Measurement of Perihematomal Edema in Intracerebral Hemorrhage

Sebastian Urday, MPhil; Lauren A. Beslow, MD, MSCE; David W. Goldstein, BA; Anastasia Vashkevich, BA; Alison M. Ayres, BA; Thomas W.K. Battey, BS; Magdy H. Selim, MD, PhD; W. Taylor Kimberly, MD, PhD; Jonathan Rosand, MD, MSc; Kevin N. Sheth, MD

Background and Purpose—Perihematomal edema (PHE) is a marker of secondary injury in intracerebral hemorrhage (ICH). PHE measurement on computed tomography (CT) is challenging, and the principles used to detect PHE have not been described fully. We developed a systematic approach for CT-based measurement of PHE.

Methods—Two independent raters measured PHE volumes on baseline and 24-hour post-ICH CT scans of 20 primary supratentorial ICH subjects. Boundaries were outlined with an edge-detection tool and adjusted after inspection of the 3 orthogonal planes. PHE was delineated with the additional principle that it should be (a) more hypodense than the corresponding area in the contralateral hemisphere and (b) most hypodense immediately surrounding the hemorrhage. We examined intra- and interrater reliability using intraclass correlation coefficients and Bland–Altman plots for interrater consistency. CT-based PHE was also compared using magnetic resonance imaging–based PHE detection for 18 subjects.

Results—Median PHE volumes were 22.7 cc at baseline and 20.4 cc at 24 hours post-ICH. There were no statistically significant differences in PHE measurements between raters. Interrater and intrarater reliability for PHE were excellent. At baseline and 24 hours, interrater intraclass correlation coefficients were 0.98 (0.96–1.00) and 0.98 (0.97–1.00); intrarater intraclass correlation coefficients were 0.99 (0.99–1.00) and 0.99 (0.98–1.00). Bland–Altman analysis showed the bias for PHE measurements at baseline and 24 hours, −0.5 cc (SD, 5.4) and −3.2 cc (SD, 5.0), was acceptably small. PHE volumes determined by CT and magnetic resonance imaging were similar (23.9±16.9 cc versus 23.9±16.0 cc, \( R^2 = 0.98, P<0.0001 \)).

Conclusions—Our method measures PHE with excellent reliability at baseline and 24 hours post-ICH. (Stroke. 2015;46:1116-1119. DOI: 10.1161/STROKEAHA.114.007565.)

Key Words: computed tomography ■ intracerebral hemorrhage

Intracerebral hemorrhage (ICH) accounts for 15% of all adult strokes and is the deadliest stroke subtype.1 Poor outcome after ICH is caused by both primary and secondary injury.2,3 The former refers to the mechanical effects from the hemorrhage and the latter includes the effects of the inflammatory response to ICH, the toxicity of blood breakdown products, and perihematomal edema (PHE).1

Volumetric measurements have been performed to explore whether PHE is an independent predictor of outcome.4 PHE has also been used as a surrogate end point in trials of neuroprotective agents targeting secondary injury.5 Most studies use computed tomography (CT) because magnetic resonance imaging (MRI) is not feasible in unstable patients. MRI has been described as superior for PHE quantification given the high contrast between the perihematomal hyperintensity thought to represent PHE and neighboring brain tissue.6 However, there is evidence that MRI may not be the best modality for PHE quantification; one study reported that the change in perihematomal MRI hyperintensity correlated poorly with the change in ipsilateral hemispheric volume.7

On CT, the hyperdense region of hemorrhage contrasts with neighboring tissue and is measured relatively easily. However, PHE manifests as a perihematomal hypodensity that can be challenging to distinguish from normal tissue and other entities that are also hypodense (eg, infarction). Furthermore, the boundaries of PHE become less clear over time. Previous studies have used threshold-based or edge-detection algorithms to measure PHE, yet the principles used to trace PHE...
have not been explicitly clarified (Table I in the online-only Data Supplement).\textsuperscript{4,8–10} Perhaps for this reason, midline shift is still used in some ICH studies in place of volumetric measurements.\textsuperscript{11} Unfortunately, midline shift correlates with total hemispheric swelling, not exclusively with PHE.\textsuperscript{12}

Here we outline an approach for CT-based measurement of PHE that combines an edge-detection algorithm and considers the pathophysiology of PHE formation. We determined the interrater and intrarater reliability of the method. We also examined the correspondence between PHE determined by CT and MRI in a group of subjects in which both neuroimaging modalities were obtained.

