Natural History of Perihematomal Edema and Impact on Outcome After Intracerebral Hemorrhage

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Background and Purpose—Edema may worsen outcome after intracerebral hemorrhage (ICH). We assessed its natural history, factors influencing growth, and association with outcome.

Methods—We estimated edema volumes in ICH patients from the Helsinki ICH study using semiautomated planimetry. We assessed the correlation between edema extension distance (EED) and time from ICH onset, creating an edema growth trajectory model up to 3 weeks. We interpolated expected EED at 72 hours and identified clinical and imaging characteristics associated with faster edema growth. Association of EED and mortality was assessed using logistic regression adjusting for predictors of ICH outcome.

Results—From 1013 consecutive patients, 861 were included. There was a strong inverse correlation between EED growth rate (cm/d) and time from onset (days): EED growth=0.162x days exp(-0.927), R²=0.82. Baseline factors associated with larger than expected EED were older age (71 versus 68; P=0.002), higher National Institutes of Health Stroke Scale score (14 versus 8; P<0.001), and lower Glasgow Coma scale score (13 versus 15; P<0.001), larger ICH volume (19.7 versus 12.7 mL; P<0.001), larger initial EED (0.42 versus 0.30; P<0.001), irregularly shaped hematoma (55% versus 42%; P<0.001), and higher glucose (7.6 versus 6.9 mmol/L; P=0.001). Patients with faster edema growth had more midline shift (50% versus 31%; P<0.001), herniation (12% versus 4%; P<0.001), and higher 6-month mortality (odds ratio, 1.60; 95% confidence interval, 1.04–2.46; P=0.032).

Conclusions—Edema growth can be readily monitored and is an independent determinant of mortality after ICH, providing an important treatment target for strategies to improve patient outcome. (Stroke. 2017;48:873-879. DOI: 10.1161/STROKEAHA.116.014416.)

Key Words: cerebral hemorrhage □ edema □ mortality □ natural history □ stroke

Edema evolution after intracerebral hemorrhage (ICH) is complex and incompletely understood. Results of early studies of edema have reported conflicting associations of edema on ICH outcome. More recent studies have associated early edema volume and early edema growth to patient outcome.

It is generally accepted that edema evolves over several stages from initial acute stage of ionic edema resulting from combination of hydrostatic pressure and clot retraction with potential contribution of energy-dependent ion channels to a subacute stage of vasogenic edema secondary to inflammation-mediated disruption of the blood–brain barrier. Limited human natural history data suggest that edema growth is rapid in the 24 hours after ictus followed by a stage of slow progressive edema growth peaking around the second week after ICH. Hematoma volume has been shown in edema studies to be highly correlated with subsequent edema volume, but the association with other clinical and laboratory factors is less clear. An improved understanding of edema evolution is vital in ICH management because edema increases intracranial pressure and can lead to neurological deterioration and death. Strategies targeting edema growth are likely to result in improved patient outcome. The aims of the present study are to provide a descriptive narrative of edema evolution, factors associated with increased edema volume and impact of edema on mortality using data from the HICHS (Helsinki ICH Study).
Methods

Patient Selection
HICHS methodology has been previously described. Briefly, HICHS is a retrospective analysis of consecutive ICH patients admitted to the Helsinki University Hospital between January 2005 and March 2010 and included 1013 patients. Data collection was performed retrospectively by chart review and etiologic classification performed by the SMASH-U classification system. For the present analysis, patients were excluded if there was no imaging available, if they had pure intraventricular hemorrhage, according to their brain stem location, if they underwent surgical evacuation, or if the baseline imaging was performed >7 days after ictus. There were no systematic follow-up visits of the HICHS patients, and for this reason, we do not have long-term functional outcome data. All-cause mortality was available for 1003 patients (99%) using national vital records up to November 2014. Institutional approval for the study was granted by the Helsinki University Hospital.

