Rate of Contrast Extravasation on Computed Tomographic Angiography Predicts Hematoma Expansion and Mortality in Primary Intracerebral Hemorrhage

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Background and Purpose—In primary intracerebral hemorrhage, the presence of contrast extravasation after computed tomographic angiography (CTA), termed the spot sign, predicts hematoma expansion and mortality. Because the biological underpinnings of the spot sign are not fully understood, we investigated whether the rate of contrast extravasation, which may reflect the rate of bleeding, predicts expansion and mortality beyond the simple presence of the spot sign.

Methods—Consecutive intracerebral hemorrhage patients with first-pass CTA followed by a 90-second delayed postcontrast CT (delayed CTA) were included. CTAs were reviewed for spot sign presence by 2 blinded readers. Spot sign volumes on first-pass and delayed CTA and intracerebral hemorrhage volumes were measured using semiautomated software. Extravasation rates were calculated and tested for association with hematoma expansion and mortality using uni- and multivariable logistic regressions.

Results—One hundred and sixty-two patients were included, 48 (30%) of whom had ≥1 spot sign. Median spot sign volume was 0.04 mL on first-pass CTA and 0.4 mL on delayed CTA. Median extravasation rate was 0.23 mL/min overall and 0.30 mL/min among expanders versus 0.07 mL/min in nonexpanders. Extravasation rates were also significantly higher in patients who died in hospital: 0.27 mL/min versus 0.04 mL/min. In multivariable analysis, the extravasation rate was independently associated with in-hospital mortality (odds ratio, 1.09 [95% confidence interval, 1.04–1.18]; P=0.004), 90-day mortality (odds ratio, 1.15 [95% confidence interval, 1.08–1.27]; P=0.0004), and hematoma expansion (odds ratio, 1.03 [95% confidence interval, 1.01–1.08]; P=0.047).

Conclusions—Contrast extravasation rate, or spot sign growth, further refines the ability to predict hematoma expansion and mortality. Our results support the hypothesis that the spot sign directly measures active bleeding in acute intracerebral hemorrhage.

Key Words: cerebral hemorrhage ■ CT angiography ■ intracerebral hemorrhage ■ mortality

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controlled trials, including the recently published Second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2) trial. This may be attributed to the challenge of accurately identifying those patients most likely to benefit from an intervention; ie, those who will experience expansion severe enough to negatively impact outcome.

Adaptation of selection tools are, therefore, warranted and contrast extravasation following computed tomographic angiography (CTA), commonly termed the spot sign, has been a widely studied phenomenon. The spot sign is thought to represent active bleeding, but the biological underpinnings of the spot sign are not fully understood. Therefore, we investigated whether the size of the spot sign changes on delayed imaging, and if so, whether the rate of change predicts hematoma expansion and mortality beyond the simple presence of the spot sign.

Methods

Study Design

Patients with primary ICH presenting to Massachusetts General Hospital, an urban academic tertiary care center, were approached for enrollment in an ongoing prospective cohort study of ICH. Written informed consent was obtained from all patients or their legally authorized healthcare proxies, or their consent was waived by a protocol specific allowance. The Institutional Review Board at Massachusetts General Hospital approved all portions of the study.

Study Subjects

During the study period April 2012 to May 2013, patients with consecutive ICH enrolled in the aforementioned prospective cohort study were considered eligible for the current analysis based on the following criteria: (1) primary ICH confirmed on CT of sufficient quality for volumetric analyses; (2) baseline (first-pass) CTA for spot sign reading and spot sign volume measurements; (3) 90-second delayed CTA for repeated spot sign reading and volumetric measurements.

Patients with secondary ICH were excluded, including vascular malformations, neoplasms, trauma, or hemorrhagic transformation of an ischemic stroke. Patients with primary intraventricular hemorrhage and those who underwent surgical evacuation were also excluded.

Clinical Data

Clinical data including age, sex, past medical history, and previous medication use (eg, oral anticoagulants) were all collected through patient interviews (or their surrogates). Prospectively recorded admission variables comprised Glasgow Coma Scale, systolic and diastolic blood pressure, and time from symptom onset to CTA. At discharge and 90 days, trained study staff ascertained mortality. The Social Security Death Index, a database of deaths reported to the United States Social Security Administration, was used to supplement mortality data.

Imaging Analyses

Experienced neurologists or neuroradiologists assigned hemorrhage locations for all patients, blinded to clinical data, functional outcome, and CTA readings. ICH location was categorized into lobar, deep, brain stem, and cerebellar. Volumetric measurements for baseline and follow-up ICH volumes were performed by experienced readers, blinded to other data points, according to previously published protocols.

