Decreased Perihematomal Edema in Thrombolysis-Related Intracerebral Hemorrhage Compared With Spontaneous Intracerebral Hemorrhage

James M. Gebel, MD; Thomas G. Brott, MD; Cathy A. Sila, MD; Thomas A. Tomwick, MD; Edward Jauch, MD; Shelia Salisbury, MS; Jane Khoury, MS; Rosemary Miller, RN; Arthur Pancioli, MD; John E. Duldner, MD; Eric J. Topol, MD; Joseph P. Broderick, MD

Background and Purpose—Intracerebral hemorrhage (ICH) is a highly morbid disease process. Perihematomal edema is reported to contribute to clinical deterioration and death. Recent experimental observations indicate that clotting of the intrahematomal blood is the essential prerequisite for hyperacute perihematomal edema formation rather than blood-brain barrier disruption.

Methods—We compared a series of patients with spontaneous ICH (SICH) to a series of patients with thrombolysis-related ICH (TICH). All patients were imaged within 3 hours of clinical onset. We reviewed relevant neuroimaging features, emphasizing and quantifying perihematomal edema. We then analyzed clinical and radiological differences between the 2 ICH types and determined whether these factors were associated with perihematomal edema.

Results—TICHs contained visible perihematomal edema less than half as often as SICHs (31% versus 69%, \(P<0.001\)) and had both lower absolute edema volumes (0 cc [25th, 75th percentiles: 0, 6] versus 6 cc [0, 13], \(P<0.0001\)) and relative edema volumes (0.16 [0.10, 0.33] versus 0.55 [0.40, 0.83], \(P<0.0001\)). Compared with SICHs, TICHs were 3 times larger in volume (median [25th, 75th percentiles] volume 69 cc [30, 106] versus 21 cc [8, 45], \(P<0.0001\)), 4 times more frequently lobar in location (62% versus 15%, \(P<0.001\)), 80 times more frequently contained blood-fluid level(s) (86% versus 1%, \(P<0.001\)), and were more frequently multifocal (22% versus 0%, \(P<0.001\)).

Conclusions—The striking qualitative and quantitative lack of perihematomal edema observed in the thrombolysis-related ICHs compared with the SICHs provides the first substantial, although indirect, human evidence that intrahematomal blood clotting is a plausible pathogenetic factor in hyperacute perihematomal edema formation. (Stroke. 2000;31:596-600.)

Key Words: brain edema ■ cerebral hemorrhage ■ hematoma ■ thrombolysis

Intracerebral hemorrhage (ICH) kills approximately 22,000 Americans annually.1 Although significant ICH-related morbidity arises from hematoma mass effect and intraventricular extension, further clinical deterioration related to rebleeding and/or perihematomal edema development often occurs.7 Recent experimental evidence3–6 suggests that hyperacute perihematomal edema results from the clotting of intrahematomal blood with liberation of remaining serum proteins into the surrounding brain tissue rather than by blood-brain barrier disruption, as traditionally thought.

Anticoagulants, such as heparin, prolong the time necessary for blood to clot. Thrombolytic drugs, such as streptokinase and tissue plasminogen activator (tPA), lead to enzymatic lysis of fibrin. Our previously reported clinicoradiological analysis of all intracranial hemorrhages complicating the GUSTO-I trial of systemic thrombolysis for acute myocardial infarction demonstrated large volumes of ICH and high frequencies of lobar hematomas, intrahematomal blood-fluid level(s), and multifocal hemorrhage compared with values typical for SICH. Furthermore, perihematomal edema was less frequent and severe than that typically seen in SICH. This largely descriptive analysis, however, did not address time from ICH symptom onset to brain CT and lacked a comparison group of SICHs.

For this report, we performed a comparative clinicoradiological analysis of a large series of acutely imaged TICHs and a large series of acutely imaged SICHs. We qualitatively and quantitatively described differences between these 2 ICH types, emphasizing perihematomal edema. By including only
patients who underwent brain CT within 3 hours of ICH symptom onset, we controlled for the important confounding factor: time. Finally, we hypothesized what these observations suggest about the pathogenesis of hyperacute perihematomal edema in humans.

