Clinical Applications of the Computed Tomography Angiography Spot Sign in Acute Intracerebral Hemorrhage

A Review

H. Bart Brouwers, MD; Joshua N. Goldstein, MD, PhD; Javier M. Romero, MD; Jonathan Rosand, MD, MSc

Spontaneous intracerebral hemorrhage (ICH) is the most fatal form of stroke, with 1-month mortality rates often exceeding 40% and rates of death or severe disability exceeding 75%.[1, 2] Nearly 20 years ago, the first observational studies demonstrated that hematoma volume on presentation was among the most potent predictors of survival and functional outcome.3 Subsequent studies identified the frequent occurrence of hematoma expansion after the initial computed tomography (CT) scan.4 Occurring in ≤40% of patients, this expansion further contributes to poor outcome.5, 6 These observations have made the arrest of expansion the most common target for acute clinical trials in ICH.7, 8

Thus far, the specific targeting of hematoma expansion in clinical trials has yet to yield improvement in clinical outcome. This may be attributed to difficulty in identifying those individuals most likely to benefit from the intervention, those who will experience hematoma expansion. Risk factors for expansion include early presentation, baseline hematoma volume, and warfarin use.4, 10, 11 Even among patients presenting within 3 hours, however, expansion severe enough to cause clinical deterioration occurs in no more than 40%.4, 6–8 The CT angiography (CTA) spot sign has emerged in recent years as a potential predictor of hematoma expansion, and a potential tool in guiding therapies in both research and clinical care.

CT Angiography Spot Sign

Definition

First described in 1999,12 the CTA spot sign has evolved in its definition from the broader concept of contrast extravasation, comprising high-density material or contrast leakage within the hematoma.12–14 to encompass foci of enhancement within the hematoma on CTA source images.15 Although definitions of the spot sign used in individual studies continue to vary, all are variations on this standard (Table 1). In 2009, a spot sign score was developed, incorporating the maximum number, maximum attenuation (in Hounsfield units), and maximum dimension of spot signs (Figure).19 Currently, the term contrast extravasation is reserved for the presence of contrast within the hematoma on postcontrast CT.16, 17 This terminology can be confusing because the spot sign is thought to represent contrast extravasation (contrast leakage from the vessels into the hematoma), whereas the neuroimaging definition of contrast extravasation is used to describe the presence of contrast on a postcontrast CT. In this review, we use the term spot sign when referring to CTA source images and contrast extravasation when discussing postcontrast CTs.

Imaging Acquisition

The identification of spot signs is dependent on technical imaging parameters of the CTA and may vary across institutions because CTAs are originally performed to visualize the cerebral vasculature. Delayed images collected after the initial study has been completed (normally obtained between 40 seconds and 3 minutes after contrast injection), can yield spot signs not visualized on the initial CTA.19, 20 Studies have shown that contrast extravasation on postcontrast CT also increases the sensitivity of the spot sign in predicting hematoma expansion.16, 17 However, both delayed CTAs and postcontrast CTs are not routinely obtained at many institutions. Other parameters of the CTA technique also influence the detection and sensitivity of the spot sign including the concentration of the contrast agent used and the speed of individual CT scanners. Technical refinement and standardization of CTA acquisition protocols may therefore be critical to further improve the accuracy of the spot sign.

Frequency

Variations in technique and the differences in definition probably account for the range of spot sign frequencies reported in the literature. The broader definition of contrast extravasation is associated with a higher frequency of 42% (139 of 329 pooled patients; range from 18% to 59%), compared with 24% (426 of 1802 pooled patients; range from 18% to 41%).
for the stricter spot sign definition (Tables 2–4). Another factor with substantial effect on the frequency with which the spot sign is observed is the time elapsed between symptom onset and CTA. As the time from symptom onset to initial CTA increases, the frequency of spot sign appearance decreases.12,18–20 Because only a few studies have examined the frequency of the spot sign in ICH patients whose initial CTA is performed beyond 6 hours of symptom onset, further research is warranted on the accuracy of the spot sign in this extended time window.

