Time Course of Early Postadmission Hematoma Expansion in Spontaneous Intracerebral Hemorrhage

Christian Ovesen, BSc; Anders Fogh Christensen, PhD; Derk W. Krieger, MD; Sverre Rosenbaum, PhD; Inger Havsteen, MD; Hanne Christensen, DMSci

Background and Purpose—Early hematoma expansion (EHE) in patients with intracerebral hematoma is a promising treatment target. To date, the time course of EHE has remained poorly described. We prospectively investigated the time course of EHE.

Methods—We included consecutive patients presenting spontaneous intracerebral hematoma within 4.5 hours. On admission, patients underwent noncontrast computed tomography (CT) and CT angiography. Serial hematoma volume estimations by transcranial B-mode ultrasound were effected through the contralateral transtemporal bone window by obtaining sagittal, transversal, and coronal diameter and calculating the ABC/2-formula. National Institute of Health Stroke Scale and transcranial B-mode ultrasound were performed consecutively every 30 minutes during the first 6 hours and from 6 to 12 hours every 2 hours. Follow-up CT and ultrasound were performed after ≈24 hours.

Results—Twenty-five patients with intracerebral hematoma were included; mean (SD) time from onset to CT was 108.6 (45.7) minutes. Ten (40%) patients had EHE. In patients with a final clinically significant hematoma expansion >12.5 mL, all EHE occurred within 6 hours after admission scan. EHE in spot sign positive patients continued during the first 5 hours after CT angiography. In spot sign–negative patients, no significant EHE was observed (Friedman test, P=0.476). Neurological deterioration occurred in 5 (20%) patients and was well temporally correlated with EHE. Transcranial B-mode ultrasound demonstrated good volume estimation compared with the follow-up CT with a maximum absolute volume deviation within 7 mL and minimal systematic error (mean deviation, 1.3 [confidence interval, −0.1 to 2.6] mL).

Conclusions—EHE was reliably reflected by transcranial B-mode ultrasound and mainly occurred within the first 7 to 8 hours after symptom onset.

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Key Words: cerebral hemorrhage ■ ultrasonography, Doppler, transcranial

Clinically significant volume expansion of primary intracerebral hematomas (ICH) occurs in ≤30% to 40% of patients after acute hospital admission.1,2 This early hematoma expansion (EHE) occurs primarily in the first hours after admission3 and has been linked to an increased probability of death and poor outcome.4,5 EHE is a treatment target in experimental interventions with hemostatic agents6 and blood pressure reduction.7,8 Because only patients with active bleeding are likely to benefit from these interventions, methods to identify patients most likely to undergo EHE are needed. In recent years, the computed tomographic angiography (CTA) based spot sign has been shown to be a promising biomarker of patients likely to undergo EHE.9

Besides knowing which patients are most likely to undergo EHE, it is also necessary to know the timing of the EHE occurrence. This period constitutes on one side a clinical unstable phase and on the other the logical treatment window if limitation of final hematoma volume is sought. This knowledge can only be achieved through frequent serial measurements of hematoma volume, which to date have not been feasible because of methodological limitations. Multiple serial CT would imply unacceptable radiation, and MRI would require unlikely collaboration from the patients, and none of these can be performed bedside. However, in recent years, transcranial B-mode ultrasound (TCU) has become available for assessment of hematoma expansion. Compared with CT and MRI, transcranial ultrasound possesses the adequate resolution, mobility, and freedom from ionizing radiation to make it an ideal tool to perform bedside serial volume measurements.10 Establishing the temporal profile of hematoma expansion would be of massive importance to future trials and would improve our understanding of the turbulent acute phase of illness in this patient group.
Consequently, the aim of this study is to describe the temporal profile of EHE in acute spontaneous ICH using serial TCU. We further aim at establishing the role of EHE in acute neurological deterioration.

**Method**

This prospective cohort study was conducted at Copenhagen University Hospital—Bispebjerg, Copenhagen, Denmark, between September 1, 2011, and December 31, 2012. Our institution has a catchment area of patients with acute stroke symptoms of ≈1.7 million inhabitants (The Capitol Region of Denmark), which every other day (even dates) receives possible thrombolysis candidates within 4.5 hours of symptom onset. The number of eligible patients arriving during the inclusion period determined the sample size.

On arrival, standard acute imaging includes CT cerebrum and—in the absence of contraindications—CTA from the aortic arch to the vertebral performed on a 64-slice multidetector CT scanner with an isovoxel resolution of 0.6 mm.