**Subjects and Methods**

We studied 2 separate study populations. The first group was derived from patients randomized into the GUSTO-1 coronary artery thrombolysis trial for acute myocardial infarction. In this trial, 268 patients suffered intracranial (parenchymal and/or subdural) hemorrhage with no identifiable underlying structural cause such as neoplasm, aneurysm, or vascular malformation. We excluded those whose CT scans of the brain were not available for review (19), those with missing CT times (13), those in whom the time difference between ICH symptom onset time and CT scan time was a negative value (which indicated inaccurate data transcription) (19), those with missing times of ICH symptom onset (6), and those with no radiological evidence of ICH (4). Finally, in the remaining group of 173 patients, those imaged >3 hours after ICH symptom onset (99 patients) were excluded, leaving 74 patients with 1 or more parenchymal hematomas imaged within 3 hours of clinical onset.

The second group was derived from a large, prospective series of 142 patients living in Greater Cincinnati and Northern Kentucky during 1988 to 1993 with “spontaneous” ICH imaged within 3 hours of clinical symptom onset. Details of this study’s design and patient recruitment have been published elsewhere. Only the initial (baseline) CT scans in this study were used for our analysis. We excluded patients with underlying structural lesions, such as neoplasm, aneurysm, or vascular malformation (12); those unable to complete the original study (10); those whose CT scans could not be located (10); those with anticoagulant-, thrombolysis-, or coagulopathy-related ICH (7); those with missing clinical symptom onset times (4); and those unable or unwilling to give informed consent (2). This left a group of 97 patients with 1 or more “spontaneous” parenchymal hematomas imaged within 3 hours of clinical symptom onset.

In both patient populations, ICH symptom onset was defined by witnessed onset of acute headache, decreased level of consciousness, or appearance of focal neurological deficits secondary to ICH identified on the subsequent noncontrast brain CT.

All noncontrast CT scans of the brain were reviewed by at least 1 principal investigator (J.M.G., T.G.B., C.A.S., or T.A.T.). Parenchymal hematoma, intraventricular hemorrhage, and edema volumes in the TICH patients were measured with computer-assisted 3D volumetric analysis (proprietary software, Center for Computer Assisted Neurosurgery, Cleveland Clinic Foundation, run on Sun Microsystems’ SparcStation I). Volumes in the SICH patient group were determined by another similar technique, the details of which have been published elsewhere. In both groups, relative edema volume was defined as the ratio of absolute perihematomal edema volume to parenchymal hematoma volume. The number of hemorrhage foci was determined. Hematoma location was classified as follows: “lobar,” defined as hematoma predominantly confined to 1 or more lobes of the brain and adjacent subcortical white matter; “deep,” defined as hematoma predominantly confined to the caudate nucleus, putamen, globus pallidus, internal capsule, and/or thalamus; or “cerebellar,” defined as hematoma confined to the cerebellar vermis and/or hemispheres. The presence or absence of hydrocephalus, mass effect, herniation (transientorial or subfalcial), and intrahematomal blood-fluid level was noted for each scan. Detailed definitions and criteria for each of these features have been published elsewhere. It should be reiterated that “blood-fluid level” is defined as the presence of uniform low attenuation above and high attenuation below a discrete line of horizontal separation within a hematoma. (Figure, bottom.)

Clinical and demographic data were obtained from the preexisting databases for each of the 2 studies. In the GUSTO-1 trial, from which the thrombolysis-related ICH patient group in the present study was derived, all patients received 160 to 325 mg aspirin on study enrollment and daily thereafter and were randomized to 1 of the following 4 thrombolytic agent and anticoagulant treatment strategies: (1) streptokinase 1.5 million U over 1 hour with subcutaneous heparin 12 500 U twice daily; (2) streptokinase 1.5 million U over 1 hour with intravenous (IV) heparin; (3) tPA 15-mg IV bolus, then 0.75 mg/kg (maximum 50 mg) over 30 minutes and 0.5 mg/kg (maximum 35 mg) over 1 hour with IV heparin; or (4) combination therapy with tPA 1.0 mg/kg (maximum 90 mg) over 1 hour with 10% given as a bolus and streptokinase 1.0 million U over 1 hour with IV heparin. The IV heparin regimen consisted of a 5000-U bolus, then 1000 U/h for 48 hours, subsequently adjusted to maintain an activated partial thromboplastin time (aPTT) of 60 to 85 seconds.

