Evolution of Computed Tomography Angiography Spot Sign Is Consistent With a Site of Active Hemorrhage in Acute Intracerebral Hemorrhage

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Background and Purpose—CT angiography spot sign predicts hematoma expansion in patients with acute intracerebral hemorrhage (ICH). The spot sign may represent a site of active extravasation, a locus of arrested hemorrhage forming fibrin globes, or represent associated epiphenomena such as hypertensive microaneurysms. We sought to describe the evolution of spot signs over 60 seconds in acute ICH using dynamic CT angiography and determine whether they grow and diffuse into the hematoma as would be expected with active extravasation.

Methods—We prospectively identified consecutive patients presenting with spontaneous ICH <6 hours from symptom onset that completed dynamic CT angiography imaging over a 60-second acquisition protocol. We determined spot positivity, quantified spot volumes, and then used repeated-measures ANOVA to assess changes in spot volume over time.

Results—We collected data on 35 patients; 13 of 35 (37%) patients were spot-positive. Spot-positive patients had larger median ICH volume compared with spot-negative patients (median 10.7 versus 49.2 mL; *p*=0.007). Maximal spot sign volumes ranged from 0.02 to 2.8 mL (median 0.17 mL). Spot sign volumes increased significantly with time (*p*<0.001) and seemed to disperse into the hematoma in all cases. Three of 13 (23%) spot-positive patients presented with 2 distinct spot signs, but the remaining patients either had only 1 spot sign or different contiguous components of an irregularly shaped spot sign.

Conclusions—In this dynamic CT angiography study of ICH, spot signs evolve consistent with sites of active extravasation. (Stroke. 2014;45:277-280.)

Key Words: cerebral hemorrhage ■ computerized tomography ■ contrast agent ■ hematoma

Intracerebral hemorrhage (ICH) is a devastating disease with extremely high rates of mortality and morbidity. Hematoma expansion (HE) occurs in up to 40% of patients with ICH and predicts clinical deterioration and outcome. Several reports proposed the CT angiography spot sign as a radiological marker predictive of HE in the acute setting.

Although the general assumption is that spot sign is the radiological correlate of active bleeding at the site of vessel rupture, its exact pathology is not known. A modest positive predictive value of 61% to predict HE suggests that spot sign may be present even when bleeding has ceased, perhaps representing a site of arrested hemorrhage or associated microvascular lesion such as a microaneurysm. Fisher summarized the pathological literature surrounding bleeding globes, which are masses of red blood cells surrounded by concentric fibrin rings thought to represent sites of hemorrhage adjacent to a small artery. These globes typically measured 0.3 to 1 mm in diameter, which is consistent with the radiological size of the spot sign. Although there was debate as to whether these were the primary site of vessel rupture or secondary vessel disruption, the globes were thought to represent regions where active bleeding was arrested by concentric fibrin formation. To date, these concepts remain unproven and uncontested.

We used dynamic CT angiography to visualize dynamic spot sign formation over 60 seconds, analogous to conventional angiography. Our objective was to describe spot sign formation in patients with acute ICH and determine whether intrahematoma contrast would continually diffuse and grow into the hematoma, consistent with a site of active bleeding, or whether it would either be constrained to a fixed compartment...
or recirculate into the vasculature, thereby suggesting a site of arrested bleeding or associated microvascular anomaly.

Methods
We prospectively identified consecutive code stroke patients presenting during daytime hours with spontaneous ICH between 2009 and 2013 (Ottawa Hospital, Ontario, Canada) who underwent CT angiography on a volume CT scanner <6 hours from symptom onset. We excluded patients with known secondary causes of ICH. We obtained local research ethics board approval, including waiver of consent.

We performed noncontrast CT head images followed by dynamic CT angiography acquisitions using a 320-row volume CT scanner (Toshiba Aquilion ONE) as previously described. A spot-positive patient was defined as meeting the published criteria for spot sign on axial images obtained from any acquisition time. We measured baseline hematoma volumes and spot volumes, including maximal spot volumes (the largest spot sign volume measured for a given patient), for each acquisition time using computerized planimetry.