Pathophysiology

Although generally assumed to reflect continued bleeding from a ruptured vessel or vessels, very little is known of biological underpinnings of the spot sign. One study showed the spot sign to be associated with faster rates of contrast leakage measured as perfusion CT–derived permeability, emphasizing the theory of continued bleeding.25 In addition, warfarin exposure has been associated with both the presence of a spot sign,19,20,26 as well as the number of spot signs on CTA.15 The association of the apolipoprotein E ε2 allele with hematoma

**Table 1. Study Definitions CT Angiography Contrast Extravasation and Spot Sign**

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Year</th>
<th>Spot Sign Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contrast extravasation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Becker et al12</td>
<td>1999</td>
<td>Visualization of high-density contrast within the clot or ventricular system.</td>
</tr>
<tr>
<td>Murai et al13</td>
<td>1999</td>
<td>Leakage of contrast medium seen as a high-density area on helical CT images.</td>
</tr>
<tr>
<td>Goldstein et al14</td>
<td>2007</td>
<td>The presence of high-density material within the hematoma.</td>
</tr>
<tr>
<td>Ederies et al16</td>
<td>2009</td>
<td>The presence of contrast puddling within the hematoma on the postcontrast CT.</td>
</tr>
<tr>
<td>Hallevi et al17</td>
<td>2010</td>
<td>A hyperdensity (relative to the hematoma) within the hematoma on the postcontrast CT.</td>
</tr>
<tr>
<td><strong>Spot sign</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wada et al15</td>
<td>2007</td>
<td>Foci of enhancement within the hematoma on CTA source images.</td>
</tr>
<tr>
<td>Kim et al18</td>
<td>2008</td>
<td>High-attenuation contrast material within the hematoma.</td>
</tr>
<tr>
<td>Delgado Almandoz et al19,20</td>
<td>2009 and 2010</td>
<td>(1) ≥1 focus of contrast pooling within the ICH; (2) with an attenuation ≥120 HU; (3) discontinuous from normal or abnormal vasculature adjacent to the ICH; and (4) of any size and morphology.</td>
</tr>
<tr>
<td>Thompson et al21</td>
<td>2009</td>
<td>Spot-like or serpiginous foci of enhancement, within the margin of a parenchymal hematoma without connection to outside vessels, &gt;1.5 mm, and an HU density at least double that of background hematoma density.</td>
</tr>
<tr>
<td>Hallevi et al17</td>
<td>2010</td>
<td>A hyperdense spot within the hematoma that was unrelated to a blood vessel.</td>
</tr>
<tr>
<td>Demchuk et al24</td>
<td>2012</td>
<td>One or more foci of contrast enhancement within an acute primary parenchymal hematoma visible on the source images of CTA (similar to Wada et al [2007]).15</td>
</tr>
</tbody>
</table>

CTA indicates computed tomography angiography; ICH, intracerebral hemorrhage; HU, Hounsfield units.
expansion and the spot sign in patients with ICH in the lobar brain regions suggests a model of cascading small vessel injury following ICH as first described by Fisher. In this model, expansion of the initial hematoma is caused by the rupture of small adjacent vessels surrounding the hematoma.

### Risk Factors

Several (clinical) risk factors for the spot sign have been identified. In addition to early presentation, anticoagulation, and apolipoprotein E ε2; large baseline hematoma volume, low Glasgow Coma Scale score on presentation, mean arterial blood pressure 100 mmHg, low serum total cholesterol, and age older than 65 years were associated with the presence of the spot sign. On univariate analysis, the risk factors associated with a spot sign were present at the time of presentation or during the course of disease. On multivariate analysis, the risk factors included in the model were early presentation, anticoagulation, and apolipoprotein E ε2; large baseline hematoma volume, low Glasgow Coma Scale score on presentation, and age older than 65 years. In this model, the multivariate analysis was performed using logistic regression, and the odds ratio with 95% confidence interval was calculated for each risk factor. The Hosmer-Lemeshow goodness-of-fit test was used to assess the fit of the model, and the area under the receiver operating characteristic curve was calculated to assess the model's discriminatory ability. The results showed that the model was well-calibrated and had good discriminatory ability.