If an ICH is demonstrated, the on-call neurologist and neurosurgeon make a consensus decision, whether acute surgical intervention or conservative treatment strategy is to be planned.

If conservative treatment approach is planned, patients are monitored in the acute stroke unit. Blood pressure during the first 24 hours after admission is controlled using Labetalol (10–20 mg up to a cumulated dose of 200 mg), aiming at systolic blood pressure <160 mmHg. If patients are on vitamin K antagonist (VKA) treatment and have international normalized ratio (INR) >1.4, coagulation factors II, VII, IX, and X (4 factor protrombin complex concentrate) are administered hyperacutely along with vitamin K and continued according to INR estimates. A follow-up CT cerebrum scan is performed ≥24 hours after admission scan.

**Inclusion and Exclusion Criteria**

We included patients with planned conservative treatment, (1) arriving within 4.5 hours after symptom onset, (2) no obvious secondary cause of hemorrhage, and (3) a CT identifiable hematoma focus. Patients were excluded if (1) unidentifiable hematoma through temporal bone window using TCU, (2) referral for hematoma evacuation or shunt placement before 12 hours after project procedure initiation, (3) no informed consent, and (4) nonspontaneous hemorrhage.

**Procedures**

Procedures were initiated as soon as feasible after cerebral CT scan on admission. Guided by this CT scan, the hyper intense hematoma was identified by transcranial ultrasound using B-mode modality. Study procedures are schematically presented in Figure I in the online-only Data Supplement.

A single observer (C.O.) performed acute serial ultrasound measurements of the 3 diameters (sagittal, transversal, and coronal) along with National Institute of Health Stroke Scale (NIHSS) every 30 minutes through the first 6 hours after initiation of the procedures. After the first 6 hours, the same procedure was repeated every second hour for the next 6 hours. Finally, ultrasonographic hematoma estimation and NIHSS were obtained after ≥24 hours after initiation of procedures. Primary end points of the study were death of the patient or completion of the observation period. The single observer (C.O.) was trained before enrollment for 9 months by an experienced transcranial ultrasound expert (S.R.) certified by the Commission for International Certification in Neurosonology and a radiologist with extensive experience in both ultrasound and neuroradiology (A.F.C.).

**CTA Spot Sign**

Spot sign was considered present when the extravasation of contrast was seen with a minimum size of 2 mm. A neuroradiological consultant (A.F.C.) and a senior neuroradiological fellow (I.H.) independently reviewed all images for spot sign status (κ=0.72). Differences were resolved by consensus. Hematoma volume on CT was calculated by means of the validated ABC/2 method.12,13

**Transcranial Ultrasound Imaging**

We used the same General Electric LOGIQ E9 (GE Healthcare, Chalfont St Giles, United Kingdom) ultrasound scanner with a 1.7- to 3.1-MHz sector probe. A standard measurement procedure was performed during all examinations. The hematoma was visualized through the temporal bone window located contralateral to the hematoma. Initially, the superficial temporal region of patient was searched using the ultrasound probe to find the window granting the best intracranial anatomic resolution. The probe was then placed in the axial plane and moved cranially until the maximum transversal diameter of the hematoma was identified. With the transducer fixed in the axial plane, the sagittal and transversal diameter of the hematoma was obtained. The transducer was turned 90 degrees clockwise into the coronal plane to obtain the cranio-caudal extent of the hematoma (coronal diameter). The size of the hematoma was estimated by the ABC/2 formula, and the images were saved and transferred to a Picture Archiving and Communication System workstation. All images were reviewed by a senior consultant neuroradiologist (A.C.), who re-evaluated all ultrasound images concerning image quality and obtained measurements. Differences were resolved by consensus.

**Statistics**

Informed consent was obtained from the patients or from their next of kin. If informed consent was obtained from a proxy, the general practitioner of the patient or the Public Medical Officer coapproved the inclusion soonest possible in accordance with Danish law. The Scientific Ethics Committee of the Capitol Region of Denmark approved this study: H-1-2011-069.