Baseline demographic and clinical risk factor variables for each patient group, and hematoma, edema, and intraventricular hemorrhage volumes were summarized as means with SDs for normally distributed continuous variables. Non-normally distributed continuous variables were summarized by median (25th, 75th percentile) values. Categorical variables were summarized as frequencies or percentages. The Student t test was used to compare differences in normally distributed continuous variable, and the Wilcoxon rank sum test was used to compare differences in non-normally distributed continuous variables. The χ² test was used to compare differences between patient groups for categorical variables. Values of P<0.05 were considered statistically significant. The correlation coefficient was used to measure the degree of linear association between 2 continuous variables. Regression analysis was also used to evaluate relationships between continuous variables.
The distribution of baseline demographic variables and ICH risk factors were similar in both patient groups, except that the TICH patients were on average 6 years older than the SICH patients (P=0.002), and the proportion of nonwhite patients was greater in the SICH group (30%) than the TICH group (12%, P=0.006). (Table 1). Mean (SD) time from ICH symptom onset to CT scanning was 1.48 (0.61) hours for the SICH group compared with 1.52 (0.78) hours for the TICH group.

Striking differences in the frequency and amount of perihematomal edema were observed between the 2 groups. Specifically, visible perihematomal edema was present less than half as often in the TICHs (31%) as in the SICHs (69%, P<0.001). Furthermore, the quantity of perihematomal edema was much lower in TICHs compared with SICHs, whether measured by absolute volume (0 cc [0, 6] versus 6 cc [0, 13], P<0.0001) or by relative volume (0.43 [0.0, 0.66] versus 0 [0, 0.10]; Table 2). Factors not associated with the presence or amount of perihematomal edema included patient age, gender, time from symptom onset to CT, hypertension, smoking, and diabetes. A statistically significant difference was observed, however, in the median absolute amount of perihematomal edema between nonwhite (1.9 cc) and white (7.6 cc, P=0.001). Those TICHs with a blood-fluid level (n=64, median [25th, 75th percentiles] volume 74.0 [43, 116]) were almost 4 times larger than those without a blood-fluid level (n=10, median [25th, 75th percentiles] volume 30 cc [7, 85], P=0.040). Finally, TICHs were much more often multifocal than SICHs (22% versus 0%, P<0.001). Table 3 describes other noteworthy radiological differences between the 2 hemorrhage types.

### Discussion

In this study, we observed a significant qualitative and quantitative lack of perihematomal edema surrounding TICHs compared with the SICHs, controlling for time from symptom onset to CT scanning. Specifically, visible perihematomal edema was present less than half as often in TICH as in with SICH, and amounts of edema in TICHs were small

3) None of the 10 hematomas with no blood-fluid level in the thrombolysis-related ICH group had visible perihematomal edema (P=0.027). However, there was a significant difference in the median time from symptom onset to imaging of these 10 hematomas (1.15 hours) versus the 64 hematomas with a blood-fluid level (1.72 hours, P=0.043).

Other important radiological differences between the 2 ICH types were that TICHs were of lobar anatomic location (61%) 4 times more often than SICHs (15%, P<0.001), and TICHs also more often contained blood-fluid level(s) (86%) than SICHs (1%, P<0.001; Table 3). Those TICHs with a blood-fluid level (n=64, median [25th, 75th percentiles] volume 74.0 [43, 116]) were almost 4 times larger than those without a blood-fluid level (n=10, median [25th, 75th percentiles] volume 30 cc [7, 85], P=0.040). Finally, TICHs were much more often multifocal than SICHs (22% versus 0%, P<0.001). Table 3 describes other noteworthy radiological differences between the 2 hemorrhage types.

### Discussion

In this study, we observed a significant qualitative and quantitative lack of perihematomal edema surrounding TICHs compared with the SICHs, controlling for time from symptom onset to CT scanning. Specifically, visible perihematomal edema was present less than half as often in TICH as in with SICH, and amounts of edema in TICHs were small

3) None of the 10 hematomas with no blood-fluid level in the thrombolysis-related ICH group had visible perihematomal edema (P=0.027). However, there was a significant difference in the median time from symptom onset to imaging of these 10 hematomas (1.15 hours) versus the 64 hematomas with a blood-fluid level (1.72 hours, P=0.043).