### Table 2. CT Angiography Contrast Extravasation and Hematoma Expansion

<table>
<thead>
<tr>
<th>Authors (y)</th>
<th>Study design</th>
<th>No. of patients</th>
<th>No. of patients with contrast extravasation (%)</th>
<th>Time window</th>
<th>Hematoma expansion definition</th>
<th>Expansion (%)</th>
<th>Point estimate multivariate analysis (95% CI)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murai et al (1999)</td>
<td>Prospective</td>
<td>24</td>
<td>5 (21)</td>
<td>&lt;12h from symptom onset</td>
<td>&gt;15 mL increase from baseline ICH volume</td>
<td>3 (14)</td>
<td>n/a</td>
<td>1.00</td>
<td>0.90</td>
<td>0.60</td>
<td>1.00</td>
<td>0.92</td>
</tr>
<tr>
<td>Goldstein et al (2007)</td>
<td>Retrospective</td>
<td>104</td>
<td>58 (56)</td>
<td>All patients</td>
<td>&gt;33% increase from baseline ICH volume</td>
<td>14 (14)</td>
<td>OR 18 (2.1–162)</td>
<td>0.93</td>
<td>0.50</td>
<td>0.22</td>
<td>1.00</td>
<td>0.96</td>
</tr>
<tr>
<td>Ederies et al (2009)</td>
<td>Retrospective</td>
<td>61</td>
<td>11 (18)</td>
<td>&lt;6h from symptom onset</td>
<td>&gt;30% or &gt;6 mL increase from baseline ICH volume</td>
<td>18 (30)</td>
<td>n/a</td>
<td>0.94</td>
<td>0.79</td>
<td>0.97</td>
<td>1.00</td>
<td>0.84</td>
</tr>
<tr>
<td>Hallevi et al (2010)</td>
<td>Prospective</td>
<td>27</td>
<td>13 (59)</td>
<td>&lt;4h from symptom onset</td>
<td>&gt;20% increase from baseline ICH volume</td>
<td>16 (57)</td>
<td>OR 77 (4–1476)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

ICH indicates intracerebral hemorrhage; 95% CI, 95% confidence interval; n/a, not available; OR, odds ratio; PPV, positive predictive value; NPV, negative predictive value; CT, computed tomography.

*These 2 studies examined contrast extravasation, so accuracy measures refer solely to contrast extravasation.

†For these 2 studies, accuracy refers to presence either of a spot sign on CTA source images or any contrast extravasation on postcontrast CT images.