Hematoma and Edema Volume Ascertainment
The planimetric methods and volume processing have been described in detail elsewhere. Briefly, computed tomographic (CT) scans were transferred in a deidentified manner in the Digital Imaging and Communications in Medicine format to a central workstation. The Digital Imaging and Communications in Medicine formats were then converted into Neuroimaging Informatics Technology Initiative format before loading on Analyze 12.0 (Biomedical Imaging Resource; Mayo Clinic). Semi-automated planimetry as reported by Volbers et al was used. Edematous regions were segmented using a fixed lower Hounsfield unit (HU) of 5 and a flexible upper limit with a ceiling of 33 HU, comparing to the unaffected hemisphere for visual estimate of edema versus leukoaraisis. For segmentation of ICH, the HU range was kept within 44 to 100 HU. A single rater (T.Y.W.) segmented ICH and edema on all scans. Volume was calculated by estimating the gantry tilt adjusted voxel depth for each slice, and an in-house script determined number of voxels within the region of interest of each slice using Matlab (The MathWorks, Inc, MA). The region of interest volume was then determined by multiplying voxel count by individual voxel volume. The reliability of this method was assessed in a separate publication consisting of 100 patients. The interrater and intrarater intraclass coefficients were 0.952 and 0.983 for edema and 0.994 and 0.999 for ICH, respectively.

Hematoma Shape Determination
Hematoma shape was rated using the 5-point visual rating scale reported by Barras et al. The hematoma shape was then dichotomized into regular (category 1) or irregular shaped (categories 2–5) hematomas for analysis.

Perihematomal Edema Metric
Edema extension distance (EED), a recently proposed novel edema metric is used in the primary analysis. The EED represents the average thickness in centimeter of the edema around the ICH and is calculated using the following equation:

\[
\text{EED} = \sqrt{\frac{\text{Edema volume} + \text{ICH volume}}{4/3\pi}} - \sqrt{\frac{\text{ICH volume}}{4/3\pi}}
\]

EED was used as the edema metric in this study over absolute edema volume or relative edema index because EED has been shown to be relatively independent of ICH volume in contrast to absolute edema volume, and it does not provide disproportionally large value in smaller hematomas as in the case of edema index.

Edema Growth-to-Time Relationship Calculation
The EED growth rate (cm/d) for each scan was estimated by change in EED since previous scan divided by time since previous scan. The EED was assumed to be zero at onset. On the basis of this assumption, the growth rate between onset and baseline imaging was calculated. Scans performed within 3 weeks of ictus were included in the growth rate estimation. The EED growth rate-to-time relationship was plotted on a scatter graph. A negative exponential formula with a ceiling growth of 10 cm/d had a best fit. The ceiling growth rate of 10 cm/d was chosen as there are no real-life observations in the first seconds or minutes from ICH onset and the observed exponential fit equates to an average growth rate of 10 cm/d at 16 minutes. This equates to an unrealistic rate of EED growth or cumulative average EED of 0.5 cm at 3 minutes. The average EED was 0.35 cm from an average of 3.5 hours from onset and truncation to maximum growth rate of 10 cm/d equates to a plausible cumulative EED of 0.12 cm at 16 minutes from onset. We, therefore, used this to calculate the expected EED at any given time point. In a secondary analysis, we derived a separate equation for calculating expected absolute edema volume at any given time point with the absolute edema volume growth rate ceiling (387 mL/d) derived from the same time point used in the EED analysis.

Edema Dichotomization
To overcome the lack of routine follow-up CT scans at fixed time points, we used the derived equation to interpolate expected EED at 72 hours. As patients were scanned at different time points in routine clinical practice, we interpolated EED from observed time of the available scan closest to 72 hours from ictus, assuming the same proportional growth to 72 hours. We used the 72-hour EED for each patient to dichotomize into groups with higher-than-expected EED or lower-than-expected EED using the modeled EED growth rate-to-time data. Baseline clinical and radiological characteristics were compared between groups to assess for potential factors associated with higher EED. We also performed the same dichotomization after interpolating absolute edema volume to 72 hours. Additionally, we calculated absolute edema growth rate in patients with available baseline (<12 hours from ictus) and day-1 (12–36 hour from ictus) CT scans using method reported by Urday et al.

Statistical Analysis
Standard descriptive statistics were used. \( \chi^2 \) or Fisher exact test was used for categorical variables and Mann–Whitney test used for continuous variables. We used mortality at 6 months, which is the norm for ICH trials as our time point of interest. Association of higher-than-expected EED with 6-month mortality was assessed with logistic regression adjusted for factors known to influence outcome: age, baseline National Institutes of Health Stroke Scale score, baseline Glasgow coma scale score, prestroke warfarin use, baseline hematoma volume, and ventricular extension. Patients with missing mortality data were included in the EED progression analysis but excluded from the logistic regression model. Testing for multicollinearity demonstrated variance inflation factor of <3.7 (range: 1.07–3.61) between variables in the logistic regression model indicating no significant multicollinearity. Receiver–operator characteristic area under the curve analysis was performed to assess the regression model fit. In the secondary analyses, we repeated the primary analysis by replacing the 72-hour EED dichotomization with different edema metrics in the multivariable model. The edema metrics were 72-hour dichotomization using interpolated absolute edema volume, interpolated 72-hour EED, interpolated 72-hour absolute edema volume and absolute edema growth rate in patients with available baseline, and day 1 CT scan. An a priori sample size calculation was not performed. Instead we used a convenience sample of all the patients in the registry. A \( P \) value of <0.05 was considered significant. All statistics were performed using SPSS 23 (IBM, Armonk, NY).