**Methods**

**Subject Identification**

Subjects were retrospectively identified from an Institutional Review Board–approved prospective cohort study of ICH performed at Massachusetts General Hospital between 2000 and 2013. Inclusion criteria were age >18 years with primary spontaneous supratentorial ICH confirmed by CT. Exclusion criteria were infratentorial hemorrhage, primary intraventricular hemorrhage, subsequent surgery, and any suspected cause of secondary ICH. Twenty randomly selected subjects with baseline and 24-hour post-ICH CT scans were included. Eighteen subjects with both CT and MRI performed in close association were also included.

**Measurements**

ICH, PHE, and intraventricular hemorrhage volumes were determined by 2 independent raters (S. Urday and D.W. Goldstein) using Analyze 11.0 (AnalyzeDirect, Overland Park, KS, USA; Figures I–VII in the online-only Data Supplement). The raters were blinded to clinical data and to each other’s measurements. Measurements were performed by outlining the hemorrhage and rim of PHE on axial slices in the software’s region of interest module with a semiautomated edge detection tool. This tool calculates boundaries for each lesion based on Hounsfield Units in the area selected by the rater, the most optimal of which is selected by the rater. Next, boundaries were adjusted after inspection of the 3 orthogonal planes in the software’s Volume Edit module, which allows for better assessment of the location and distribution of each lesion beyond the 2-dimensional axial plane. The 3-dimensional view is especially helpful to visualize the extent of PHE throughout the brain in large hemor- rhages. To delineate PHE, the additional principles that it should be (a) more hypodense than the corresponding region in the contralateral hemisphere and (b) most hypodense immediately surrounding the hemorrhage were used. The rationale for the latter is that after ICH, transendothelial water flux from the intravascular to the interstitial compartments, both before and after frank blood–brain barrier disruption, occurs initially immediately adjacent to the hematoma.\textsuperscript{13} Therefore, if a less hypodense area adjacent to the hematoma is followed by a more hypodense area further outward, the latter could represent another entity like an old infarct. Measurements were repeated by one rater (S. Urday) after a 4-month interval to determine intrarater reliability. All measurements were reviewed by 2 stroke neurologists (L.A. Beslow and K.N. Sheth). Figure 1 depicts a representative example of a subject’s ICH and PHE measurements. PHE volumes were determined on MRI (fluid-attenuated inversion recovery sequence) using the semiautomated edge detection tool to delineate the perihematomal hyperintensity.

**Statistical Analysis**

Statistical analysis was performed using STATA Version 12.1 (Stata Corp, College Station, Texas). Intrarater and interrater reliability were measured with intraclass correlation coefficients (ICCs) using 1-way analysis of variance. An ICC was considered moderate agreement if 0.41 to 0.60, substantial agreement if 0.61 to 0.80, and almost perfect (excellent) if 0.81 to 1.00.\textsuperscript{14} Wilcoxon rank-sum tests were used to determine whether measurements differed significantly. Bland–Altman

![Figure 1](example.com). Example of region of interest object maps used to measure intracerebral hemorrhage (ICH) and perihematomal edema (PHE) volumes. **Left**, Left putaminal hemorrhage. **Right**, ICH (red) and PHE (cyan) delineated with an edge-detection algorithm.

![Figure 2](example.com). Bland–Altman plots of interrater consistency of perihematomal edema (PHE) measurements at baseline and 24 hours post-intracerebral hemorrhage (ICH). Dashed black line represents the bias (mean of the difference between measurements). Dashed gray lines represent the limits of agreement (mean±1.96 SD).
plots were constructed to verify that there was no systematic bias using GraphPad Prism 6.00 (GraphPad Software, La Jolla, CA). Linear regression analysis was performed to compare PHE volumes on CT and MRI; the parameter $R^2$ was reported as the measure of concurrent validity.

**Results**

ICH was lobar in 8 and deep hemispheric in 12 subjects (Table II in the online-only Data Supplement). ICH (Table III in the online-only Data Supplement), PHE (Table), and intraventricular hemorrhage (Table IV in the online-only Data Supplement) volumes at both baseline and 24 hours post-ICH for the 2 raters did not differ. Intrarater measurements also did not differ (Table; Tables III and IV in the online-only Data Supplement).