Other important radiological differences between the 2 ICH types were that TICHs were of lobar anatomic location (61%) 4 times more often than SICHs (15%, P<0.001), and TICHs also more often contained blood-fluid level(s) (86%) than SICHs (1%, P<0.001; Table 3). Those TICHs with a blood-fluid level (n=64, median [25th, 75th percentiles] volume 74.0 [43, 116]) were almost 4 times larger than those without a blood-fluid level (n=10, median [25th, 75th percentiles] volume 30 cc [7, 85], P=0.040). Finally, TICHs were much more often multifocal than SICHs (22% versus 0%, P<0.001). Table 3 describes other noteworthy radiological differences between the 2 hemorrhage types.

### Discussion

In this study, we observed a significant qualitative and quantitative lack of perihematomal edema surrounding TICHs compared with the SICHs, controlling for time from symptom onset to CT scanning. Specifically, visible perihematomal edema was present less than half as often in TICH as in with SICH, and amounts of edema in TICHs were small

3) None of the 10 hematomas with no blood-fluid level in the thrombolysis-related ICH group had visible perihematomal edema (P=0.027). However, there was a significant difference in the median time from symptom onset to imaging of these 10 hematomas (1.15 hours) versus the 64 hematomas with a blood-fluid level (1.72 hours, P=0.043).

Other important radiological differences between the 2 ICH types were that TICHs were of lobar anatomic location (61%) 4 times more often than SICHs (15%, P<0.001), and TICHs also more often contained blood-fluid level(s) (86%) than SICHs (1%, P<0.001; Table 3). Those TICHs with a blood-fluid level (n=64, median [25th, 75th percentiles] volume 74.0 [43, 116]) were almost 4 times larger than those without a blood-fluid level (n=10, median [25th, 75th percentiles] volume 30 cc [7, 85], P=0.040). Finally, TICHs were much more often multifocal than SICHs (22% versus 0%, P<0.001). Table 3 describes other noteworthy radiological differences between the 2 hemorrhage types.

### Discussion

In this study, we observed a significant qualitative and quantitative lack of perihematomal edema surrounding TICHs compared with the SICHs, controlling for time from symptom onset to CT scanning. Specifically, visible perihematomal edema was present less than half as often in TICH as in with SICH, and amounts of edema in TICHs were small

3) None of the 10 hematomas with no blood-fluid level in the thrombolysis-related ICH group had visible perihematomal edema (P=0.027). However, there was a significant difference in the median time from symptom onset to imaging of these 10 hematomas (1.15 hours) versus the 64 hematomas with a blood-fluid level (1.72 hours, P=0.043).

Other important radiological differences between the 2 ICH types were that TICHs were of lobar anatomic location (61%) 4 times more often than SICHs (15%, P<0.001), and TICHs also more often contained blood-fluid level(s) (86%) than SICHs (1%, P<0.001; Table 3). Those TICHs with a blood-fluid level (n=64, median [25th, 75th percentiles] volume 74.0 [43, 116]) were almost 4 times larger than those without a blood-fluid level (n=10, median [25th, 75th percentiles] volume 30 cc [7, 85], P=0.040). Finally, TICHs were much more often multifocal than SICHs (22% versus 0%, P<0.001). Table 3 describes other noteworthy radiological differences between the 2 hemorrhage types.

### Discussion

In this study, we observed a significant qualitative and quantitative lack of perihematomal edema surrounding TICHs compared with the SICHs, controlling for time from symptom onset to CT scanning. Specifically, visible perihematomal edema was present less than half as often in TICH as in with SICH, and amounts of edema in TICHs were small

3) None of the 10 hematomas with no blood-fluid level in the thrombolysis-related ICH group had visible perihematomal edema (P=0.027). However, there was a significant difference in the median time from symptom onset to imaging of these 10 hematomas (1.15 hours) versus the 64 hematomas with a blood-fluid level (1.72 hours, P=0.043).

Other important radiological differences between the 2 ICH types were that TICHs were of lobar anatomic location (61%) 4 times more often than SICHs (15%, P<0.001), and TICHs also more often contained blood-fluid level(s) (86%) than SICHs (1%, P<0.001; Table 3). Those TICHs with a blood-fluid level (n=64, median [25th, 75th percentiles] volume 74.0 [43, 116]) were almost 4 times larger than those without a blood-fluid level (n=10, median [25th, 75th percentiles] volume 30 cc [7, 85], P=0.040). Finally, TICHs were much more often multifocal than SICHs (22% versus 0%, P<0.001). Table 3 describes other noteworthy radiological differences between the 2 hemorrhage types.
even when present—less than one third the amount of that seen in SICH, in relative terms (Table 3).

