

# Natural History of Perihematomal Edema in Patients With Hyperacute Spontaneous Intracerebral Hemorrhage

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**Background and Purpose**—The natural history of perihematomal edema in human hyperacute spontaneous intracerebral hemorrhage (ICH) has not been well described.

**Methods**—This study was a secondary analysis of a previously reported prospective, population-based study of hematoma growth in 142 patients with spontaneous ICH. Patients were first imaged within 3 hours of onset, then 1 and 20 hours later. We excluded patients with anticoagulant use (n=7), underlying aneurysm/vascular malformation (n=9), trauma (n=1), incomplete data (n=20), infratentorial ICH (n=17), and no consent (n=2), leaving an overall study population of 86 patients. From this overall group we further excluded patients with intraventricular extension (n=38), subsequent surgery (n=5), or death (n=2) before 20-hour postbaseline CT. This second, “restricted” analysis group of 41 patients was relatively devoid of clinical or radiological variables likely to confound edema measurement. Absolute and relative edema volumes (edema volume divided by hematoma volume) were descriptively summarized. Correlations between baseline edema volumes and relevant clinical and radiological variables were then performed.

**Results**—Overall, median absolute edema volume increased from 6.93 to 14.4 cm<sup>3</sup> during the first 24 hours after ICH, and median relative edema volume increased from 0.47 to 0.81. In the restricted group, median absolute edema volume was 7.4 cm<sup>3</sup> at baseline and 11.0 cm<sup>3</sup> at 24 hours after ICH, and median relative edema volume increased from 0.55 to 0.81. Baseline relative edema volume was significantly negatively correlated with subsequent change in relative edema volume from baseline to 20-hour CT ( $r=0.57$ ,  $P=0.0002$ ) but was not significantly correlated with other clinical and radiological variables, including hematoma volume or change in hematoma volume.

**Conclusions**—Perihematomal edema volume increases by approximately 75% during the first 24 hours after hyperacute spontaneous ICH. Patients with the least amounts of baseline relative edema volume were most likely to develop significant additional amounts of edema during the first 24 hours after spontaneous ICH. (*Stroke*. 2002;33:2631-2635.)

**Key Words:** computed tomography ■ intracerebral hemorrhage ■ natural history

Intracerebral hemorrhage (ICH) remains the most common type of hemorrhagic stroke in the United States<sup>1</sup> but causes a disproportionate amount of stroke mortality and disproportionately affects those of Asian and sub-Saharan African descent.<sup>2,3</sup> The natural history and pathogenesis of perihematomal edema in human spontaneous intracerebral hemorrhage (SICH) are just beginning to be understood, particularly in the hyperacute setting. Carefully documenting the genesis and evolution of edema is a necessary first step in understanding the pathogenesis of edema and whether it might be altered by treatment strategies aimed at reducing edema-related morbidity and mortality. This study is a secondary analysis of data prospectively collected during a population-based study of hematoma growth after hyperacute SICH, whose original results have been previously reported.<sup>4</sup> Patients in this study systematically underwent baseline CT scanning within 3

hours of clinical ICH onset, with repeated studies at 1 and 20 hours after baseline CT. We sought (1) to summarize edema volumes in both absolute and relative terms (see below) and (2) to explore the presence of associations between edema volume and relevant clinical and radiological variables.

## Subjects and Methods

### Study Design

This study was a secondary analysis of data prospectively collected during a previously published study of the natural history of hematoma growth in 142 patients with hyperacute SICH first imaged within 3 hours of clinical onset.<sup>4</sup> The study population on which this study was performed has been described in detail elsewhere<sup>4</sup> and consisted of 142 patients with SICH presenting to emergency departments in a 5-county study region over a 6-year period, all of whom were imaged by noncontrast brain CT within 3 hours of ICH onset. Nearly all patients underwent a second brain CT scan 1 hour

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later, and most underwent a third 20-hour postbaseline (24 hours after ICH) CT scan.

## Data Collection

Relevant demographic, clinical, laboratory, and outcome data were prospectively collected as part of the original study, with the exception of relative edema volume values, which were calculated post hoc several years later when a study comparing hyperacutely imaged thrombolysis/anticoagulant-related ICH with hyperacutely imaged SICH was performed.<sup>5</sup> All data were collected before the present study was conceived and implemented.