All intrarater and intrarater ICCs were excellent at both baseline and 24 hours post-ICH (Table; Tables III and IV in the online-only Data Supplement). For PHE, at baseline and 24 hours post-ICH, intrarater ICCs were 0.98 (0.96–1.00) and 0.98 (0.97–1.00); intrarater ICCs were 0.99 (0.99–1.00) and 0.99 (0.98–1.00). The Bland–Altman plots of interrater consistency of PHE measurements revealed a bias of −0.5 cc (SD, 2.4) and −3.2 cc (SD, 5.0) at baseline and 24 hours post-ICH, respectively (Figure 2; Figures VIII and IX in the online-only Data Supplement). There was a single outlier at both baseline and 24 hours that corresponded to a 118 cc frontal lobe hemorrhage, which was the most difficult to measure because of marked irregularity and diffuse swelling that made delineation of boundaries challenging.

In the 18 subjects with both CT and MRI scans available, median time between scans was 17 hours (8–37 hours). PHE volumes on CT and MRI did not differ (Table). There was a high correlation between modalities. In regression analysis, $R^2$ for the CT and MRI measurements was 0.98, slope 1.05 (95% confidence interval, 0.97–1.12), intercept −1.00, and $P<0.0001$. The ICC between the CT and MRI measurements was 0.99 (95% confidence interval, 0.98–1.00). Bland–Altman analysis revealed that CT and MRI-based PHE measurements were consistent, with a small bias of 0.07 cc (SD, 2.4; Figure X in the online-only Data Supplement).

**Discussion**

Our approach for CT-based PHE measurement capitalizes on a quantitative edge-detection algorithm plus knowledge of the pathophysiology of PHE formation to delineate boundaries. The method has excellent interrater and intrarater reliability and measurements are comparable to those obtained on MRI. We observed an acceptably small bias in measuring PHE, considering a difference in 10 cc of PHE on admission tripled the odds of poor discharge outcome in one study. This could represent a method for researchers to explore further the prognostic significance of PHE and test therapies that reduce secondary injury.

Our data showed decreased interrater consistency in PHE measurements for large hemorrhages in which there is diffuse swelling. Appelboom et al showed PHE volume was an independent predictor of outcome only in patients with ICH volumes ≤30 cc. Therefore, secondary injury and PHE may be less likely to be clinically relevant in ICH patients with large hemorrhages. These patients are likely to have a poor prognosis regardless, as a result of the direct mechanical effects from the large hemorrhage (primary injury). In this pool of subjects with moderate ICH volumes, our method had excellent interrater and intrarater consistency. Our findings should be confirmed in a larger, prospective data set.

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**Disclosures**

Dr Rosand has a consulting relationship with Boehringer Ingelheim. The other authors report no conflicts.

**References**

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http://stroke.ahajournals.org/content/suppl/2015/03/20/STROKEAHA.114.007565.DC1

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SUPPLEMENTAL MATERIAL

Measurement of Peri-Hematomal Edema in Intracerebral Hemorrhage

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Online Supplemental Methods

Figures I-VII outline the steps for ICH and PHE measurement using Analyze 11.0 (AnalyzeDirect, Overland Park, KS, USA).

Figure I. In the Region of Interest module, click on the Add Limit icon and trace a limit line around the ICH. In this way the software’s edge detection tool only calculates boundaries within the selected area.
Figure II. Click on the AutoTrace tool icon (edge-detection tool) and then click on a hyperdense area of hemorrhage to set a ‘seed point’. Once the ‘seed point’ is set, a slider bar appears (arrow). Grow the ICH boundary by dragging either side of the bar. Select the optimal boundary defining the hyperdense region of hemorrhage.
Figure III. Click Apply to set the ICH boundary. The step above can be repeated if needed to define multiple hemorrhages.
Figure IV. Click on the Add Limit icon and trace a limit line around a region that contains PHE. The rim of PHE is defined with the principle that it should be (a) more hypodense than the corresponding region in the contralateral hemisphere and (b) most hypodense immediately surrounding the hemorrhage. As before, click on the Autotrace tool icon. Then click on a hypodense area of PHE to set a ‘seed point’. Once the ‘seed point’ is set, a slider bar appears. Grow the PHE boundary by dragging either side of the bar. Select the optimal boundary defining the hypodense region of PHE.
Figure V. Click Apply to set the PHE boundary.
Figure VI. Example showing how the principle above was used to delineate PHE. Here a limit line is used to exclude a region that is more hypodense further out from the hemorrhage, rather than immediately surrounding the hemorrhage. In this case it corresponds to a sulci from the contralateral hemisphere.
Figure VII. The Volume Edit module (shown above) provides a three-dimensional view of each lesion. It can be used to better visualize the extent and distribution of each lesion. It can be opened in parallel with the Region of Interest module to aid the operator in the selection of the optimal boundary for the lesion.
# Online Supplemental Results

