Anatomic Pattern of Intracerebral Hemorrhage Expansion
Relation to CT Angiography Spot Sign and Hematoma Center

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Background and Purpose—We sought to identify baseline determinants of the anatomic pattern of hematoma expansion in patients with intracerebral hemorrhage and spot sign.

Methods—We coregistered baseline and follow-up CT scans from 15 intracerebral hemorrhage patients and measured growth at each surface node from baseline to follow-up hematoma. We analyzed the effects of proximity to the spot sign or hematoma center on distance of expansion, controlling for covariates.

Results—There was substantial node-to-node variation in the extent of expansion around each hematoma surface (mean coefficient of variation for expansion distance, 0.43; 95% confidence interval, 0.39–0.48), indicating nonuniform expansion. Closer proximity to the hematoma center was independently associated with increased expansion (0.185 mm greater expansion for each 1 mm closer to the center; P<0.0001). Closer proximity to the spot sign was not independently associated with increased expansion in models including both terms.

Conclusions—Hemorrhages expand nonuniformly around their surface with a tendency for greater expansion closer to their center. These findings provide a novel framework for analyzing mechanisms underlying hemorrhage growth and response to treatment. (Stroke. 2014;45:00-00.)

Key Word: cerebral hemorrhage

Hemorrhage expansion (HE) is an important contributor to the poor outcome of intracerebral hemorrhage (ICH). A barrier to developing effective treatments for preventing HE is our limited understanding of its underlying mechanisms. Various risks for HE have been identified, including the CT angiography (CTA) spot sign thought to represent active bleeding, but few data exist on the features and mechanisms of this phenomenon. Neuropathological evidence suggests HE could partly entail secondary rupture of surrounding vessels, potentially offering new approaches to prevention.

In the current study, we developed and applied tools for quantifying the anatomic pattern of HE. We specifically tested the uniformity of expansion around the hematoma surface and its relation to the spot sign and hematoma center.

Methods
This study is a retrospective analysis of prospectively collected CT and clinical data from patients enrolled in an ongoing ICH study approved by the institutional review board. Full details are in the online-only Data Supplement.

Subjects met the following criteria: (1) baseline CT/CTA with primary ICH, volume ≥100 mL, and ≥1 spot sign, and (2) follow-up noncontrast CT <72 hours showing expansion by ≥5% of baseline volume. Patients with >5 mL intraventricular, subarachnoid, or subdural extension or surgical evacuation before follow-up were excluded. From 1994 to 2010, 63 patients fulfilled the inclusion criteria, but 44 were excluded and 4 had unavailable or unsuitable images, leaving 15 for analysis. Baseline CTA and follow-up CTs were acquired and spot signs identified as previously described.

After coregistration of baseline and follow-up scans and ICH and spot segmentation, HE was analyzed by computation of the expansion distance from baseline to follow-up hematoma surface at each analyzed location (node) on the baseline surface and the distances from each node to the volumetric centers of the spot sign and baseline hematoma (Figure 1). Statistical analyses assessed the coefficient of variation (standard deviation divided by mean) of each subject’s node-by-node expansion distances and the determinants of expansion distance at a given node by linear mixed-effects models controlling for other known determinants of HE.2

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.114.004844/-/DC1.

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Results
The characteristics of the 15 ICH subjects are in the Table. There was marked nonuniformity of expansion around the surface of baseline hematomas, with mean node-to-node coefficient of variation of 0.43 (95% confidence interval, 0.39–0.48; Table I in the online-only Data Supplement). The coefficient of variation was observed to be greater in the 8 nonanticoagulated ICHs than the 7 warfarin-related ICHs ($P=0.05$).