## Creation of Analysis Groups

We analyzed 2 groups of patients in this study. The first group was created by excluding patients with anticoagulant use ( $n=7$ ), underlying aneurysm or vascular malformation ( $n=9$ ), head trauma ( $n=1$ ), incomplete clinical or CT data ( $n=20$ ), or no consent ( $n=2$ ). This left a group of 103 patients with true SICH and reasonably complete data, from which we further excluded those with infratentorial ICH ( $n=17$ ) because of concern about petrous apex streak artifact potentially obscuring edema borders and consequently lessening accurate measurement of edema volume. The remaining 86 patients constituted the first "overall" (supratentorial ICH) patient analysis group.

To generate the second "restricted" (natural history) patient analysis group, we started with the overall group and further excluded those patients with initial or subsequent intraventricular extension of their hemorrhage ( $n=38$ ) because of concerns about admixture of cerebrospinal fluid and edema confounding edema evolution and/or measurement. The remaining 48 patients constituted the second restricted (natural history) patient analysis group. We further excluded patients who died or underwent subsequent surgical intervention ( $n=7$ ) from any analyses performed with the use of 1-hour and 20-hour postbaseline CT scan data because of concerns about surgery destroying the original hematoma and edema-hematoma relationship. We analyzed both the overall group, whose results we believed would be most generalizable to clinical practice, and the restricted group, which we believed would better represent the natural evolution of edema.

## Definition and Measurement of Hematoma and Perihematomal Edema Volumes

Specifically, each brain CT image was scanned by a charge-coupled device camera into the computer, digitized at  $512 \times 492$  resolution, and automatically aligned with the use of cross-correlation between the reference image and other images. Images were then preprocessed to standardize brightness levels of brain tissue and hematoma, thus compensating for variations in brightness and contrast between CT images from different CT scanners and institutions. K-means histogram-based clustering was used to determine the standardized brightness (attenuation) values for background (noise) level, brain tissue level, and skull level for each CT scan slice. The skull was then extracted from each digitized image, leaving brain parenchyma including the hematoma and perihematomal edema in each slice.

The study neuroradiologist (T.A.T.) marked the center of each hematoma, which defined the center of the region of interest for subsequent hematoma and edema volume measurement. Once again, the same K-means clustering algorithm was used to divide the region of interest into foreground (hematoma) and background (perihematomal edema and brain parenchyma). On the basis of the algorithm-generated threshold value to differentiate hematoma from edema, the number of contiguous 3-dimensional voxels within the foreground (hematoma) is summed to yield hematoma volume. Subsequently, ICH edema segmentation is accomplished by "growing" thin layers (rings) sequentially outward from the edge of the hematoma. Each such ring of pixels is examined with the use of 1 of several computer-generated K-means clustering algorithm-based threshold values for edema, the most optimal of which is selected by the operator. For each layer, the number of pixels falling within the selected range of pixel attenuation is summed and added to the

previous layer's number of edema pixels. This iterative process is continued until no new pixels are selected in the current (final) layer. The sum total of pixels in all layers falling within the range of edema values represents the (absolute) perihematomal edema volume.

In a 5-patient study, the reproducibility of this automated method was verified between 3 different operators, and its accuracy was verified by correlation of the automatic method volumes with conventional manually traced (by a fourth operator) planimetric (volumetric) measurement of both hematoma and edema volumes, with an overall Spearman correlation coefficient (between standard volumetric versus automated edema and hematoma volumes) of 0.9744.<sup>6</sup>

Relative edema volume was defined as absolute edema volume divided by hematoma volume, yielding a unitless ratio variable that expresses absolute edema volume as a percentage of the associated hematoma volume. When very small, unmeasurable amounts of edema were present, absolute and relative edema volume values of zero were assigned.

## Statistical Methods

Data management and analysis was done with the use of SAS software (SAS Institute). Hematoma volumes and edema volumes (both absolute and relative) were summarized as median and range. Correlations between relative edema volume and other continuous variables were performed by the Spearman correlation coefficient (nonparametric) technique. Associations between relative edema volume and categorical variables were analyzed with the Kruskal-Wallis test. Repeated-measures ANOVA was used to examine changes in absolute edema volume and relative edema volume from 0- to 1-, 1- to 20-, and 0- to 20-hour CT scans.