### Table 3. CT Angiography Spot Sign and Hematoma Expansion

<table>
<thead>
<tr>
<th>Authors (y)</th>
<th>Study design</th>
<th>No. of patients</th>
<th>No. of spot-positive patients (%)</th>
<th>Time window</th>
<th>Hematoma expansion definition</th>
<th>Expansion (%)</th>
<th>Point estimate multivariate analysis (95% CI)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wada et al (2007)</td>
<td>Prospective</td>
<td>39</td>
<td>13 (33)</td>
<td>&lt;3h from symptom onset</td>
<td>&gt;30% or &gt;6 mL increase from baseline ICH volume</td>
<td>11 (28)</td>
<td>LR 8.5 (2.9–25)</td>
<td>0.91</td>
<td>0.89</td>
<td>0.78</td>
<td>0.78</td>
<td>0.92</td>
</tr>
<tr>
<td>Delgado et al (2009)</td>
<td>Retrospective</td>
<td>367</td>
<td>71 (19)</td>
<td>All patients</td>
<td>&gt;30% or &gt;6 mL increase from baseline ICH volume</td>
<td>56 (15)</td>
<td>OR 92 (37–227)</td>
<td>0.88</td>
<td>0.93</td>
<td>0.84</td>
<td>0.84</td>
<td>0.90</td>
</tr>
<tr>
<td>Ederies et al (2009)</td>
<td>Retrospective</td>
<td>61</td>
<td>21 (34)</td>
<td>&lt;6h from symptom onset</td>
<td>&gt;30% or &gt;6 mL increase from baseline ICH volume</td>
<td>18 (30)</td>
<td>OR 77 (4–1476)</td>
<td>0.78</td>
<td>0.84</td>
<td>0.75</td>
<td>0.85</td>
<td>0.82</td>
</tr>
<tr>
<td>Hallevi et al (2010)</td>
<td>Prospective</td>
<td>27</td>
<td>11 (41)</td>
<td>&lt;4h from symptom onset</td>
<td>&gt;20% increase from baseline ICH volume</td>
<td>16 (57)</td>
<td>n/a</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>0.85</td>
</tr>
<tr>
<td>Wang et al (2011)</td>
<td>Retrospective</td>
<td>312</td>
<td>76 (24)</td>
<td>&lt;3h from symptom onset</td>
<td>&gt;30% or &gt;6 mL increase from baseline ICH volume</td>
<td>77 (25)</td>
<td>n/a</td>
<td>0.93</td>
<td>0.94</td>
<td>0.93</td>
<td>0.84</td>
<td>0.99</td>
</tr>
<tr>
<td>Li et al (2011)</td>
<td>Prospective</td>
<td>139</td>
<td>30 (22)</td>
<td>&lt;6h from symptom onset</td>
<td>&gt;33% or &gt;12.5 mL increase from baseline ICH volume</td>
<td>32 (23)</td>
<td>n/a</td>
<td>0.72</td>
<td>0.72</td>
<td>0.72</td>
<td>0.84</td>
<td>0.72</td>
</tr>
<tr>
<td>Demchuk et al (2012)</td>
<td>Prospective</td>
<td>228</td>
<td>61 (27)</td>
<td>&lt;6h from symptom onset</td>
<td>&gt;33% or &gt;6 mL increase from baseline ICH volume</td>
<td>73 (32)</td>
<td>RR 2.3 (1.6 – 3.1)</td>
<td>0.51</td>
<td>0.51</td>
<td>0.51</td>
<td>0.51</td>
<td>0.51</td>
</tr>
</tbody>
</table>

ICH indicates intracerebral hemorrhage; 95% CI, 95% confidence interval; LR, likelihood ratio; OR, odds ratio; n/a, not available; RR, relative risk; PPV, positive predictive value; NPV, negative predictive value; CT, computed tomography.

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pressure of >120 mm Hg, and the presence of intraventricular hemorrhage have been associated with risk of spot sign.12,14,19,20

**Clinical Applications**

**Hematoma Expansion**

Multiple retrospective single-center cohort studies have confirmed that contrast extravasation and the spot sign are potent, independent predictors of hematoma expansion (Tables 2 and 3). In addition, a single study has shown that a higher spot sign score is associated with risk of subsequent hematoma expansion.19 Of note, definitions of hematoma expansion vary across studies, but different definitions have all been robustly associated with poor outcome.8 Recently, the multicenter prospective Prediction of Haematoma Growth and Outcome in Patients with Intracerebral Haemorrhage Using the CT Angiography Spot Sign (PREDICT) study confirmed these findings and showed a strong association (relative risk, 2.3 [95% confidence interval {CI}, 1.6–3.1]) between spot sign and development of hematoma expansion of >6 mL or >33% from baseline ICH volume.24 Most studies have been restricted to patients receiving their CTA within 6 hours of symptom onset. However, in studies that included patients whose initial CTAs were performed substantially later in the course of their ICH, the spot sign remained an independent predictor of hematoma expansion, even after adjusting for time from symptom onset to CTA.14,19,20

**Functional Outcome and Mortality**

Several studies have examined the value of the spot sign as a predictor of functional outcome and short-term and long-term mortality (Table 4). All studies show a robust association of the CTA spot sign with both functional outcome and mortality. Similarly, the spot sign score has shown to be associated with both in-hospital mortality and poor clinical outcome at 3 months.20 In the PREDICT study, the 3-month mortality hazard ratio was 2.4 (95% CI, 1.4–4.0) for spot sign–positive patients compared with spot sign–negative patients.24

**Secondary Intracerebral Hemorrhage**

Secondary causes of ICH (eg, aneurysms, trauma, and brain tumors) are generally excluded from spot sign studies because of presumed differences in pathophysiology and the relatively frequent need for surgical treatment. Such secondary causes can mimic a spot sign, and vascular and nonvascular mimics are frequent and can impair its accuracy.20 However, 1 study showed the spot sign also to be predictive of functional outcome in secondary ICH.30 An association with hematoma expansion in secondary ICH could not be assessed because nearly two thirds of patients did not have a follow-up CT available because of early endovascular or surgical intervention.30