We used Fisher exact tests, t tests, and Mann–Whitney U tests as appropriate to compare baseline demographics, hematoma volumes, and medication/medical history between spot-positive and spot-negative patients. We used 1-way repeated-measures ANOVA to assess spot volume change over time in spot-positive patients. We used SPSS v17 and SAS v9.2 for all statistical analyses.

Results
Between 2009 and 2013, we collected data on 35 patients meeting study criteria. Spot sign was present in 13 of 35 (37%) patients; spot-positive patients had larger median ICH and total hematoma volumes but were otherwise comparable (online-only Data Supplement I). Median (IQR) onset-to-imaging time for spot-positive patients was 74.5 (35) minutes.

Spot-positive patients met spot sign criteria as early as 15 seconds and as late as 39 seconds after contrast bolus (median 17 [IQR 6]). Once spot sign criteria were met, all spots continued to meet the criteria throughout the remaining time sequences as they diffused into the hematoma, although the spot sign margins became more irregular and less distinct at later time points (Figure 1). Spot sign volumes were significantly different between patients (P<0.001); maximal spot sign volumes ranged from 0.02 to 2.8 mL (median [IQR], 0.17 mL [0.21]). Spot sign volumes increased significantly with time (P<0.0001; online-only Data Supplement II), and contrast appeared to disperse into the hematoma in all cases.

Three of 13 (23%) spot-positive patients presented with 2 distinct spot signs. In the remaining 10 spot-positive patients, axial images either revealed only 1 spot sign or different contiguous components of a single irregularly shaped spot sign (Figure 2).

Discussion
CT angiography spot sign is a validated radiological marker that predicts HE after ICH. However, its pathology and exact relationship to the hematoma is unclear. In this dynamic CT angiography study, we found that our first 13 consecutive spot-positive patients all had spot signs that grew and diffused into the hematoma, which is consistent with the expected

![Figure 1. A through C. Axial images from 3 representative patients demonstrating the appearance and persistence of spot sign (arrow) over time.](http://stroke.ahajournals.org/)

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radiological appearance of active extravasation. This finding is corroborated in 2 recent CT perfusion studies.\textsuperscript{11,12}

Historical autopsy studies revealed the existence of intrahematoma and perihematoma fibrin globes possibly formed from physiological hemostasis during ICH\textsuperscript{7}; the size and descriptions of the globes are remarkably consistent with the CT angiography spot sign. More intuitively, spot sign and postcontrast leakage are frequently thought to represent the site of vessel rupture and active hemorrhage.\textsuperscript{3} Our dynamic CT angiography findings are compatible with all these hypotheses: we postulate that spot signs can have different pathological characteristics depending on when they are imaged in relation to the onset of the hemorrhage. In the early phase of ICH, spot sign is a site of rupture and active extravasation, whereas in later phases, it represents a point of resolved hemorrhage after physiological hemostasis or tamponade from rising intracranial pressures. It would then follow that spot sign can have variable predictive values for HE, depending on the timing of imaging. This could in part explain the high variability in positive predictive values reported in spot sign literature (24\% to 79\%).\textsuperscript{2,5,6}

In this study, we noted that active extravasation gives rise to large irregular patterns of intrahematoma contrast that mimic the appearance of multiple spot signs when viewed in the axial plane (Figure 2; online-only Data Supplement III). The presence of multiple spot signs is a robust predictor of HE\textsuperscript{13,14}; the positive predictive value for significant expansion increases from 61\% for 1 spot sign to 100\% for $\geq 4$ spot signs.\textsuperscript{14} It is possible that the finding of multiple spot signs at a single CT angiography acquisition time is at times an artifactual appearance because of axial imaging of a ruptured vessel with a high extravasation rate.

We report a higher proportion of spot-positive patients compared with 2 recent spot sign studies that also enrolled patients <6 hours. This likely reflects our prolonged image acquisition that captures late spots during the venous phase and is consistent with the higher spot-positive prevalence reported in a CT perfusion study using similarly prolonged acquisitions.\textsuperscript{15}

This study is largely descriptive and has several limitations. Because of its small size, the patients included may not be reflective of the general ICH population. Furthermore, although dynamic CT angiography allows the visualization of spot sign formation over 60 seconds, it is still only a snapshot in time relative to a hematoma evolving over hours. It is possible that spot signs can resolve and disappear over time or form because of tissue transection and secondary vessel rupture from an expanding hematoma. Finally, our study does
not attempt to correlate the appearance of active extravasation with HE and clinical outcome; this question is the basis of a larger ongoing dynamic CT angiography study.