Spot signs tended to be located almost as far from the hematoma center as the median hematoma surface node (center-to-spot distance = 87.0±30.8% of median center-to-node distance), indicating relatively eccentric placement of spots (Figure 2A and 2D). Controlling for time from symptom onset to baseline CT, baseline volume, and warfarin use, the proximity to hematoma center was associated with increased extent of expansion (Table II in the online-only Data Supplement). For each 1 mm closer distance to the centroid, the extent of expansion increased by 0.185 mm. Conversely, expansion increased by only 0.014 mm for each 1 mm closer proximity to the spot sign, and this effect did not remain independent in models including both distance terms (Table II in the online-only Data Supplement). Additional models containing an interaction term for subject-specific quartiles of centroid distance (see the online-only Data Supplement) found the greatest effect of centroid distance on expansion in the quartile of nodes closest to the center.

Qualitative inspection (Figure 2) supported quantitative findings and suggested no predisposition for expansion in particular anatomic directions, other than the requirement for study inclusion that the hematoma remain largely confined to the brain parenchyma.

Discussion
Our quantitative analysis of the pattern of HE demonstrates that expansion occurs with substantial variation around the surface of baseline ICH. The only factor found to increase expansion along the surface is proximity to the hematoma center. Although proximity to the spot sign was also weakly associated with increased expansion, this effect was attributable to confounding by proximity to the hematoma center.

The marked node-to-node variations in expansion observed in the current analysis seemed consistent with Fisher’s neuropathological model of hemorrhage growth occurring via secondary shearing of adjacent vessels triggered by the growing hemorrhage. The Fisher avalanche model has also been supported by the observation of multiple contrast spots within a single hematoma and by a recent computer simulation in which virtual hematomas expanded in a strikingly nonuniform fashion.

The mechanism for increased expansion closer to the hematoma center is unclear and raises the possibility that the physical features of the hematoma–parenchyma interface might favor a spherical shape. The absence of a strong effect of spot sign proximity on expansion, conversely, suggests that this snapshot of

Table. Subject Characteristics
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.9±11.0</td>
</tr>
<tr>
<td>Men</td>
<td>10 (67%)</td>
</tr>
<tr>
<td>Warfarin treatment</td>
<td>7 (47%)</td>
</tr>
<tr>
<td>Antplatelet treatment</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Symptom onset to baseline CT, h</td>
<td>3.0±2.7</td>
</tr>
<tr>
<td>Baseline CT to follow-up CT, h</td>
<td>28.5±18.2</td>
</tr>
<tr>
<td>Baseline ICH volume, mL</td>
<td>25.3±15.8</td>
</tr>
<tr>
<td>Volume of expansion, mL</td>
<td>9.3±9.1</td>
</tr>
<tr>
<td>Proportional expansion, % baseline</td>
<td>29.1 (14.2, 50.2)</td>
</tr>
<tr>
<td>Patients with 2 spots</td>
<td>4 (27%)</td>
</tr>
</tbody>
</table>

Values are mean±SD or median (interquartile range) as appropriate. ICH indicates intracerebral hemorrhage.
ongoing bleeding may be too limited a sampling to predict the overall pattern of future growth. The short time window sampled by the CTA spot sign may also explain its imperfect ability to predict expansion (only 61% positive predictive value and 78% negative predictive value for significant expansion in the Predicting Haematoma Growth and Outcome in Intracerebral Haemorrhage Using Contrast Bolus CT (PREDICT) study). An important limitation was our inability to analyze the effects quantitatively of surrounding tissue structure on expansion. We also note that our results apply only to expansion between baseline and follow-up imaging, though a hyperacute ICH serendipitously captured by neuroimaging also found markedly asymmetrical growth. Finally, the results apply only to hemorrhages meeting our inclusion/exclusion criteria.

HE remains an important, potentially modifiable target for acute ICH therapies. The current results add to our understanding of the mechanisms of expansion and indicate that locations close to the hematoma center are more likely to grow. This approach also provides an analytic framework applicable to ongoing and future clinical trials aimed at limiting HE.

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Disclosures
None.