## Results

### Perihematomal Edema Volumes

The summary values of absolute and relative edema volume for the 2 analysis groups are presented in Table 1. Overall, one third of patients lacked measurable edema on baseline CT, but nearly all had measurable edema volume by their 20-hour CT. There was a median 37% increase in absolute edema volume from baseline to 1-hour brain CT scan, whereas relative edema volumes remained unchanged during this interval. The increases in absolute edema volume were largely confined to those patients undergoing hematoma growth during this time. Absolute edema volume doubled during the first 24 hours. There was an approximately 75% increase in the median amount of relative edema volume from baseline CT to 20-hour CT scan. A repeated-measures ANCOVA performed on the overall group demonstrated that the differences in both absolute and relative edema volumes at baseline and at 1 and 20 hours were highly statistically significant ( $P<0.001$  each). In the restricted patient group, comparable changes in absolute and relative edema volumes were observed (Table 1).

### Relationship Between Perihematomal Edema and Other Clinical and Radiological Variables

In an attempt to better understand the relationship between the development of edema and other important clinical and radiological variables, correlations were performed between baseline absolute and relative edema volume and various clinical and radiological variables. The results of these correlations are summarized in Table 2.

Of the many clinical variables tested in both groups, only 1 statistically significant association was observed: a negative association between baseline relative (but not absolute)

**TABLE 1. Absolute and Relative Perihematoma Edema Volumes in Overall and “Restricted” (No Intraventricular Hemorrhage or Surgery) Patient Groups**

Edema	Overall Patient Group (n=86)			Restricted Natural History Patient Group (n=41)		
	Baseline CT (n=86)	1-h CT (n=86)	20-h CT (n=54)*	Baseline CT (n=41)	1-h CT (n=41)	20-h CT (n=38)†
Hematoma volume, cm <sup>3</sup>	19.1 (0.41–131)	23.6 (0.46–148)	16.5 (0.67–120)	11.3 (0.42–86.7)	15.5 (0.46–98.1)	12.4 (0.67–101)
Absolute edema volume, cm <sup>3</sup>	6.93 (0–90.5)	9.47 (0–82.9)	14.4 (0–120.3)	7.41 (0–40.5)	8.38 (0–43.3)	11.0 (0–50.9)
Relative edema volume	0.466 (0–4.14)	0.469 (0–4.19)	0.814 (0–5.13)	0.546 (0–4.13)	0.586 (0–4.19)	0.811 (0–5.12)

Values are median (range).

\*Twenty-five patients underwent surgery and 2 died between 1-h postbaseline and 20-hour postbaseline CT scans. Five patients had missing 20-hour CT scan data.

†Three patients died between 1-hour postbaseline and 20-hour postbaseline CT scans.

edema volume and subsequent treatment with mannitol in the overall group ( $P=0.0326$ ). Thus, patients with lesser amounts of baseline relative edema volume were more likely to receive subsequent mannitol treatment. However, no associ-

ation between 1-hour and 20-hour relative edema volumes and mannitol treatment was observed in this group. In the restricted group, no association between mannitol treatment and relative or absolute edema volume was observed at any of the 3 time points.

**TABLE 2. Correlation Between Baseline Relative Perihematoma Edema Volume and Selected Baseline Clinical and Radiological Variables in 41 Patients With SICH Without Intraventricular Extension or Surgery (Restricted Analysis Group)**

Variable	Correlation Coefficient (r) or $\chi^2$	P
Admission glucose	0.0950	0.525
PT	−0.147	0.320
PTT	−0.110	0.456
Admission platelet count	0.321	0.028
Fibrinogen level (n=31)	−0.166	0.370
Systolic blood pressure	−0.086	0.601
Diastolic blood pressure	−0.032	0.846
Mean arterial blood pressure	−0.057	0.727
Time from symptom onset to baseline CT scan	0.208	0.193
Admission NIHSS score	0.092	0.541
Absolute edema volume	0.630	<0.0001
Hematoma volume	0.128	0.426
Change in relative edema, baseline to 1-h CT	−0.524	0.0004
Change in hematoma volume, baseline to 1-h CT	−0.007	0.960
Change in relative edema, baseline to 20-h CT	−0.572	0.0002
Change in hematoma volume, baseline to 20-h CT	−0.160	0.337
Diabetes mellitus	0.745*	0.389
Antiplatelet drug use	0.349*	0.556
Current smoker	2.59*	0.108
History of hypertension	0.031*	0.860
Mass effect (any)	0.071*	0.790
Midline pineal shift (any)	0.694*	0.405
Hemorrhage growth	1.76*	0.184
Race	2.84*	0.091
Mannitol treatment	1.37*	0.241
Hematoma location (deep vs lobar)	0.0003*	0.987

NIHSS indicates National Institutes of Health Stroke Scale. All correlations are Spearman coefficients for continuous variables. Categorical variables were analyzed by the Kruskal-Wallis test.

