Spontaneous intracerebral hemorrhage (ICH) accounts for 8% to 15% of all strokes and is the most fatal form of stroke, with a mortality rate of ≈50% within the first month, and 80% rate of dependency at 6 months from onset. The incidence of spontaneous ICH has not changed in the past 3 decades, and remains without a proven specific treatment. Several factors have been implicated as predictors of morbidity and mortality, including baseline hematoma volume, Glasgow Coma Scale score, presence of intraventricular hemorrhage, and age. Independent of these factors, hematoma expansion has been described as a determinant of both mortality and functional outcome, making attenuation of growth an attractive and potentially modifiable therapeutic target.

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A trial of recombinant activated factor VII (rFVIIa) generated optimism by demonstrating reduction in hematoma expansion; however, it failed to show improvement in clinical outcome and raised questions about the safety of rFVIIa given the thromboembolic complications. The discrepant results may have been because of inclusion of a large number of subjects that did not expand and were therefore not likely to benefit from hemostatic therapy.

Recently, the computed tomography angiography (CTA) spot sign has been validated in several studies as an imaging biomarker for hematoma expansion and poor outcome. CTA spot sign has various descriptions and the outcome variables and definitions of hematoma expansion are not constant across studies, the results are consistent irrespective of definition, spot sign presence reliably predicts expansion. The largest prospective study, Prediction of Haematoma Growth and Outcome in Patients With Intracerebral Haemorrhage Using the Spot Sign on 90-Second Delayed Computed Tomography Angiography Improves Sensitivity for Hematoma Expansion and Mortality

**Background and Purpose**—The computed tomography angiography (CTA) spot sign is a validated biomarker for poor outcome and hematoma expansion in intracerebral hemorrhage. The spot sign has proven to be a dynamic entity, with multimodal imaging proving to be of additional value. We investigated whether the addition of a 90-second delayed CTA acquisition would capture additional intracerebral hemorrhage patients with the spot sign and increase the sensitivity of the spot sign.

**Methods**—We prospectively enrolled consecutive intracerebral hemorrhage patients undergoing first pass and 90-second delayed CTA for 18 months at a single academic center. Univariate and multivariate logistic regression were performed to assess clinical and neuroimaging covariates for relationship with hematoma expansion and mortality.

**Results**—Sensitivity of the spot sign for hematoma expansion on first pass CTA was 55%, which increased to 64% if the spot sign was present on either CTA acquisition. In multivariate analysis the spot sign presence was associated with significant hematoma expansion: odds ratio, 17.7 (95% confidence interval, 3.7–84.2; P=0.0004), 8.3 (95% confidence interval, 2.0–33.4; P=0.004), and 12.0 (95% confidence interval, 2.9–50.5; P=0.0008) if present on first pass, delayed, or either CTA acquisition, respectively. Spot sign presence on either acquisitions was also significant for mortality.

**Conclusions**—We demonstrate improved sensitivity for predicting hematoma expansion and poor outcome by adding a 90-second delayed CTA, which may enhance selection of patients who may benefit from hemostatic therapy. (Stroke. 2014;45:3293-3297.)

Key Words: cerebral hemorrhage ■ computed tomography angiography ■ mortality
CT-Angiography Spot Sign (PREDICT), demonstrated sensitivity of 51% for hematoma expansion when the spot sign was present on routine arterial phase imaging. Additional studies have shown that the spot sign is a dynamic entity, which is also present on delayed CTA, venous phase CTA, dynamic CTA, postcontrast CT, and CT perfusion (CTP). We investigated whether the addition of a 90-second delayed CTA acquisition would capture additional ICH patients with the spot sign and increase the sensitivity for predicting hematoma expansion and poor outcome.

Methods

Patients

The study protocol was approved by the Massachusetts General Hospital institutional ethics review board. Subjects were enrolled prospectively, from February 2012 to August 2013, at a single academic center. Consecutive patients with spontaneous ICH who underwent a noncontrast CT (NCCT) followed by CTA with 90-second delayed acquisition at the time of presentation were included. Patients with secondary ICH, including trauma, an underlying neoplasm or vascular malformation, hemorrhagic venous infarct or hemorrhagic conversion of ischemic stroke were excluded from the study. Patients were not excluded based on time from symptom onset to CTA. Patients who underwent surgery for hematoma evacuation or died before a follow-up CT was performed were excluded from the primary analysis, but included in a secondary analysis assessing functional outcome.