References
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Anatomic Pattern of Intracerebral Hemorrhage Expansion:
Relation to CT Angiography Spot Sign and Hematoma Center

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Cover Title: Pattern of Intracerebral Hemorrhage Expansion

Table I. Within-hematoma variability in distance of expansion
Table II. Determinants of distance of expansion

Key Words: Intracerebral Hemorrhage, Spot Sign, Expansion
Subject terms: [43] Acute Cerebral Hemorrhage, [62] Intracerebral Hemorrhage

Word count: 1302

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**Supplemental Methods**

**Imaging acquisition and processing information**

Clinical data on patient age, sex, blood pressure, medication use, and time to initial and follow-up CT were collected from review of the medical record and interviews with the patient or caregiver as previously described.¹

Baseline CTA scans of the head were acquired at 1.25 mm slice thickness, 0.6 mm gap following injection of iodinated contrast as described.² Follow-up CT scans were acquired at 5mm slice thickness, 2 mm gap. Both scans used a matrix of 512x512. Spot signs on the baseline CT were identified without reference of the follow-up CT by two trained raters (G.B. and H.B.B.) using validated criteria ³ with differences adjudicated by consensus.

The procedure for identifying and analyzing the anatomy of hematoma expansion entailed 1) coregistration of the baseline and follow-up images, 2) segmentation of ICH on both scans, and 3) computation of the distance of expansion from baseline to follow-up images for each analyzed location (or “node”) on the surface of the baseline hematoma. Affine registration of the baseline and follow-up CT-Scans was performed using 3D-Slicer’s Fast-Affine-Registration Module (http://www.slicer.org).⁴ The baseline and follow-up intracerebral hemorrhages (ICH₁ and ICH₂) and spots were then segmented by semi-automated methods using the 3D Slicer standard thresholding painting tool with subsequent manual correction. We have previously demonstrated ICH segmentation with very high interrater reliability (interrater correlation coefficient 0.99).⁵ The result of these steps was to create binary masks for ICH₁, ICH₂, and each spot sign (Fig. 1C).

The coregistered binary masks for ICH₁ and ICH₂ were then resampled to 1mm isometric volumes and converted to three-dimensional surfaces (meshes) using the Matlab (MathWorks Inc, Natick, MA) iso2mesh toolbox, recreating the hematoma surface as a series of small flat triangles (Fig. 1D). The surfaces were subsequently down-sampled (retaining 80% of the original nodes) to simplify calculations and force nodes to be evenly spaced and smoothed using two iterations (alpha = 0.5). The distance of expansion for each ICH₁ node was then calculated as the distance along the vector normal to the small triangular surface to the first intersection with the surface of ICH₂, using a Matlab ray-tracing algorithm.⁶ All distances throughout the analysis were measured in millimeters.
We measured distances from the spot center to each ICH\textsubscript{1} node. When two spots were present on a single baseline image, we used the distance from the closest spot for each node. To account for possible additional influence of the more distant spot sign, we also performed exploratory analysis calculating the cumulative effect of the two spots (S) on each node by the inverse of the spot-to-node distances (I and II), per the formula \(1/S = 1/I + 1/II\). This alternative calculation method had no substantial effect on the reported results.

To evaluate the specificity of any effects of node-to-spot sign distance on extent of expansion, we also analyzed the effect of node-to-hematoma center distance. For this purpose, centroids were identified as the volumetric centers of ICH\textsubscript{1} with Matlab’s region props command and centroid-to-node distances measured as above.

**Statistical analysis**

Summary statistics were derived for mean and standard deviation (for normally distributed variables) or mean and 25\textsuperscript{th}-75\textsuperscript{th} percentiles (for non-normally distributed). To analyze uniformity of hemorrhage expansion, we performed a square-root transformation of the distances of expansion to create approximately normal distributions. Since the standard deviations of this measurement were linearly proportional to their means, we used the coefficient of variation (standard deviation divided by the mean) for each subject’s node-by-node expansion distances as a marker of within-subject variability. The confidence interval for the coefficient of variation was calculated from the bootstrap distribution (2000 resamples) and statistical comparisons for this variable performed by permutation testing.