Results
Patient Characteristics
From a pool of 1013 patients, we excluded 152, leaving 861 patients for the analysis (Figure 1). A total of 1463 scans were...
used for EED growth calculation, and 362 patients (42%) had at least 2 scans. The median time to baseline imaging was 8.3 hours. Patients included in this analysis had a median age of 69 years, and 503 patients (58%) were men. Baseline information was missing for heart failure in 14 patients (2%), statin use in 14 patients (2%), dyslipidemia in 10 patients (1%), and glucose in 14 patients (2%), whereas 9 patients (1%) had missing mortality data. International normalized ratio was performed in 740 patients (86%). The median baseline National Institutes of Health Stroke Scale score was 11, median baseline hematoma volume was 14.0 mL, baseline absolute edema volume was 11.9 mL, and baseline EED was 0.35 cm. Osmotic agent was used in 54 patients (6%). Hematoma shape was considered irregular in 403 patients (47%). There was a strong inverse relationship between EED growth rate and time, EED growth rate = 0.162*days−0.927, which was used in the Figure in the online-only Data Supplement.

**Modeled Edema Progression**

There was a strong inverse relationship between EED growth rate (cm/d) and time, EED growth rate = 0.162*days−0.927, R²=0.820 (Figure 2). The most rapid growth occurred within the first few hours after ictus followed by an exponential slowing of the EED growth rate. On average, the EED thickness was already 60% of peak by 24 hours. The fitted model for edema volume expressed as EED up to 3 weeks is shown on Figure 3. The EED growth rate formula yields a mathematical formula of EED=2.210×days0.0731−1.478, which was used to calculate the expected EED at 72 hours from onset for the patients included in the analysis. The derived growth model for absolute edema volume is represented in the Figure in the online-only Data Supplement.

**Factors Associated With Higher Peak EED**

Three hundred and fifty-eight patients (42%) in the study had EED that was above expected at 72 hours compared with 503 patients (58%) who had lower-than-expected EED (Table 1). Univariate analysis of clinical and radiological variables, larger-than-expected EED was associated with older age (71 versus 68; P=0.002); higher baseline National Institutes of Health Stroke Scale score (14 versus 8; P<0.001); lower baseline Glasgow Coma scale score (13 versus 15; P=0.001); higher baseline glucose (7.6 versus 6.9 mmol/L; P=0.001); larger baseline hematoma volume (19.7 versus 12.7 mL; P=0.001); irregularly shaped hematoma (55% versus 42%; P<0.001); larger baseline EED (0.42 versus 0.30 cm; P<0.001); larger baseline absolute edema volume (18.1 versus 9.3 mL; P<0.001); larger baseline relative edema, a unit-less ratio calculated by edema volume/ICH volume (0.90 versus 0.72; P<0.001); shorter onset to baseline CT time (2.1 versus 7.9 hours; P<0.001), with more patients with midline shift (n=177 [50%] versus n=157 [31%]; P<0.001) and herniation (n=43 [12%] versus n=20 [4%]; P<0.001). Previous warfarin use was associated with increased edema growth (P=0.037), whereas osmotic agent use was not (P=0.153). There was more do-not-resuscitate order (n=161 [45%] versus n=149 [30%]; P<0.001) and higher 6-month mortality (n=162 [46%] versus n=131 [26%]; P<0.001) for patients with larger than expected EED.

**Association of Higher EED With Mortality**

After excluding 9 patients with missing mortality data (7/503 patients [1%] with below-expected EED and 2/358 patients [1%] with above-expected EED), 852 patients were included in the logistic regression analysis. In the multivariable model, higher-than-expected EED was independently associated with mortality at 6 months (odds ratio [OR], 1.60 [95% confidence interval [CI], 1.04–2.46; P=0.032) after adjusting for age, male sex, previous warfarin use, baseline National Institutes of Health Stroke Scale score, Glasgow Coma scale score, ventricular extension, and baseline ICH volume (Table 2). There was no interaction by anticoagulant (P=0.545) or osmotic agent use (P=0.755) or hematoma shape (P=0.112) on the association of EED and mortality. Neither osmotic agent use (OR, 0.77; 95% CI, 0.37–1.63; P=0.502) nor hematoma shape (OR, 1.06; 95% CI, 0.66–1.71; P=0.797) was associated with 6-month mortality when added to the logistic regression model. The logistic regression model was of good fit (area under the curve 0.91; 95% CI, 0.89–0.93).