Clinical Information

Baseline demographic and clinical variables are listed in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Spot Sign Positive (n=36)</th>
<th>Spot Sign Negative (n=85)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>74±16</td>
<td>69±15</td>
<td>0.12</td>
</tr>
<tr>
<td>Sex (male), n (%)</td>
<td>22 (61%)</td>
<td>45 (53%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Warfarin, n (%)</td>
<td>6 (17%)</td>
<td>10 (12%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>29 (81%)</td>
<td>63 (75%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Admit glucose, median (IQR), mg/dL</td>
<td>156.5 (128.5–185)</td>
<td>131 (112.5–165.5)</td>
<td>0.048</td>
</tr>
<tr>
<td>Time from symptom onset to CTA, median (IQR), h</td>
<td>2.8 (1.2–5.3)</td>
<td>5.6 (3.1–11.0)</td>
<td>0.0036</td>
</tr>
<tr>
<td>Baseline hematoma volume, median (IQR), mL</td>
<td>81.1 (37.1–123.0)</td>
<td>19.7 (5.3–45.4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 1. Baseline Characteristics

Image Acquisition

All patients enrolled in this study underwent NCCT, immediately followed by CTA of the head or head and neck, with a 90-second delayed acquisition through the hematoma volume, using strict standard departmental protocols on a 16- or 64-section helical multi-detector computed tomography scanner. The first pass CTA acquisition was performed using a semiautomated attenuation triggering SmartPrep (GE Healthcare) technique, injecting 65 to 85 mL at 4 to 5 mL/s. For first pass CTA, the following parameters were applied: 120 kV, 235 mA, 0.5 s/rotation, table speed of 20.6 mm/rotation, and 0.625-mm section thickness. To mitigate radiation, the delayed CTA acquisition included only the hematoma volume of interest and mAs was reduced by almost half (125 mA; 0.5 s/rotation). A follow-up NCCT of the head was performed within 24 hours of the CTA examination.

Statistical Analysis

We performed a prospective analysis of retrospectively collected data. Discrete variables are summarized as count (percentage [%]) and continuous variables as mean (SD) or median (interquartile range) when appropriate. We assessed the spot sign and its potential association with hematoma expansion (dichotomous outcome), starting with univariate logistic regression. Predictors significant at the P<0.20 level in univariate analysis, in addition to age and sex, were subsequently tested for an independent association with the outcome of interest in a multivariable logistic regression model. No interaction terms were included because these are not well known in the appearance of spot sign. Subsequently, we calculated sensitivity, specificity, positive predictive value, negative predictive value, and accuracy, using standard methods, to determine the accuracy of the spot sign in predicting hematoma expansion on first pass, delayed, or either CTA acquisition, separately. The threshold of significance was set at P<0.05. All statistical analyses were performed using JMP Pro version 9.0 (SAS Institute Inc., Cary, NC).

Results

Although a total of 121 patients met the inclusion criteria, only 74 (61%) had a follow-up NCCT within 24 hours and therefore met the primary outcome criteria for assessing hematoma expansion. For the secondary analysis, assessing inhospital mortality, all 121 patients were included. In addition, functional status at discharge was available for 117 (97%) of patients (the remaining 4 subjects had incomplete medical records/discharge summaries). Of the 47 patients excluded from the primary analysis, 25 died before follow-up, 9 underwent surgery, 7 had a follow-up MRI rather than CT, and 6 had no follow-up for unknown reasons. These excluded patients had a high spot sign–positive rate of 45%, and 90% died in hospital.

Delayed Spot Sign Correlation With Hematoma Expansion

All baseline characteristics are summarized in Tables 1 and 2. In summary, of the 74 patients included in the primary analysis, 15 had a spot sign present on first pass, delayed, or both CTA acquisitions. The rate of hematoma expansion overall was 15%, with 47% expansion in the spot sign–positive group and 7% expansion in the spot sign–negative group. The median baseline hematoma volume was 19.1 mL (interquartile range,
5.0–40.9) in the spot sign–negative group and 54.6 (interquartile range, 28.5–86.5) in the spot sign–positive group.

Accuracy measures for the spot sign on first pass CTA were sensitivity 55%, specificity 94%, positive predictive value 60%, negative predictive value 92%, and accuracy 88%. Accuracy measures for the spot sign on delayed CTA were sensitivity 55%, specificity 87%, positive predictive value 43%, negative predictive value 92%, and accuracy 82%. Accuracy measures for the spot sign on either CTA acquisition were sensitivity 64%, specificity 87%, positive predictive value 47%, negative predictive value 93%, and accuracy 84%. These values are summarized in Table 3.