Analyze was used for semiautomated volume segmentation. Significant hematoma expansion, assessed as secondary end point, was defined as either an absolute volume increase of 6 mL or a relative increase of 33% between the first and the second CTA.

Of note, delayed CTA imaging became standard of care at our institution in April 2012 and encompasses a 90-second delayed postcontrast CT (without a new bolus of contrast). This acquisition will be termed delayed CTA throughout this article for consistency with definitions used in the recent literature.

Spot sign status (absent or present) was assigned by 2 blinded readers in accordance with standard methods with excellent interrater reliability. Spot sign volumes on first-pass and delayed CTA were measured using the previously described Analyze software (Figure 1). Contrast extravasation rates were calculated using the following formula: follow-up spot sign volume minus baseline spot sign volume divided by time elapsed between first-pass and delayed CTA (formula at end of the paragraph). Following this formula, spot sign-negative patients were assigned a contrast extravasation rate of zero.

\[ \text{CER} = \frac{\text{SSV}_{FU} - \text{SSV}_{BL}}{t_{DEL-FP}} \]

where CER is the contrast extravasation rate, SSV_{FU} is the spot sign volume (follow-up), SSV_{BL} is the spot sign volume (baseline), and t_{DEL-FP} is the time delayed minus first-pass CTA

Statistical Analyses

Discrete variables are presented as count and percentage (%), whereas continuous variables are presented as mean and SD or median and interquartile range (IQR) where appropriate. CTA contrast extravasation rates are presented as milliliter per minute (mL/min) or milliliter per hour (mL/h). The primary analysis comprised uni- and multivariable logistic regressions to test the relationship between contrast extravasation rate and in-hospital mortality. Hematoma expansion was tested as a secondary end point in the subgroup of patients with an available follow-up CT. Multivariable models included age, sex, and variables with P<0.20 in the univariable analyses. Collinear variables, measured using the variance inflation factor, were removed from the multivariable model as appropriate. Of note, the spot sign was not included in the multivariable models because of strong collinearity with contrast extravasation rate. All analyses were also repeated using interaction terms, returning identical results (data not shown).

In addition, median contrast extravasation rates were compared for spot sign–positive patients. All statistical analyses were performed using JMP Pro version 11.0 (SAS Institute Inc, Cary, NC). The threshold for significance was set at P<0.05.
Results

Study Population
During the study period, 225 patients presented to our institution with primary ICH and had an available CTA. After application of the eligibility criteria, 162 patients had a first-pass and delayed CTA of sufficient quality for analysis (Figure 2). Baseline cohort characteristics are provided in Table 1. Briefly, the mean age was 73 (SD, 13) years, 65 (40%) were women, and 31 (19%) patients were taking warfarin before admission. One hundred and twenty-five (77%) patients had a follow-up CT available for analysis. Patients without an available follow-up CT were more likely to be on preadmission oral anticoagulation, had lower Glasgow Coma Scale scores at hospital admission, larger baseline ICH volumes, and higher in-hospital mortality rates (all \( P < 0.05 \)).

CT and CTA Imaging
Of the 162 patients included, 81 (50%) had lobar, 60 (37%) had deep, 14 (9%) had cerebellar, and 7 (4%) had brain stem ICH. Median baseline ICH volume was 23 mL (IQR, 7–66 mL). At least 1 spot sign was identified in 41 (25%) patients on first-pass CTA and in 48 (30%) patients on delayed CTA (median delay, 84 seconds [IQR, 65–141 seconds]). Median spot sign volumes on first-pass and delayed CTA were 0.04 mL (IQR, 0.01–0.09 mL) and 0.4 mL (IQR, 0.06–0.91 mL), respectively. Hematoma expansion was present in 26 of the 125 (21%) patients with an available follow-up CT.

Contrast Extravasation Rates
Median contrast extravasation rate was 0.23 mL/min (IQR, 0.06–0.64 mL/min) among spot sign–positive patients (spot sign–negative patients were assigned a rate of zero). Median extravasation rates were significantly higher in spot sign–positive patients who died in hospital versus those who survived: 0.27 mL/min (IQR, 0.13–0.77 mL/min) versus 0.04 mL/min (IQR, 0.009–0.08 mL/min), \( P < 0.0001 \). Among spot sign–positive patients, those who experienced significant expansion had higher median extravasation rates: 0.30 mL/min (IQR, 0.06–0.68 mL/min) versus 0.07 mL/min (IQR, 0.03–0.29 mL/min), \( P = 0.16 \). Patients with a lobar ICH had higher median extravasation rates than those with deep ICH: 0.33 mL/min (IQR, 0.11–0.77 mL/min) versus 0.11 mL/min (IQR, 0.05–0.26 mL/min), \( P = 0.046 \).