\* $\chi^2$  values.

For radiological variables, a moderate correlation was observed between baseline absolute perihematoma edema volume and hematoma volume ( $r=0.393$ ,  $P=0.0002$ ) in the overall group. Importantly, however, little correlation between baseline relative edema volume and hematoma volume was observed ( $r=-0.110$ ,  $P=0.309$ ). Similarly, little correlation was observed between 1- and 20-hour relative edema volume and respective 1- and 20-hour hematoma volumes. Relative and absolute edema volumes were strongly positively correlated with each other at baseline ( $r=0.761$ ,  $P<0.0001$ ) and 1-hour postbaseline CT scans ( $r=0.606$ ,  $P<0.0001$ ). However, there was only a weak association by the time 20-hour CTs were obtained ( $r=0.226$ ,  $P=0.0995$ ).

Significant negative correlations were observed between baseline relative edema volume and subsequent change in relative edema volume from baseline to 1-hour CT ( $r=-0.4506$ ,  $P<0.0001$ ) and for subsequent change in relative edema volume from baseline to 20-hour CT (n=54 patients;  $r=-0.4506$ ,  $P=0.0004$ ). When this analysis was repeated for the restricted patient group, even stronger negative correlations were observed between baseline relative edema volume and subsequent change in relative edema volume from baseline to 1-hour CT ( $r=-0.524$ ,  $P=0.0004$ ) and subsequent change in relative edema volume from baseline to 20-hour CT scan ( $r=-0.572$ ,  $P=0.0002$ ). Little correlation between baseline relative edema volume and subsequent percent (or absolute) change in hematoma volume from baseline to 1-hour CT ( $r=0.130$ ,  $P=0.227$ ) or baseline to 20-hour CT ( $r=-0.0869$ ,  $P=0.5319$ ) was observed in both analysis groups. No significant correlations between absolute edema volume and subsequent changes in absolute edema volume or hematoma volume were observed.

## Discussion

This study represents the first descriptive analysis of the natural history of hyperacute perihematoma edema in a prospective, population-based study of patients with hyperacute SICH. The systematic, time-standardized points of repeated measurement of edema volumes in the study patients and statistically adequate sample size are distinctive features

of this study. We observed a 75% median increase in relative edema and 100% median increase in absolute edema volume over the first 24 hours after ICH. Patients with the smallest amounts of baseline relative edema experienced the largest subsequent increases in relative edema volume, with all of the increase in edema occurring from 1 to 20 hours. No such correlations were observed with baseline absolute edema volume. Thus, when we controlled for hematoma volume, perihematomal edema remained essentially constant for the first hour and then subsequently underwent significant expansion during the ensuing 20 hours. Absolute edema volumes and hematoma volumes correlated with each other, but the magnitude of this correlation was only mild to moderate ( $r=0.393$ ).

The minimal association between relative edema volume and hematoma volume at all 3 time points confirmed that relative edema volume measures perihematomal edema in the context of its underlying hematoma, as intended. Thus, hematoma volume does not confound relative edema volume measurement. No associations were observed between relative edema volume and hematoma location, mass effect, time from symptom onset to baseline CT scan, subsequent hematoma growth, or any other clinically meaningful potential confounding variables. Thus, we conclude that the variations in the amounts of relative edema volume at each time point, as well as subsequent changes in edema volume, are inherent to the individual hematoma and patient and are not the artifactual result of other variables or any obvious selection bias.