We used κ statistics to evaluate the differences in observations between spot sign observers. A κ value >0.6 was regarded as good agreement. Precision of the ultrasound measurements was analyzed by comparing the last ultrasound measurements with the follow-up CT. We used the measurements agreement method proposed by Bland and Altman to determine the mean (95% confidence interval [CI]) deviation along with the 95% agreement intervals (AIs; ±2SD) for the 3 diameters (sagittal, transversal, and coronal) along with volume. The diameters (sagittal, transversal, and coronal) measured at 12 and 24 hours were compared with control for intraobserver variation using intraclass correlation. To determine the expansion rates (mL/h) throughout the first 12 hours, we subtracted the hematoma volume measured within the relevant hour from the volume measured 1 hour before, thus leaving us with the difference in mL/h. After 6 hours, we enforced the same principle, however, we divided the obtained difference by 2 to reach the expansion rate per hour. We used nonparametric repeated measurements ANOVA (Friedman test) to test if significant different expansion rates existed throughout the first 12 hours. If >1 hour passed from the admission scan to the first ultrasound scan, an even expansion rate within the first hour was assumed. Last, we reconstructed the entire expansion profile for patients with spot sign on admission. P<0.05 was considered significant. Data were analyzed using SPSS version 20 statistical software (IBM Corp, Armonk, NY).

**Results**

Forty-four patients eligible for inclusion arrived during the study period (Figure 1). Two patients were excluded because of lack of temporal bone window. In 3 patients, the hematoma could not be demonstrated, despite adequate bone window: 1 patient with a pontine hemorrhage and 2 patients with small lobar bleeds and a high cranial location.
One patient presented with a primary intraventricular hemorrhage with no identifiable focus. No differences were found between the 25 patients included in the final analysis and the 19 excluded eligible patients in terms of time to admission scan, age, admission volume, admission NIHSS, and VKA treatment (all \( P > 0.25 \)). Study procedures were completed in 22 patients, and 3 patients died during study period. The baseline characteristics for the 25 patients are displayed in the Table. The mean (range) hematoma size on admission CT was 19.4 (0.7–89.4) mL.

### Table. Baseline Values

| Male sex | 18 (72%) |
| Age, y   | 70.4 (13.1) |
| NIHSS   | 15 (8–23.5) |
| Former stroke | 4 (16%) |
| Atrial fibrillation | 5 (20%) |
| Hypertension | 20 (80%) |
| Diabetes mellitus | 3 (12%) |
| Antplatelet use | 5 (20%) |
| VKA treatment | 6 (24%) |
| Volume, mL | 19.4 (20.9) |
| Basal ganglia | 22 (88%) |
| Lobar | 3 (12%) |
| Spot sign* | 10 (40%) |
| IVE on admission scan | 8 (32%) |
| Time: onset to CT, min | 108.6 (45.7) |
| Time: CT to ultrasound, min | 61.1 (26.6) |
| Time: admission to follow-up CT, h | 19.9 (5.73) |

Interval scale data: mean (SD), ordinal scale data: median (IQR), and categorical scale data: frequency (%). CT indicates computed tomography; IQR, interquartile range; IVE, intraventricular extension; NIHSS, National Institute of Health Stroke Scale; and VKA, vitamin K antagonist.

*CT angiography available in 21 patients.

### Agreement

When comparing the 24 hours ultrasound scan and follow-up CT, the mean deviations of the sagittal (0.03 cm; CI: −0.1 to 0.2) and the transversal (~0.09 cm; CI: −0.2 to 0.01) measurement were both close to zero. The coronal mean deviations was slightly greater (0.26 cm; CI: 0.1–0.4; Figure II in the online-only Data Supplement). However, for all 3 diameters, we found no change in precision related to hematoma size. Intraobserver variation between 12 and 24 hours absolute volume was excellent with an intraclass correlation of 0.95 (CI: 0.90–0.98). Only in 1 patient, TCU identified a clinical significant EHE, which did not also meet the 12.5 mL criteria for clinical significant EHE on follow-up CT.

When comparing the absolute volume estimation by the follow-up CT and the 24 hours ultrasound scan (Figure 2A), we saw a good 95% AI (−5.2 to 7.8 mL). We observed a tendency toward a shift in the value of the SD with increasing hematoma size, and therefore calculated the relative deviation (Figure 2B). The 95% AI showed (AI: −25.5% to 27.4%) an obvious visual trend toward lower relative deviation when hematoma volume increased.