We limited the time from ICH symptom onset to neuroimaging to ≤3 hours in both patient groups for several reasons. First, we wished to control as much as possible for the important confounding effects of time. Second, limiting this time window allowed us to observe these 2 very different ICH types as close to their clinical origins as realistically possible. Finally, we sought to identify important factors in the pathogenesis of perihematomal edema formation in hyperacute human ICH. It should be emphasized up front, however, that both restricting our analysis to those patients imaged within 3 hours of clinical onset and not having follow-up scans available for any of the TICH patients prevent us from drawing direct conclusions about delayed perihematomal edema formation and its pathogenic factors. All edema measurements had been completed in both patient groups by experienced technicians before our study was conceived or implemented; thus, the possibility of bias related to knowledge of its anticipated results by the investigators is minimal.

As noted above, in attempting to understand the observed differences in perihematomal edema formation between the 2 patient groups, our first goal was to eliminate time from symptom onset to CT scanning as a confounding variable. In this regard, the first and foremost relevant observation is that no significant difference existed between times from clinical symptom onset to imaging between the TICH and SICH groups. Thus, as intended, a difference in timing of imaging between the 2 patient groups does not explain the observed differences.

Regarding whether a longer time or some minimum absolute amount of time might be required for perihematomal edema formation within the TICH patient group itself, we note the following observations. The frequency and amounts of perihematomal edema reported in the acutely imaged TICH patient group in this study do not appreciably differ from the overall results previously reported for the entire GUSTO-1 intracranial hemorrhage population, which included patients whose times from ICH symptom onset to neuroimaging were delayed up to 96 hours. This observation argues strongly against an obligatory minimum time requirement for hyperacute perihematomal edema formation as a likely explanation for the greatly diminished amount of perihematomal edema observed in the TICH patient group in our study. Other supportive observations for this conclusion are that neither time from thrombolytic treatment to symptom onset nor time from symptom onset to neuroimaging correlated with perihematomal edema volume within the overall GUSTO-1 intracranial hemorrhage population.

Given that there is no evidence to support either the hypotheses that more prompt imaging of the TICH group explains the greatly diminished perihematomal edema formation in this group, and no evidence to support the hypothesis that some minimum amount of time (≥3 hours) is necessary for perihematomal formation in this group, we next considered whether or not any associations between ICH clinical risk factors or demographic variables and amount of perihematomal edema might explain the observations. In reviewing available data for important demographic or clinical pathogenetic factors, none approached statistical significance when related to perihematomal edema in a univariate analysis, except for race within the SICH group only. Although nonwhite patients had a significantly greater median absolute perihematomal edema volume than white patients in this group, this association was not sustained when relative perihematomal edema amounts were compared. This in essence means that total ICH volumes were smaller in the nonwhite subgroup of this population. Thus, no apparent clinical risk factor or demographic variable adequately explains the differences in perihematomal edema volume observed between the TICH and SICH patients.

Because neither time nor clinical risk factor or demographic variables were associated with the observed differences in perihematomal edema formation between the 2 patient groups, the remaining logical possibility is that the thrombolytic agents and/or heparin themselves were responsible for the observed decreased amount of perihematomal edema formation in the TICH patient group. Regarding this possibility, we should first reiterate that all patients in the TICH group had received aspirin, heparin, and 1 or more thrombolytic agents prior to their ICH onset. However, each of the 4 thrombolytic/anticoagulant treatment regimens used within the TICH group was different. No significant differences in edema frequency and volume were observed between the 268 patients in each of the 4 treatment groups in the overall GUSTO-1 trial, indicating that a unique biological action specific to tPA, streptokinase, or subcutaneous versus IV heparin to explain the lack of edema is unlikely. All of the drugs used within each of the 4 thrombolytic treatment regimens, however, share the common feature of preventing (heparin and aspirin) or actively degrading (streptokinase and tPA via fibrinolysis) blood clotting. The very high frequency of blood-fluid layers observed in the hematomas of the TICH patients strongly supports the notion that blood within these hematomas is indeed largely unclotted.