## Table I. Selection of studies investigating PHE

<table>
<thead>
<tr>
<th>Study</th>
<th>Software package for PHE quantification</th>
<th>Interrater/Intrarater ICCs (95% CI) for PHE quantification</th>
<th>Validation against MRI</th>
<th>Number of patients used for MRI validation</th>
<th>Method for PHE measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gebel et al.¹</td>
<td>In-house software</td>
<td>NA/NA</td>
<td>No</td>
<td>NA</td>
<td>Authors used a statistical algorithm. The principles used to differentiate PHE from other entities that are also hypodense, or the thresholds used, are not specified</td>
</tr>
<tr>
<td>Sansing et al.²</td>
<td>MCID</td>
<td>NA/NA</td>
<td>No</td>
<td>NA</td>
<td>Authors used software with semiautomated edge detection. PHE was determined by selection of the hypodense area immediately surrounding the hemorrhage. The principles used to differentiate PHE from other entities that are also hypodense, or whether thresholds were used, are not specified</td>
</tr>
<tr>
<td>McCarron et al.³</td>
<td>Not specified</td>
<td>NA/0.96 (0.90-0.98)</td>
<td>No</td>
<td>NA</td>
<td>Authors used a modified version of the ABC/2 method. The principles used to differentiate PHE from other entities that are also hypodense, or whether thresholds were used, are not specified</td>
</tr>
<tr>
<td>Levine et al.⁴</td>
<td>Alice</td>
<td>0.98/NA</td>
<td>No</td>
<td>NA</td>
<td>Not specified</td>
</tr>
<tr>
<td>Mehdiratta et al.⁵</td>
<td>Not specified</td>
<td>0.90/0.95</td>
<td>No</td>
<td>NA</td>
<td>Authors used “automated threshold values”*. The principles used to differentiate PHE from other entities that are also hypodense, or the thresholds used, are not specified</td>
</tr>
<tr>
<td>Arima et al.⁶</td>
<td>MIStar Version 3.2</td>
<td>0.91 (0.87-0.94)/NA</td>
<td>No</td>
<td>NA</td>
<td>Authors used computer-assisted multislice planimetric and voxel threshold techniques. The principles used to differentiate PHE from other entities that are also hypodense, or the thresholds used, are not specified</td>
</tr>
<tr>
<td>Volbers et al.⁷</td>
<td>Leonardo V</td>
<td>0.96 (0.93-0.99)/0.96 (0.93-0.99)</td>
<td>Yes</td>
<td>15</td>
<td>Authors used the 5-33 HU threshold. Authors differentiated PHE from other entities that are also hypodense by comparison to the contralateral hemisphere and a more restrictive definition of the region of interest</td>
</tr>
<tr>
<td>Appelboom et al.⁸</td>
<td>MIPAV</td>
<td>0.88/NA</td>
<td>No</td>
<td>NA</td>
<td>Not specified</td>
</tr>
<tr>
<td>McCourt et al.⁹</td>
<td>Analyze 11.0</td>
<td>0.99 (0.98-0.99)/NA</td>
<td>No</td>
<td>NA</td>
<td>Authors first manually traced PHE and then applied the 5-23 HU threshold. The principles used to differentiate PHE from other entities that are also hypodense are not specified</td>
</tr>
<tr>
<td>Present study</td>
<td>Analyze 11.0</td>
<td>0.98 (0.96-1.00)/0.99 (0.99-1.00)</td>
<td>Yes</td>
<td>18</td>
<td>Boundaries were outlined with an edge-detection tool and adjusted after inspection of the three orthogonal planes. PHE was delineated with the additional principle that it should be (a) more hypodense than the corresponding area in the contralateral hemisphere and (b) most hypodense immediately surrounding the hemorrhage.</td>
</tr>
</tbody>
</table>
HU, Hounsfield unit; ICC, intraclass correlation coefficient; NA, not applicable; PHE, peri-hematomal edema