Predictors of In-Hospital Mortality and Hematoma Expansion
In univariable analysis, baseline ICH volume, CTA spot sign, and contrast extravasation rate were all associated with in-hospital mortality (Table 2). In multivariable analysis (adjusted for age, sex, and warfarin use), time to CTA, baseline ICH volume, and contrast extravasation rate were all independently associated with in-hospital mortality (Table 3). Contrast extravasation rate was also associated with 90-day mortality (available for all patients; odds ratio, 1.15 [95% confidence interval, 1.08–1.27]; \( P = 0.0004 \)).

Baseline ICH volume, CTA spot sign, and contrast extravasation rate were also associated with hematoma expansion, as well as shorter time to CTA, in univariable analysis (Table 2). A limited multivariable analysis (based on only 26 outcome events) showed an association with hematoma expansion for shorter time to CTA (odds ratio, 1.10 [95% confidence interval, 1.02–1.32]; \( P = 0.01 \)) and contrast extravasation rate (odds ratio, 1.03 [95% confidence interval, 1.01–1.08]; \( P = 0.047 \); Table 3).

Discussion
This study demonstrates that CTA contrast extravasation rate predicts hematoma expansion, in-hospital death, and 90-day mortality.
Contrast Extravasation Rate Predicts Mortality

Table 1. Cohort Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>162</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>73 (13)</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>65 (40)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>131 (82)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37 (24)</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>82 (51)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>31 (19)</td>
</tr>
<tr>
<td>GCS, median (IQR)</td>
<td>12 (6–15)</td>
</tr>
<tr>
<td>SBP, median (IQR)</td>
<td>176 (155–204)</td>
</tr>
<tr>
<td>Time to CTA, h, median (IQR)</td>
<td>4 (2–8)</td>
</tr>
<tr>
<td>ICH location</td>
<td></td>
</tr>
<tr>
<td>Lobar</td>
<td>81 (50)</td>
</tr>
<tr>
<td>Deep</td>
<td>60 (37)</td>
</tr>
<tr>
<td>Brain stem</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>14 (9)</td>
</tr>
<tr>
<td>Baseline ICH volume, median (IQR)</td>
<td>23 (7–66)</td>
</tr>
<tr>
<td>Intraventricular extension</td>
<td>94 (58)</td>
</tr>
<tr>
<td>Baseline IVH volume, median (IQR)*</td>
<td>7 (2–16)</td>
</tr>
<tr>
<td>Spot sign presence</td>
<td></td>
</tr>
<tr>
<td>First-pass CTA</td>
<td>41 (25%)</td>
</tr>
<tr>
<td>Delayed CTA</td>
<td>48 (30%)</td>
</tr>
<tr>
<td>Spot sign volume, median (IQR)</td>
<td></td>
</tr>
<tr>
<td>First-pass CTA</td>
<td>0.04 (0.01–0.09)</td>
</tr>
<tr>
<td>Delayed CTA</td>
<td>0.4 (0.06–0.91)</td>
</tr>
<tr>
<td>Extravasation rate, mL/min</td>
<td>0.23 (0.06–0.64)</td>
</tr>
<tr>
<td>Extravasation rate, mL/h</td>
<td>13.8 (3.58–38.42)</td>
</tr>
<tr>
<td>Hematoma expansion†</td>
<td>26 (21%)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>65 (40%)</td>
</tr>
<tr>
<td>90-d mortality</td>
<td>70 (43%)</td>
</tr>
</tbody>
</table>

CTA indicates computed tomographic angiography; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IQR, interquartile range; IVH, intraventricular hemorrhage; and SBP, systolic blood pressure.

*Data refer only to ICH patients with intraventricular extension only (n=94; 58%).
†Data refer only to ICH patients with a follow-up CT (n=125; 77%).

Our results add to the body of literature, suggesting that spot sign represents active bleeding and may additionally help to better select patients for clinical trials aimed at the attenuation of hematoma expansion.

The CTA spot sign is strongly correlated with both hematoma expansion and poor functional outcome.12–15 It has been widely hypothesized that the spot sign represents active contrast extravasation and therefore serves as a visual manifestation of continued bleeding.14,16 Additional hypotheses of what the spot sign represents include Charcot–Bouchard aneurysms, microdissections, and pseudoaneurysms.12,20 Our findings lend credence to the active bleeding theory because spot signs were shown to increase in size between the first-pass and delayed CTAs (Table 1). The solely positive extravasation rates likely mark an increase in blood (mixed with contrast agent) leaving the injured vessel and entering the brain parenchyma over time. The association of higher extravasation rates with more hematoma expansion (ie, larger final ICH volumes) further supports this active bleeding theory. This demonstration of active bleeding, as well as the increase in the number of spot signs visible on delayed CTA, provides additional evidence for an avalanche expansion model of cascading small-vessel injury as originally proposed by Dr Fisher.21 Based on the observation of multiple recently ruptured vessels at the periphery of serially sectioned hematomas, this model describes the process of hematoma expansion as secondary mechanical shearing of neighboring vessels caused by expansion of the initial hemorrhage.21 When these neighboring vessels rupture, contrast leaks out and is seen as an additional spot sign on the delayed CTA.