CT angiography spot sign is a useful radiological marker predictive of HE and a promising therapeutic target for emerging ICH therapies. Our study explores the underlying pathology of spot sign and adds to recent studies suggesting that in the early phase of ICH, spot sign is a site of active extravasation.

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Disclosures
Drs Dowlatshahi, Demchuk, and Aviv are investigators in the SPOTLIGHT trial. All other authors have nothing to disclose.

References
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### Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Spot-negative</th>
<th>Spot-positive</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N (%)</strong></td>
<td>22 (63)</td>
<td>13 (37)</td>
<td></td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>12 (55)</td>
<td>3 (23)</td>
<td>0.492</td>
</tr>
<tr>
<td><strong>Age, mean (±standard deviation)</strong></td>
<td>67.4 ±16.0</td>
<td>70.8 ±12.2</td>
<td>0.529</td>
</tr>
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</table>

### Prior Medical History (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Spot-negative</th>
<th>Spot-positive</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>5 (22.7)</td>
<td>2 (15.4)</td>
<td>0.689</td>
</tr>
<tr>
<td>ICH</td>
<td>3 (13.6)</td>
<td>1 (7.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>MI/CAD</td>
<td>2 (9.1)</td>
<td>0 (0)</td>
<td>0.519</td>
</tr>
<tr>
<td>PE/DVT</td>
<td>1 (4.5)</td>
<td>2 (15.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>HTN</td>
<td>14 (63.6)</td>
<td>3 (23.1)</td>
<td>0.071</td>
</tr>
<tr>
<td>DM</td>
<td>3 (13.6)</td>
<td>2 (15.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Afib</td>
<td>1 (4.5)</td>
<td>1 (7.7)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

### Medication History (%)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Spot-negative</th>
<th>Spot-positive</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>8 (36.4)</td>
<td>3 (23.1)</td>
<td>0.478</td>
</tr>
<tr>
<td>Plavix</td>
<td>2 (9.1)</td>
<td>2 (15.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>ASA/dipyridamole</td>
<td>2 (9.1)</td>
<td>0 (0)</td>
<td>0.519</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1 (4.5)</td>
<td>2 (15.4)</td>
<td>0.541</td>
</tr>
<tr>
<td>Heparin</td>
<td>1 (4.5)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

| Measurement                | Spot-negative | Spot-positive | p-value |
|-----------------            | 107.5 (103)   | 74.5 (35)     | 0.080   |
| Onset-to-CTA time, median minutes (IQR) |            |              |         |
| GCS, median (IQR)       | 14 (4)        | 14.5 (7)     | 0.842   |
| Hematoma volume, median mL (IQR) | 10.69 (31)   | 49.22 (26)   | 0.007   |
| Baseline IVH (%)        | 6 (27)        | 4 (31)       | 1.000   |

**Supplemental I:** Baseline patient characteristics. ICH = intracerebral hemorrhage, MI = myocardial infarction, CAD = coronary artery disease, PE = pulmonary embolism, DVT = deep vein thrombosis, HTN = hypertension, DM = diabetes mellitus, Afib = atrial fibrillation, CTA = CT-angiogram, IQR = inter-quartile range, GCS = Glasgow Coma Scale, IVH = intraventricular hemorrhage.
Supplemental II: Trendlines demonstrate individual patient spot sign volumes over time. Repeated measures ANOVA confirms spot volumes increase over time (p<0.001).
Supplemental III (video): A 60-second dynamic CT-angiography 3D reconstruction reveals the formation of a large irregularly shaped spot sign, which originates from two anatomically distinct spot signs. This patient had urgent open hematoma evacuation surgery, which did not reveal any evidence of a vascular malformation intra-operatively or pathologically. A conventional cerebral angiogram done one week after hematoma evacuation, and a repeat CT-angiogram done 4 months later similarly did not reveal any vascular malformations.