Table II. Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>64.6 (12.8)</td>
</tr>
<tr>
<td>Male, n, (%)</td>
<td>12 (60)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>20 (100)</td>
</tr>
<tr>
<td>GCS score, median (IQR)</td>
<td>14 (9-15)</td>
</tr>
<tr>
<td>Location of Hematoma, n (%)</td>
<td></td>
</tr>
<tr>
<td>Lobar</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Deep</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>Presence of IVH, n, (%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>ICH volume, cc, median (IQR)</td>
<td>24.0 (10.5-39.6)</td>
</tr>
<tr>
<td>Onset to first scan, hours, median (IQR)</td>
<td>4.2 (2.9-8.9)</td>
</tr>
</tbody>
</table>

SD, standard deviation; n, number; cc, cubic centimeters; IQR, interquartile range

Table III. Summary of ICH measurements

<table>
<thead>
<tr>
<th></th>
<th>Volume cc, median (IQR)</th>
<th>Wilcoxon rank-sum p-value</th>
<th>Interrater ICC (95% CI)</th>
<th>Intrarater ICC (95%, CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline R1, R2</td>
<td>23.2 (10.9-35.6), 24.0 (11.5-38.7)</td>
<td>0.81</td>
<td>0.99 (0.99-1.00)</td>
<td>NA</td>
</tr>
<tr>
<td>R1 retest</td>
<td>24.2 (11.2-39.1)</td>
<td>0.91</td>
<td>NA</td>
<td>0.99 (0.99-1.00)</td>
</tr>
<tr>
<td>24-hours post-ICH R1, R2</td>
<td>23.3 (11.0-36.5), 24.1 (11.7-38.9)</td>
<td>0.85</td>
<td>0.99 (0.99-1.00)</td>
<td>NA</td>
</tr>
<tr>
<td>R1 retest</td>
<td>24.2 (11.7-39.8)</td>
<td>0.94</td>
<td>NA</td>
<td>0.99 (0.99-1.00)</td>
</tr>
</tbody>
</table>

R1, Rater 1; R2, Rater 2; cc, cubic centimeters; IQR, interquartile range; ICC, intraclass correlation coefficient; CI, confidence interval; NA, not applicable

Table IV. Summary of IVH measurements

<table>
<thead>
<tr>
<th></th>
<th>Volume cc, median (IQR)</th>
<th>Wilcoxon rank-sum p-value</th>
<th>Interrater ICC (95% CI)</th>
<th>Intrarater ICC (95%, CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline R1, R2</td>
<td>0 (0-5.1), 0 (0-5.6)</td>
<td>0.95</td>
<td>0.99 (0.99-1.00)</td>
<td>NA</td>
</tr>
<tr>
<td>R1 retest</td>
<td>0 (0-5.6)</td>
<td>0.98</td>
<td>NA</td>
<td>0.99 (0.99-1.00)</td>
</tr>
<tr>
<td>24-hours post-ICH R1, R2</td>
<td>0 (0-3.1), 0 (0-3.9)</td>
<td>0.81</td>
<td>0.99 (0.98-1.00)</td>
<td>NA</td>
</tr>
<tr>
<td>R1 retest</td>
<td>0 (0-3.8)</td>
<td>0.98</td>
<td>NA</td>
<td>0.99 (0.99-1.00)</td>
</tr>
</tbody>
</table>

R1 indicates Rater 1; R2, Rater 2; cc, cubic centimeters; IQR, interquartile range; ICC, intraclass correlation coefficient; CI, confidence interval; NA, not applicable
Figure VIII. Bland-Altman plots of inter-rater consistency of ICH measurements. Dashed black line represents the bias (mean of the difference between measurements). Dashed red lines represent the limits of agreement (mean ± 1.96 SD). At baseline and 24-hours post-ICH the bias was -1.6 cc (SD, 2.8) and -1.2 cc (SD, 2.0), respectively. The outliers corresponded to irregularly shaped hemorrhages.

Figure IX. Bland-Altman plots of inter-rater consistency of IVH measurements. Dashed black line represents the bias (mean of the difference between measurements). Dashed red lines represent the limits of agreement (mean ± 1.96 SD). At baseline and 24-hours post-ICH the bias was -0.1 (SD, 0.5) and -0.3 (SD, 0.7), respectively. The outliers corresponded to hemorrhages with a faint boundary between ICH and IVH.

Figure X. Bland-Altman plots comparing CT and MRI-based PHE measurement. The dashed black line represents the bias (mean of the difference between measurements). The dashed red lines represent the limits of agreement (mean ± 1.96 SD). The bias was 0.07 cc (SD, 2.4).
Online Supplement References