To analyze the determinants of expansion distance at a given node, we created a linear mixed effects model with expansion distance as dependent variable, subject as a random effect, spot distance and centroid distance as fixed effects. The mixed effects models also included as fixed effects the other known determinants of hematoma expansion\textsuperscript{1}: baseline ICH volume, time from symptom onset to baseline CT, and use of warfarin. In additional mixed effects models, we added terms for interactions between centroid distance and subject-specific quartiles of centroid distance, allowing for different random effect variances for the four quartiles.
Supplemental References


Supplemental Tables

**Table I** Within-hematoma variability in distance of expansion

<table>
<thead>
<tr>
<th>Subject</th>
<th>Number of nodes</th>
<th>25\textsuperscript{th} percentile expansion (mm)</th>
<th>50\textsuperscript{th} percentile expansion (mm)</th>
<th>75\textsuperscript{th} percentile expansion (mm)</th>
<th>Coefficient of variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>456</td>
<td>3.28</td>
<td>6.65</td>
<td>8.90</td>
<td>0.36</td>
</tr>
<tr>
<td>2</td>
<td>650</td>
<td>1.90</td>
<td>5.79</td>
<td>13.61</td>
<td>0.58</td>
</tr>
<tr>
<td>3</td>
<td>306</td>
<td>2.24</td>
<td>3.56</td>
<td>5.17</td>
<td>0.39</td>
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<td>4</td>
<td>337</td>
<td>2.29</td>
<td>3.68</td>
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<tr>
<td>5</td>
<td>325</td>
<td>0.78</td>
<td>2.32</td>
<td>5.09</td>
<td>0.63</td>
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<tr>
<td>6</td>
<td>384</td>
<td>1.65</td>
<td>2.70</td>
<td>4.02</td>
<td>0.33</td>
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<tr>
<td>7</td>
<td>333</td>
<td>1.85</td>
<td>3.11</td>
<td>5.89</td>
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<tr>
<td>8</td>
<td>360</td>
<td>1.70</td>
<td>2.94</td>
<td>4.37</td>
<td>0.37</td>
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<tr>
<td>9</td>
<td>419</td>
<td>2.38</td>
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<td>9.86</td>
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<tr>
<td>10</td>
<td>235</td>
<td>2.50</td>
<td>4.04</td>
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<td>0.32</td>
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<tr>
<td>11</td>
<td>402</td>
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<tr>
<td>13</td>
<td>413</td>
<td>1.49</td>
<td>3.48</td>
<td>8.04</td>
<td>0.51</td>
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<tr>
<td>14</td>
<td>550</td>
<td>1.63</td>
<td>3.57</td>
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<tr>
<td>15</td>
<td>157</td>
<td>0.53</td>
<td>1.14</td>
<td>2.04</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Values shown are each subject’s number of nodes analyzed on the baseline hematoma, 25\textsuperscript{th}, 50\textsuperscript{th} and 75\textsuperscript{th} percentile for the nodes’ distances of expansion, and coefficient of variation for the distances of expansion.
Table II  Determinants of distance of expansion

<table>
<thead>
<tr>
<th>Model with individual distance terms</th>
<th>Model with both distance terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node-to-spot distance</td>
<td></td>
</tr>
<tr>
<td>Model coefficient</td>
<td>-0.014 (0.007)</td>
</tr>
<tr>
<td>(standard error)</td>
<td>p=0.046</td>
</tr>
<tr>
<td>p=0.003</td>
<td></td>
</tr>
<tr>
<td>Node-to-centroid distance</td>
<td></td>
</tr>
<tr>
<td>Model coefficient</td>
<td>-0.185 (0.011)</td>
</tr>
<tr>
<td>(standard error)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>-0.200 (0.012)</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

All linear mixed effect models include baseline ICH volume, time from symptom onset to baseline CT, and presence or absence of warfarin as fixed effects and subject as a random effect. Negative coefficients indicate that shorter distances (from node to spot or node to centroid) are associated with greater extents of expansion.