Our results show that the contrast extravasation rate better distinguishes between expanders and nonexpanders than the CTA spot sign alone. Further refinement of the CTA spot sign as a prognostic tool is needed because the sensitivity for predicting significant hematoma expansion in 2 recent prospective validation studies reached only 0.51 and 0.64, with positive predictive values of 0.61 and 0.52, respectively.15,22 By the superior selection of those patients most likely to expand, clinical trials will also be more likely to show a benefit for treatments aimed at arresting expansion because the potential benefit of any treatment must be balanced against its potential harms.11 The enhanced selection of those patients who are actively bleeding while in the CT scanner is an important first step in this process.

Additional provocative data come from the raw extravasation rates in spot sign–positive patients: 0.24 mL/min (IQR, 0.06–0.64 mL/min), which translates into an hourly bleeding rate of ≈14 mL/h (Table 1). In the phase III recombinant factor VIIa trial, the mean increase in ICH volume between the baseline and 24-hour CT was only 7.5 mL (95% confidence interval, 5.4–9.6) in the nontreated (placebo) arm.7 Therefore, the bleeding rate of 14 mL/h described here seems high although this only represents spot sign–positive patients. Such a bleeding rate seems unsustainable given the limited intracranial volume and would probably lead to rapid deterioration and mortality in patients with primary ICH.
Table 3. Multivariable Analysis of In-Hospital Mortality and Hematoma Expansion

<table>
<thead>
<tr>
<th>Variable</th>
<th>In-Hospital Death OR (95% CI)</th>
<th>P Value</th>
<th>Hematoma Expansion OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.00 (0.96–1.05)</td>
<td>0.90</td>
<td>1.00 (0.96–1.05)</td>
<td>0.90</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1.70 (0.54–5.62)</td>
<td>0.37</td>
<td>1.70 (0.54–5.62)</td>
<td>0.37</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1.70 (0.28–14.00)</td>
<td>0.59</td>
<td>1.70 (0.28–14.00)</td>
<td>0.59</td>
</tr>
<tr>
<td>Time to CTA†</td>
<td>1.11 (1.02–1.23)</td>
<td>0.02</td>
<td>1.11 (1.02–1.23)</td>
<td>0.02</td>
</tr>
<tr>
<td>Baseline ICH volume</td>
<td>1.04 (1.03–1.07)</td>
<td>&lt;0.0001</td>
<td>1.01 (1.00–1.02)</td>
<td>0.10</td>
</tr>
<tr>
<td>Extravasation rate, mL/h</td>
<td>1.09 (1.04–1.18)</td>
<td>0.004</td>
<td>1.03 (1.01–1.08)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CTA, computed tomographic angiography; ICH, intracerebral hemorrhage; and OR, odds ratio.

*Data refer only to ICH patients with a follow-up CT (n=125; 77%). Analysis restricted to 3 covariates based on the rule of 1 covariate per 10 outcome events (n=26).

†Odds ratio for shorter time to CTA.

ey early death in these patients. These amounts of hematoma expansion were typically not seen on follow-up CTs in our cohort. It is, therefore, more plausible that hematoma expansion occurs at a variable pace as opposed to a linear fashion. The inherent downside of these findings is that interventions aimed at the restriction of expansion need to be implemented early in the course of disease because extravasation rates are high in the acute phase (when patients undergo their CTA) and may plateau later on although the latter needs to be established in future studies. This brings to mind similarities with the time-dependent effectiveness of intravenous tissue-type plasminogen activator for the treatment of acute ischemic stroke.23

Our study has several strengths, including its prospective design, the standard acquisition of delayed CTAs at our institution since 2012, and the large sample size when compared with previous studies assessing the role of delayed CTA acquisitions. Nevertheless, 162 patients is still a limited number to establish definitive associations. Furthermore, our study is limited by its single-center design and the lack of follow-up CTs in almost one quarter of the patients. The latter is a recurring problem in all nonrandomized (observational) studies without standardized follow-up imaging. Finally, our study is limited by its outcome measures of expansion and mortality; more refined measures like quality of life were not collected as a part of the present study.

In conclusion, our results demonstrate that contrast extravasation rate (ie, spot sign growth) further refines the ability to predict hematoma expansion and in-hospital mortality. These data support the hypothesis that the spot sign directly measures active bleeding in the acute phase of ICH.

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