### Early Hematoma Expansion

During the study, 10 (40%) patients had hematoma enlargement. Seven of those were in the spot sign–positive group. CTA was available in 21 patients. In the spot sign–positive group, a significant difference existed between the volume of the admission scan and the last ultrasound volume (mean [SD]: 28.5 [28.4] versus 59.4 [43.6] mL; \( P = 0.03 \)) compared with no difference in the spot sign–negative group (mean [SD]: 8.8 [5.9] versus 9.8 [5.6] mL; \( P = 0.108 \)). The time from onset to CTA was comparable between spot sign–positive and spot sign–negative patients (mean [SD): 113.9 [61.5] versus 98.4 [29.2] minutes; \( P = 0.447 \)). When we stratified for patients with a final clinically significant expansion (>12.5 mL), we observed that expansion rates significantly changed throughout the 12 hours (\( P < 0.001 \); Figure 3A) and that an active positive expansion rate occurred during 6 hours after admission scan. When we extrapolated the mean (SD) time from symptoms onset to CT of 108.6 (45.7) minutes, hematoma expansion occurred within 7 to 8 hours after symptom onset. After stratifying for the presence of spot sign (Figure 3B), significantly different expansion rates throughout the first 12 hours (\( P < 0.001 \)) were observed. In this study, EHE occurred within
a period of 5 hours after spot sign demonstration. In the reconstructed expansion profile for patients with spot sign (4 examples in Figure 4 and all in Figure III in the online-only Data Supplement), uneven expansion rates throughout the active expansion period were observed even within the same patient. In the reconstructed expansion profiles demonstrated in the 2 figures, we further plotted the 95% AI (−5.2; 7.8 mL) around all the estimated volumes, showing that although considering the maximum uncertainty observed, the picture with uneven expansion rates within the active expansion period was still visible. In patients without spot sign, we observed insignificantly different expansion rates throughout the first 12 hours (P=0.476; Figure 3C).

Six patients in VKA treatment were included; 2 (33%) patients had an INR >3 (INR: 3.6 and 3.7, respectively). The others were in therapeutic range (INR: 2–3). Three (50%) were spot sign positive. The individual expansion profile of the 3 spot sign–positive patients can be seen in Figure IIIA, IIИH, and IIИJ in the online-only Data Supplement. Of the 3 patients, only patient A (Figure 4A) had an INR above the therapeutic range (INR >3). No obvious distinct expansion profile linked to VKA treatment was observed.

Neurological Deterioration
Neurological deterioration (≥3 NIHSS-point increase) was observed in 5 (50%) patients in the spot sign–positive group and improvement (≥3 NIHSS-point decrease) in 5 (42%) in the spot sign–negative group. When we superimposed the NIHSS score on the individual expansion profiles of the spot sign–positive patients (4 examples in Figure 4 and all in Figure III in the online-only Data Supplement), a good correlation was observed between hematoma expansion and neurological progression even after taking the 95% AI (−5.2 to 7.8 mL) into account. However, NIHSS was a less capable tool in tracking EHE in patients with more devastating brain damage and pending coma (Figure 4A).

Discussion
We found that EHE occurs as an on-going process for ≈7 to 8 hours after symptom onset. We think this finding documents a significant treatment window for therapies aiming at stopping hematoma expansion. The reconstruction of the entire expansion profile of the spot sign–positive patients reveals that the expansion rate is not uniform—not even for the individual patient—and plateau phases with no or minimal expansion exist between phases with active expansion. We also saw that NIHSS responds well to EHE in the acute cause of illness.

We document that transcranial ultrasound is valid in measuring known ICH volume and processes an excellent precision in measuring hematoma volume with a mean deviation close to zero and with acceptable AIs, especially when the absolute volume is considered.

The major strengths of this study include the detailed serial volume measurements, allowing the entire expansion profile to be documented. The good ability of TCU to measure absolute hematoma volume with a limited AI is reassuring because an absolute hematoma expansion is proposed to be more clinically relevant compared with relative hematoma expansion.1 A clinically significant hematoma expansion has been defined as 12.5 mL.1 Our data are in line with Pérez et al10 also demonstrating excellent correlation between ultrasound and CT measurements. The hyperacute fashion, in which the patients were admitted and the study procedures started, allowed us to describe an extensive part of the expansion period. We observed no selection bias in terms of important clinical or radiological differences between patients eligible for inclusion and patients included in final analysis granting our conclusions more generalizability.

The present study has certain limitations including the small number of patients sampled. However, as an observational study with extensive protocolled procedures, we think that we have reached an acceptable sample size. Another limitation is the lack of follow-up CT scans in patients, who succumbed during study procedures because of ethical reasons.
We think that good correlation between 24-hour ultrasound scans and the follow-up CT scans in the remaining population demonstrates the overall validity of our ultrasound volume estimations. Although the ABC/2 formula is a validated and widely used way of measuring hematoma volume, it may induce a higher degree of imprecision compared with computer-assisted volumetric analysis.13 We observed a shift in the precision of TCU hematoma volume measurement relating to size (Figure 2). The largest disagreement between CT and TCU was observed in hematomas with larger volumes. The precision of TCU in obtaining the diameters (sagittal, transversal, and coronal) did not relate to size (Figure II in the online-only Data Supplement). Because of this, we think that some of the uncertainty observed in the volume estimations is an inherent feature in the volume formula (ABC/2). In larger hematomas, just a small measurement error in one of the diameters will affect the estimated volume proportionally more compared with smaller hematomas.