In the univariate analysis, warfarin, time to scan, initial volume, and spot sign presence were associated with significant hematoma expansion. In multivariate analysis adjusted for age, sex, warfarin use, time to CTA, and baseline hematoma volume, the spot sign on both CTA acquisition and warfarin remained associated with hematoma expansion (Table 4).

Delayed Spot Sign Correlation With Mortality and Functional Status

The secondary analysis included 121 patients, 36 of which had a spot sign present on first pass, delayed, or both CTA acquisitions. The spot sign was present on first pass CTA only in 1 patient, both acquisitions in 20 patients, and on the delayed 90-second acquisition only in 15 patients.

In univariate analysis, glucose, hypertension, spot sign presence, and warfarin were associated with mortality. Multivariable analysis determined that the spot sign on either CTA acquisition ($P \leq 0.0001$) and glucose ($P = 0.04$) was independent predictors of mortality (Table 4).

Modified Rankin Scale at discharge ranged from 1 to 6 in all groups. The median modified Rankin Scale in the spot sign–negative groups was 4, with 79.5% of patients having a poor outcome (modified Rankin Scale $\geq 3$). The median modified Rankin Scale in the groups of patients with a spot sign on first pass CTA, delayed CTA, or either CTA acquisition was 6.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>SS on First Pass CTA</th>
<th>SS on Delayed CTA</th>
<th>SS on Either CTA Acquisition</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects (%)</td>
<td>74 (100.0)</td>
<td>59 (79.7)</td>
<td>10 (13.5)</td>
<td>14 (18.9)</td>
</tr>
<tr>
<td>Baseline ICH volume, median (IQR)</td>
<td>24.3 (5.8 to 53.5)</td>
<td>19.1 (5.0 to 40.9)</td>
<td>32.9 (22.3 to 64.7)</td>
<td>62.5 (27.4 to 88.6)</td>
</tr>
<tr>
<td>Follow-up ICH volume, median (IQR)</td>
<td>23.1 (5.7 to 55.9)</td>
<td>20.2 (5.2 to 39.5)</td>
<td>54.7 (27.1 to 113.7)</td>
<td>79.3 (27.1 to 112.8)</td>
</tr>
<tr>
<td>Intraventricular extension</td>
<td>31 (41.9)</td>
<td>23 (39.0)</td>
<td>5 (50.0)</td>
<td>7 (50.0)</td>
</tr>
<tr>
<td>Time to follow-up CT, median (IQR), h</td>
<td>6.4 (4.8 to 10.5)</td>
<td>6.4 (4.9 to 11.5)</td>
<td>4.7 (4.0 to 7.2)</td>
<td>6.0 (4.1 to 8.0)</td>
</tr>
<tr>
<td>Hematoma expansion &gt;6 mL or 33%</td>
<td>11 (14.9)</td>
<td>4 (6.8)</td>
<td>6 (60.0)</td>
<td>6 (42.9)</td>
</tr>
<tr>
<td>Absolute change in volume, median (IQR), mL</td>
<td>0.05 (−1.8 to 1.4)</td>
<td>−0.1 (−1.8 to 0.7)</td>
<td>12.1 (1.0 to 30.2)</td>
<td>2.9 (−3.4 to 20.0)</td>
</tr>
<tr>
<td>Absolute change in volume, median (IQR), %</td>
<td>0.8 (−8.2 to 7.7)</td>
<td>−2.2 (−9.2 to 5.0)</td>
<td>49.4 (2.8 to 82.6)</td>
<td>5.1 (−4.1 to 74.2)</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>121 (100.0)</td>
<td>85 (70.2)</td>
<td>21 (17.4)</td>
<td>35 (28.9)</td>
</tr>
<tr>
<td>Inhospital mortality</td>
<td>48 (39.7)</td>
<td>22 (25.9)</td>
<td>15 (71.4)</td>
<td>26 (74.3)</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; CTA, computed tomography angiography; ICH, intracerebral hemorrhage; IQR, interquartile range; mRS, modified Rankin Scale; and SS, spot sign.
Discussion