In considering the pathogenesis of hyperacute perihematomal edema, experimental evidence strongly supports the hypothesis that it is largely composed of the remaining, peripherally exuded serum proteins after clotting of the hematoma and consumption of plasma clotting factors.<sup>7-15</sup> Recent porcine experiments confirm that intrahematomal heparin can prevent such hyperacute perihematomal edema formation and that intrahematomal tissue plasminogen activator instillation can reduce it.<sup>16</sup> Further supportive human study evidence includes data from a prospective pilot study designed to analyze the effects of thrombocytopathia and/or thrombocytopenia and SICH.<sup>17</sup> This study demonstrated an association between platelet dysfunction and/or thrombocytopenia and increased hematoma volume.<sup>17</sup> Another supportive study is our previous report comparing relative edema volumes in hyperacute thrombolysis/anticoagulant-related ICH with hyperacute SICH.<sup>5</sup> In this study we observed much lower amounts of perihematomal edema in thrombolysis/anticoagulant-related ICH than in SICH.

We did not observe any significant association between absolute or relative edema volume and admission platelet counts or prothrombin time (PT)/partial thromboplastin time (PTT) values in this study, although there was a weak correlation between admission platelet count and baseline relative edema volume in the restricted group only (Table 2). However, all PT/PTT and platelet count values were normal in the study population analyzed because we excluded patients with presumptively or possibly coagulopathy-related ICH. This would consequently lessen the chance of observing any such associations. We also previously failed to observe any association between PT/PTT values, admission platelet

count, or antiplatelet drug use and hematoma volume in this same study population.<sup>4</sup> However, we did not systematically test for indices of platelet dysfunction such as bleeding time.

We did not observe any association between baseline absolute or relative edema volume and subsequent hematoma growth, whether measured categorically ( $>33\%$ )<sup>4</sup> or continuously. The lack of such an association suggests that in noncoagulopathic SICH patients, initial clotting of the hematoma and generation of hyperacute edema does not significantly influence overall rebleeding rates. It also indicates that lack of perihematomal edema on presentation is not simply the result of an actively bleeding, expanding hematoma obliterating the edema rim. Furthermore, it is clear from our data that subsequent changes in relative edema volume over time are not simply the result of subsequent clot expansion or retraction because there were no significant correlations between these variables. Alternatively, it is possible (but not likely) that the number of subsequently growing hematomas was too small to allow detection of a statistically significant association.

Finally, in considering the possibility that treatment effect may have accounted for amounts of absolute or relative edema volume, only a negative association between baseline (but not 1- or 20-hour) relative edema volume and subsequent mannitol treatment in the overall group was observed. Whether this indicates that patients with the least baseline relative perihematomal edema volume were more likely to require or receive osmotic therapy for subsequent edema and/or associated hematoma mass effect is unclear because this study examined only perihematomal edema within the first 24 hours after ICH.

It is important to acknowledge that this study has a number of largely unavoidable limitations. First, we were limited by the fact that this was a secondary analysis. We analyzed both absolute and relative edema volumes strictly within a hyperacute to acute time frame. Whether the evolution of perihematomal edema in this very early period bears any relationship to more delayed, vasogenic edema or any edema beyond the first 24 hours after ICH is unknown. Second, while we attempted to investigate associations between all available clinically important variables and edema formation, there may have been other unavailable factors, such as differences between treating physicians in individual patient care, that may have confounded the associations observed. Any future studies should attempt to standardize treatment protocols to minimize potential bias and/or excess nondifferential misclassification resulting from such variations. Third, although the method of perihematomal edema volume measurement used was semiautomated and hypothetically more objective and accurate than conventional planimetric edema volume measurement by manual tracing and summation of edema borders, the methodology used still required subjective input on the part of the study neuroradiologist, specifically in selecting the most appropriate of the computer algorithm-generated threshold values differentiating perihematomal edema from adjacent brain tissue. Thus, it is possible that systematic error was introduced into the perihematomal measurements, and the results of the study must be interpreted within this context. Finally, the observed changes in



edema volumes from 1 to 20 hours were limited to those patients not undergoing surgery after their 1-hour CT. This introduces potential bias in these values.

We conclude that, on average, perihematomal edema increases by approximately 75% during the first 24 hours after ICH in patients with hyperacute, supratentorial SICH. Patients with the least amounts of relative edema on baseline CT are most prone to subsequently develop large amounts of additional perihematomal edema during this 24-hour period. Further studies are needed to more clearly address whether such patients are at greater risk to neurologically deteriorate, require surgery, or have poor outcome and to determine the physiological and biochemical basis of variation in edema formation and evolution beyond the limited 24-hour time frame addressed in this study.

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