**Clinical Implications and Ongoing Trials**

The search for effective treatments that improve outcomes in patients with ICH continues to be challenging. The arrest of hematoma expansion continues to be a target for reducing final ICH volume and improving clinical outcome.5,6 Selection of patients at highest risk for expansion has therefore been a strategy in recent clinical trials searching to improve outcomes.7–9 Early presentation (within 4–6 hours) has been used in these trials as a surrogate for hematoma expansion, but even of the patients presenting ultraearly only 40% experience...
significant hematomas. Therefore, more than half of enrolled patients may be exposed to an intervention without an opportunity to benefit. This challenge provides a potential role for the spot sign as a selection tool. With the spot sign as a strong predictor of hematoma expansion, it may be possible to identify ICH patients who are most likely to have poor outcomes and treat them aggressively. Ongoing clinical trials including Spot Sign for Predicting and Treating ICH Growth (STOP-IT) (ClinicalTrials.gov NCT00810888) and Spot Sign Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT) (ClinicalTrials.gov NCT 01359202) are using the spot sign to select patients for treatment with recombinant factor VIIa. Aggressive blood pressure lowering, as currently tested in nonselected patients by Second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2) and Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-II) may also be guided by spot sign status. The ancillary study of ATACH-II, the Spot Sign Score in Restricting ICH Growth (SCORE-IT, National Institutes of Health—National Institute of Neurological Disorders and Stroke [NIH—NINDS] R01NS073344) study, is currently testing the hypothesis that patients with the highest spot sign scores benefit most from aggressive antihypertensive treatment.

Challenges and Future Directions

Although the CTA spot sign represents a substantial advantage for the prediction of hematoma expansion in ICH, several important challenges remain. First, the relatively low sensitivity of the current definition of the spot sign. In PREDICT, only 37 (51%) of 73 patients with hematoma expansion demonstrated a spot sign, highlighting that a substantial number of patients will expand despite the absence of a spot sign. Thus, because the spot sign–negative group was ~3 times the size of the spot sign–positive group, the absolute number of expanders either with or without a spot sign is roughly the same. Therefore, a study selecting its patient population based on the spot sign would leave the same number of expanders untreated (36 versus 37 in PREDICT). Technical refinement of the CTA spot sign may increase the sensitivity of the spot sign to capture more patients destined to expand and thus reduce the number of potentially treatable patients excluded from any trial.

Second, a potential benefit found in one of the ongoing trials using the spot sign as selection tool, will only be generalizable to those who can undergo CTA. Although CTA does not seem to increase risk of nephropathy in ICH, it has yet to be routinely applied in acute ICH other than for the purpose of identifying secondary causes of ICH.

Third, all past and current studies only include patients in the first hours after symptom onset. So a considerable number of patients are left untreated, based solely on their presentation time. Although early presenters are certainly at higher individual risk for hematoma expansion, the spot sign is an independent predictor of hematoma expansion when adjusting for presentation time. This may allow the inclusion of patients within a broader time frame and should therefore be considered in future trials.

Future directions include phase II and phase III clinical trials to evaluate the spot sign as a selection tool for aggressive medical management and technical refinement of the spot sign to increase sensitivity. An unexplored field includes the possibility of patient selection for surgical treatment. No data are currently available on the rebleeding rate in surgically treated spot sign–positive patients. If the spot sign represents extensive small vessel damage, the risk of rebleeding may be heightened and a spot sign should then may preclude patients from undergoing surgical evacuation.

Despite the shortcomings of the spot sign, and biomarkers in general, its consistent association with hematoma expansion provides us with a robust radiographic marker of hematoma expansion. Therefore, phase III randomized clinical trials are the only way to assess clinical effectiveness of patient selection by spot sign status. A potentially beneficial outcome from such a study can at least be seen as the first step in the long-awaited direction of treatment success in ICH.

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References


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