**Association Between Other Edema Metrics and Mortality**

When dichotomization was performed using interpolated 72-hour absolute edema, the association was not significant (OR, 1.45; 95% CI, 0.91–2.33; P=0.122). When edema metrics were used as a continuous variable, the 72-hour absolute edema volume was associated with mortality (OR, 1.02 per mL; 95% CI, 1.01–1.02; P<0.001), whereas 72-hour EED demonstrated a trend toward increased mortality (OR, 1.58 per cm; 95% CI, 0.92–2.71; P=0.101). In 96 patients with baseline and day-1 CT scans available, the absolute edema growth rate (mL/h) was associated with mortality (OR, 2.95 per mL/h; 95% CI, 1.41–6.14; P=0.004).
Discussion

There are 2 main findings from this study. First, there is a strong inverse relationship between edema growth and time from ICH onset; second patients with larger-than-expected edema are associated with increased mortality.

We present a model of edema growth derived from a large real-life data set of ICH patients. We demonstrate that edema growth was most rapid within the first 24 hours after ICH with significantly slower growth rate in the subacute period in agreement with previous natural history studies in humans.

Results from the pooled INTERACT studies (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial; n=1110) and a single-center study (n=86) demonstrated doubling of absolute edema volume from baseline (under 6 hours from onset) to 24 hours. Natural history studies with edema data ≤28 days (n=1102) indicate that peak edema volume is usually reached between week 2 and 3 after ICH onset.

Our model of edema growth is also consistent with the putative 2-stage edema progression. The first stage is characterized by an initial rapid growth largely driven by clot retraction and

<table>
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<tr>
<th>Table 1. Patient Clinical and Radiological Characteristics</th>
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<tr>
<td><strong>Total (n=861)</strong></td>
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<td>Age, y</td>
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<td>Male sex</td>
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<td>Hypertension</td>
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<td>Diabetes mellitus</td>
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<td>Baseline glucose*</td>
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<td>Ischemic heart disease</td>
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<td>Warfarin</td>
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<td>Statin use*</td>
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<td>Antihypertensive use</td>
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<td>Osmotic agent use†</td>
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<td>Baseline NIHSS</td>
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<td>Onset to baseline scan, hours</td>
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<td>Do-not-resuscitate order</td>
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<td>6-mo mortality*</td>
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<td>Midline shift</td>
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All values are median (interquartile range) or n (%). BP indicates blood pressure; CT, computed tomography; EED, edema extension distance; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; INR, international normalized ratio; and NIHSS, National Institutes of Health Stroke Scale.

*Missing data for mortality in 9 patients (1%), heart failure in 14 patients (2%), dyslipidemia in 10 patients (1%), statin use in 14 patients (2%), and baseline glucose in 14 patients (2%). Baseline INR was available in 740 patients (86%).

†Osmotic agent use indicates use of hypertonic saline, glycerol, or mannitol alone or in combination.
hydrostatic pressure. Clot retraction occurs in response to hemostatic activation designed to limit the primary injury at the site of hemorrhage and increases intraclot pressure leading to shift of serum fluid into the adjacent brain parenchyma. At this acute stage, the blood–brain barrier is relatively intact in contrast to the subacute stage of slower edema growth characterized by vasogenic edema associated with blood–brain barrier breakdown likely mediated by iron-related toxicity and accompanying inflammation. The course of edema progression in previous studies and our model suggests that further growth beyond week 3 is possible, but the significance of late edema on ICH outcome is uncertain.

We found larger baseline ICH volume to be significantly associated with larger-than-expected edema volume. This finding continues to support the consistently reported association of hematoma blood components with edema pathophysiology. Studies have also indicated an association of surrogate markers of iron load such as hematocrit and serum...
Our analysis demonstrated that by 24 hours, on average, the EED thickness is already 60% of peak (Figure 3). It is likely that early edema growth exerts its impact on outcome via a volume-dependent manner at a stage of ICH evolution that is also characterized by hematoma growth. Consistent with this notion is the higher proportion of patients with larger EED with midline shift (50% versus 31%; \( P<0.001 \)) and herniation (12% versus 4%; \( P<0.001 \)) noted in the present study. Further patients with faster EED growth are more likely to have do-not-resuscitate orders in place (45% versus 30%; \( P<0.001 \)), likely influenced by neurological deterioration associated with increasing mass effect. Strategies targeting this early phase of edema growth are likely to alter the edema growth trajectory with reduced peak edema and may result in improved outcome.