The addition of a delayed CTA acquisition captures additional patients destined to undergo significant hematoma expansion and increases the predictive ability of the spot sign. We observed a sensitivity of 55% for predicting hematoma expansion if the spot sign was present on first pass CTA, which increased to 64% if the spot sign was present on either CTA acquisition. Previous studies of the spot sign in predicting hematoma expansion have reported sensitivities ranging from 51% to 100%.9,10,12–15,18,25,26; however, many of these studies were limited by a small number of patients, their retrospective nature, and heterogeneity in definitions of the spot sign and hematoma expansion. PREDICT was the largest prospective study, reporting sensitivity of 51%; however, it was a multicenter trial with CTA protocol varying by institution.15 The authors of PREDICT recently performed a post hoc analysis on their data and found that ≥20% of their CTAs were acquired in the venous phase, and that later image acquisition improved the frequency of spot sign detection.23

The spot sign is a dynamic entity, when present on the first pass CTA acquisition usually persists on the delayed acquisition (all but 1 patient), and that almost half of spot sign–positive patients (15/36) only demonstrated the sign on the delayed CTA acquisition.

Previous retrospective studies have examined the use of contrast extravasation or leakage on postcontrast CT. Hallevi et al14 demonstrated that contrast extravasation on postcontrast CT was a more sensitive predictor of hematoma expansion than the spot sign, and Ederies et al15 demonstrated that postcontrast CT leakage in addition to the spot sign improved sensitivity for hematoma expansion. More recent studies using dynamic CTA17 and CT perfusion20,21 showed improved detection of the spot sign and increased accuracy for predicting outcome and hematoma expansion. Although it is clear that the spot sign is a dynamic finding, there is no accepted consensus on the timing of image acquisition. In our experience, the 90-second delayed CTA acquisition produces optimal and reproducible results. Some of the uncertainty on optimal timing for capturing the CTA spot sign has to do with the biological underpinnings of the finding, which is not well understood. In patients with underlying vascular disease such as hypertensive lipohyalinosis, the primary source of hemorrhage is likely from rupture of a diseased vessel, which triggers a cascade of secondary bleeding as a result of mass effect that stretches and disrupts surrounding arteries as proposed by Fisher.27

Our prospective design included patients with large base-line hematoma volumes and late or unknown time to presentation and different follow-up imaging, which differs from prior studies, to not exclude late expanders. PREDICT excluded patients with baseline ICH volume >100 mL and time from symptom onset >6 hours, which may have included patients destined to undergo hematoma expansion and may partly explain its modest reported sensitivity. Our results are concordant with other studies, which have shown that patients with the spot sign have larger hematoma volumes at presentation and present earlier,15,28 and that warfarin is an independent predictor of hematoma expansion.4,99 Glucose, as in prior reports, was a predictor of mortality.29

Goldstein et al10 demonstrated that contrast extravasation on CTA was a significant predictor of hematoma expansion independent of time to presentation, and Brouwers et al50 showed that the CTA spot sign accurately predicts hematoma expansion even in patients with a delayed presentation (beyond 6 hours) or unknown symptom onset. Given that there is no proven treatment of benefit for ICH, more inclusive patient selection criteria may be key in designing future trials of hemostatic therapy.

Limitations of our study include that it was performed at a single center with a selected population, with a high rate of inhospital mortality and therefore lack of follow-up imaging on a large number of patients. Patients without follow-up imaging also had a high proportion of spot sign, which may have underestimated the predictive value of the spot sign for ICH expansion. There was no standardized timing for the follow-up NCCT, which ranged from 0.9 to 23.9 hours. The additional 90-second delayed CTA acquisition leads to increased radiation to the patient; however, we modified our protocol to keep radiation dose as low as possible.

The spot sign has proven itself as an attractive selection tool for therapeutic interventions in patients with ICH, in an attempt to halt or decrease hematoma expansion. There are several trials ongoing, including the Spot Sign for Predicting and Treating ICH Growth Study (STOP-IT) and Spot Sign Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT), comparing rFVIIa to placebo in spot sign–positive patients. An ancillary study of Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-II) seeks
to determine whether patients with the spot sign will benefit from intensive blood pressure reduction.\textsuperscript{31}

Conclusions

The discovery of imaging biomarkers such as the spot sign is an ever expanding field of study with encouraging results. We demonstrate improved sensitivity for predicting hematoma expansion and poor outcome by adding the 90-second delayed acquisition to our standard CTA protocol, which may enhance selection of patients who may benefit from hemostatic therapy.

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Disclosures

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Spot Sign on 90-Second Delayed Computed Tomography Angiography Improves Sensitivity for Hematoma Expansion and Mortality: Prospective Study
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