82 (62%)</td>
<td>22 (43%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19 (14%)</td>
<td>4 (8%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>52 (39%)</td>
<td>17 (33%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Smoking</td>
<td>65 (49%)</td>
<td>15 (29%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Characteristics at admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>154±24</td>
<td>150±21</td>
<td>0.40</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>83±15</td>
<td>81±15</td>
<td>0.27</td>
</tr>
<tr>
<td>Serum glucose, mmol/L</td>
<td>6.8±2.1</td>
<td>6.9±1.8</td>
<td>0.65</td>
</tr>
<tr>
<td>Initial NIHSS score</td>
<td>12 [8–18]</td>
<td>18 [15–21]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delays</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from onset-to-initial MRI, min</td>
<td>118 [88–158]</td>
<td>117 [86–158]</td>
<td>0.89</td>
</tr>
<tr>
<td>Time from onset-to-treatment, min</td>
<td>150 [120–184]</td>
<td>155 [120–190]</td>
<td>0.70</td>
</tr>
<tr>
<td>MRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal (ICA and/or M1) occlusion</td>
<td>63 (47%)</td>
<td>51 (100%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initial DWI volume, mL</td>
<td>16 [7–42]</td>
<td>31 [11–96]</td>
<td>0.001</td>
</tr>
<tr>
<td>PWI–DWI mismatch profile*</td>
<td>50 (60%)</td>
<td>21 (66%)</td>
<td>0.55</td>
</tr>
<tr>
<td>PWI–DWI mismatch volume, mL*</td>
<td>36 [15–61]</td>
<td>78 [54–121]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardioembolic stroke</td>
<td>60 (45%)</td>
<td>25 (49%)</td>
<td>0.63</td>
</tr>
<tr>
<td>24-h recanalization†</td>
<td>61 (54%)</td>
<td>7 (14%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mRS score at 3 months‡</td>
<td>1 [0–3]</td>
<td>4 [2–5]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Numbers are mean±SD or median [interquartile range]. BP indicates blood pressure; CBS, clot burden score; DWI, diffusion-weighted imaging; ICA, internal carotid artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and PWI, perfusion-weighted imaging.

*PWI available in 116 patients.
†24-h recanalization assessable in 163 patients.
‡mRS score at 3 months available in 177 patients.
Although CTA- and T2*-CBS provide congruent prognostic information, there are notable differences between them. First, the original CTA-CBS was based on luminography and, consequently, its adaptation to MRI would logically be based on MRA. However, time-of-flight MRA does not fully capture clot length, especially its distal part. Second, T2*-CBS likely underestimates full clot extent, given that the susceptibility effect depends on thrombus composition and age. A clot might, therefore, be only partly visible on T2*, because of its heterogeneous composition, or not visible at all. Of note, the above-mentioned underestimation of clot length on T2* is likely partly counterbalanced by well-established size magnification because of susceptibility artifacts.

Our study has several limitations. First, we used time-of-flight MRA to assess vessel occlusion and recanalization, which is not optimal. However, whenever necessary, PWI and fluid-attenuated inversion recovery vessel signal changes provided more comprehensive information on vessel status, and we excluded patients in whom recanalization could not be reliably assessed. Second, 24-hour recanalization may include both early and delayed (ie, less clinically useful, reperfusion). Third, the original CTA-CBS and its adaptation to T2* are weighted toward proximal occlusion, assigning higher points to terminal internal carotid artery and M1 clot locations. This score is, therefore, by essence more useful for predicting outcome in proximal occlusions. A different weighting, favoring distal clots, might increase its predictive value for distal occlusions. Fourth, despite recent CT-based data showing that absolute measurement of clot size (cut-off 8 mm) is a predictor of response to treatment, we elected not to measure clot size on T2* sequence because of the size magnification caused by susceptibility artifacts.

**Conclusion**

T2*-CBS is a simple and reproducible tool for the semiquantitative assessment of clot burden in anterior circulation stroke imaged within the 4.5-hour time window. High clot burden is associated with proximal occlusion, more severe clinical deficit, larger DWI and PWI–DWI mismatch.
volumes, and most importantly, lower 24-hour recanalization rate, and less favorable 3-month clinical outcome. T2*-CBS needs external validation, as was done for the CTA-CBS. These scores may help identify which occlusions are less prone to recanalization after IV thrombolysis, together with other easily derived imaging and clinical parameters, and be useful in stroke trials for patient stratification based on thrombus burden, irrespective of the imaging screening method.

Disclosures

None.

References

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e-Figure 1. ROC curve analysis for T2*-CBS prediction of complete recanalization.