Different edema metrics were used in our analyses including EED, a more recent definition of edema. The association between EED and mortality was significant when patients were dichotomized into higher-than-expected versus lower-than-expected edema growth, whereas the association only demonstrated a trend when used as a continuous variable. The converse was true when absolute edema volume was used in the multivariable analysis. Parry-Jones et al\(^8\) noted that EED may reduce the sample size required to detect a treatment effect when compared with absolute edema volume. Our findings suggest that this may not always be the case.

We acknowledge the limitations associated with this study. First, this study is exposed to biases inherent to retrospective single-center studies, and the results may not be generalizable. Selection bias is minimized by including consecutive ICH patients admitted to Helsinki University Hospital during the study period. Furthermore, data ascertainment was systematically obtained, and mortality data derived from a reliable source was available in 99% of the cohort. Second, we were unable to evaluate edema at regular time intervals as repeat imaging at predefined intervals from stroke onset was not routinely performed during the study period. This is also unlikely to be a routine practice outside of randomized trials and research setting. However, we were able to evaluate the growth trajectory and estimated the growth trajectory between individual time points using information derived from \( \approx 1500 \) scans from consecutive unselected patients. The predictive model enabled evaluation of edema relative to the expected trajectory of edema growth and allowed us to dichotomize patients by EED growth at a fixed time point. Although we were able to interpolate the edema volume and EED at 72 hours, this volume may not accurately represent the natural edema evolution in every patient. However, the trajectory is consistent with previous natural history data of edema evolution, indicating the robustness of the model. Third, the EED is an exact measure of edema thickness only when the hematoma and edema are fully ellipsoid in nature. In our study, only half of the ICH was regularly shaped. However, there was no influence of hematoma shape on mortality or the association of EED and mortality. Fourth, we do not have information on functional recovery and could potentially have underestimated the impact of edema on secondary injury. Mortality is, however, a robust measure of ICH outcome. Finally, all the scans were segmented by one rater, which may have resulted in ascertainment bias. This is minimized by using a reliable semiautomated planimetric technique, which has been shown to produce reliable measurements when validated against magnetic resonance imaging,\(^1\) and in our own sample, we had excellent interrater and intrarater agreement (intraclass coefficients 0.952 and 0.983, respectively).\(^1\)

**Conclusions**

Edema growth is strongly correlated with time from stroke onset, influenced by baseline hematoma volume and associated with long-term mortality. Edema growth is an important treatment target for strategies to improve patient outcome.
Sources of Funding
T.Y. Wu is supported by grants from the Neurological Foundation of New Zealand (grant number 1313-CF) and Royal Melbourne Hospital Neuroscience Foundation; T. Tatlisumak is supported by the Helsinki University Hospital and Sahlgrenska University Hospital grants for ICH research; A. Meretoja is supported by grants from National Health and Medical Research Council (Australia), Academy of Finland, and the Finnish Medical Foundation. D. Strbian is supported by grants from the Helsinki University Hospital and the Finnish Medical Foundation.

Disclosures
None.

References
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Stroke. 2017;48:873-879; originally published online March 8, 2017;
doi: 10.1161/STROKEAHA.116.014416

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/48/4/873

An erratum has been published regarding this article. Please see the attached page for:
/content/48/10/e319.full.pdf

Data Supplement (unedited) at:
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Correction to: Natural History of Perihematomal Edema and Impact on Outcome After Intracerebral Hemorrhage

In the article by Wu et al, “Natural History of Perihematomal Edema and Impact on Outcome After Intracerebral Hemorrhage,” which published online on March 8, 2017, and appeared in the April 2017 issue of the journal (Stroke. 2017;48:873–879. DOI: 10.1161/STROKEAHA.116.014416), a correction was needed.

On page 874, the pi symbol (π) has been added to the denominator on each side of the equation.

This correction has been made to the current online version of the article, which is available at http://stroke.ahajournals.org/content/48/4/873.
Supplementary figure*

Scan closest to 72 hours
All other scans
Average edema growth trajectory

Edema growth equation = 72.144*days^{0.09628} - 42.49

* 2 outlier scans with >200mL edema volume not presented in this figure