In this study, we encountered a higher frequency of patients on VKA treatment compared with other acute studies.5,7,15,16 All patients treated with VKA included in this study were treated on admission with protrombin complex concentrate according to weight and INR. Although never proven clinically effective in a randomized clinical trial, protrombin complex concentrate’s ability to reverse INR has been demonstrated in observational studies.17 However, VKA treatment is likely to have increased the initial hematoma expansion, and protrombin complex concentrate is likely to have stopped the expansion. Nevertheless, no distinct expansion profile linked to VKA treatment compared with other acute studies.9,15,16 All patients treated with VKA included in this study were treated on admission with protrombin complex concentrate according to weight and INR. Although never proven clinically effective in a randomized clinical trial, protrombin complex concentrate’s ability to reverse INR has been demonstrated in observational studies.17 However, VKA treatment is likely to have increased the initial hematoma expansion, and protrombin complex concentrate is likely to have stopped the expansion. Nevertheless, no distinct expansion profile linked to VKA treatment could be observed.

Brott et al3 introduced EHE as a frequent observation in ICH by documenting its occurrence in 26% of the patients within 1 hour after admission and in additional 12% of patients between 1 hour and 24 hours. Our results support this conclusion. In a large retrospective study, Kazui et al3 stratified patients by onset to scan time and found an increasing tendency toward hematoma expansion when patients arrived earlier. Furthermore, they found that the period, in which patients have hematoma expansion, seemed to be several hours. This finding is supported by our data. However, the precision of Kazui et al3 was limited by the retrospective nature of the study. It is likely that our small sample size made us miss the more rare cases of late hematoma expansion.

In this study, EHE was followed by neurological deterioration in patients with milder baseline deficits. This observation is not surprising because patients with high NIHSS values are likely to have extensive brain damage and thus already massive or even maximal neurological deficits with little room to register further deterioration. The Glasgow Coma Scale might be useful in patients with maximum neurological deficits and possibly pending coma.14 In line with our observations, previous studies have linked hematoma expansion to early neurological deterioration in the acute phase.2,5 EHE and the spot sign are linked to poor functional outcome and mortality.4,9 Using coagulation factor 7, Mayer et al20 reported a reduction in hematoma size but failure to improve outcome.20 The authors proposed that it is necessary to select patients at high risk of hematoma expansion (eg, by means of the CTA spot sign). The attention on the spot sign was underlined in the newly published Predicting Haematoma Growth and Outcome in Intracerebral Haemorrhage Using Contrast Bolus CT (PREDICT) study,9 which documented that the negative predictive value of the spot sign is as high as 80%, however, with a slightly lower positive predictive value of 61%. Other studies support these findings.11,21 Our data support these findings because not all patients with spot sign showed EHE and that the mean expansion rate in patients without the spot sign was close to zero. Compared with this, patients with spot sign showed hematoma expansion as late as 4 to 5 hours after the spot sign was demonstrated. We confirm that the spot sign is useful in selecting patients with on-going bleeding, who might theoretically benefit from hemostatic therapy.

Conclusions

This study shows that hematoma expansion represents an active on-going process even several hours after admission and, therefore, leaving a treatment window for hemostatic therapy. TCU is a valid tool in bedside monitoring of hematoma progression.

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Disclosures

None.

References


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Supplementary figure I:

Illustration showing study procedures. Upon arrival in the stroke ward, patients undergo CT and CTA (A). Patients are monitored using transcranial ultrasound for a total duration of 12 hours (B). Subsequently, patients undergo follow-up CT and last ultrasound (C).
Supplementary figure II:

Bland-Altman diagram showing the precision of the final ultrasound measurement compared to the follow-up CT for the individual dimension. MD: Mean deviation, AI: Agreement interval.
Supplementary figure III:

Individual expansion profile and NIHSS development for patients with spot sign on admission. Time 0 denotes symptom onset, and first volume measurement is admission CT-scan. Individual A, F and J succumbed within 12 hours after admission. VKA: Vitamin K antagonist treatment.
特発性脳内出血における入院後の早期血腫増大の経時的変化

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Christian Ovesen, BSc; Anders Fogh Christensen, PhD; Derk W. Krieger, MD

1 Department of Neurology; 2 Radiology, Copenhagen University Hospital – Bispebjerg, Copenhagen, Denmark; and 3 Department of Neurology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark.

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