A number of recent experimental animal model observations closely parallel those seen in our study. Lee et al, in a murine model, confirmed that clotting cascade activation is a necessary prerequisite for hyperacute perihematomal edema formation. Wagner et al, in a porcine lobar ICH model, demonstrated significant hyperacute perihematomal edema development despite an intact blood-brain barrier. Furthermore, the separation of unclotted plasma and red cells, manifest radiologically by blood-fluid layer(s) in our TICH patients, was reproduced experimentally by Xi and colleagues when heparinized blood injected into porcine brain white matter produced an unclotted, RBC-serum layered clot with no perihematomal edema at 4 hours. Such a blood-serum separation has not, to the best of our knowledge, ever been observed and reported in this or any other animal ICH model when normal whole blood was injected.

These experimental observations collectively suggest that in animal models, hyperacute perihematomal edema formation within the time frame observed in our human study results from clotting of intrahematomal blood, which allows remaining serum proteins to diffuse from the clotted RBC-fibrin central hematoma mass into brain parenchyma. This
event may represent the first in a cascade of hematological and biochemical reactions that ultimately mediate significant tissue injury in ICH. Lee and colleagues have furthermore observed that in murine models, thrombin itself may be directly neurotoxic and is uniquely linked to hyperacute perihematomal edema formation. These observations provide a more specific plausible explanation for the biochemical mechanisms through which heparin and/or fibrinolytic agents such as streptokinase and tPA might plausibly inhibit such edema formation.

We hypothesize, therefore, based on both these collective experimental observations and the clinicoradiological observations reported in this study, that clotting of intrahematomal blood is a plausible pathogenetic factor in the formation of hyperacute perihematomal edema in humans. We acknowledge that our evidence to support this hypothesis is indirect. However, ethical considerations in humans preclude the type of systematic, sequential, direct measurement techniques of specific intrahematomal substances or blood-brain barrier permeability in perihematomal brain tissue employed in animal models. Thus, we do not have specific evidence in this or other human studies to differentiate whether prevention of blood clotting in a general sense, or some more specific known or unknown biochemical interaction (such as active degradation of fibrin and/or other serum proteins by the thrombolytic agents) between the thrombolytic agents and/or heparin and adjacent perihematomal brain tissue (or blood vessels) explains the inhibition of hyperacute perihematomal edema formation observed in the TICH patient group in our study.

Therapeutic implications of such hypotheses are significant, and deserve to be investigated both experimentally and, to whatever extent is ethically feasible, clinically. The durable absence of perihematomal edema observed beyond 3 hours in the overall GUSTO-I intracranial hemorrhage population, in particular, suggests the possibility of therapeutic intrahematomal instillation of tPA or other thrombolytic agent to reduce perihematomal edema. In this regard, Wagner et al recently reported that perihematomal edema at 24 hours can be reduced by >70% by early (3.5 hours) tPA-induced clot lysis and aspiration and that tPA also likely lyses interstitial fibrin and removes edemagenic plasma proteins.

In summary, we observe a greatly diminished frequency and amount of hyperacute perihematomal edema formation in thrombolysis-related ICHs as compared with spontaneous ICH. We hypothesize, based on available experimental and clinical evidence, that clotting of intrahematomal blood is a plausible and probable pathogenetic factor associated with hyperacute perihematomal edema formation in humans. More research is needed to elucidate the precise mechanisms of hyperacute edema formation in human ICH and subsequent associated brain injury events. Understanding these events could engender development of novel therapeutic strategies aimed at antagonizing or preventing such events in an illness which, to date, has little proven effective therapy.

Acknowledgments
This study was partially funded by NINDS grant RO1-NS26933-01. We wish to gratefully acknowledge the manuscript preparation assistance of Amy Hess and Kerri Jackson, and the contributions of Kenneth R. Wagner, PhD, in reviewing the scientific content of the manuscript’s discussion.

References
Decreased Perihematomal Edema in Thrombolysis-Related Intracerebral Hemorrhage Compared With Spontaneous Intracerebral Hemorrhage


Stroke. 2000;31:596-600
doi: 10.1161/01.STR.31.3.596

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/31/3/596