CT Evolution of Hematoma and Surrounding Hypodensity in a Cadaveric Model of Intracerebral Hemorrhage

Shahram Majidi, Basit Rahim, Sarwat I. Gilani, Waqas I. Gilani, Malik M. Adil, Adnan I. Qureshi
From the Zeenat Qureshi Stroke Institute, St Cloud, MN (SM, BR, SIG, WIG, MMA, AIQ) and Department of Neurology, the George Washington University, Washington, D.C. (SM).

ABSTRACT

BACKGROUND: The evolution of intracerebral hematoma and perihematoma edema in the ultra-early period on computed tomographic (CT) scans in patients with intracerebral hemorrhage (ICH) is not well understood. We aimed to investigate hematoma and perihematoma changes in “neutral brain” models of ICH.

METHODS: One human and five goat cadaveric heads were used as “neutral brains” to provide physical properties of brain without any biological activity or new bleeding. ICH was induced by slow injection of 4 ml of fresh human blood into the right basal ganglia of the goat brains. Similarly, 20 ml of fresh blood was injected deep into the white matter of the human cadaver head in each hemisphere. Serial CT scans of the heads were obtained immediately after hematoma induction and then 1, 3, and 5 hours afterward. Analyze software (AnalyzeDirect, Overland Park, KS, USA) was used to measure hematoma and perihematoma hypodensity volumes in the baseline and follow-up CT scans.

RESULTS: The initial hematoma volumes of 11.6 ml and 10.5 ml in the right and left hemispheres of the cadaver brains gradually decreased to 6.6 ml and 5.4 ml at 5 hours, showing 43% and 48% retraction of hematoma, respectively. The volume of the perihematoma hypodensity in the right and left hemisphere increased from 2.6 ml and 2.2 ml in the 1-hour follow-up CT scans to 4.9 ml and 4.4 ml in the 5-hour CT scan, respectively. Hematoma retraction was also observed in all five goat brains ICH models with the mean ICH volume decreasing from 1.49 ml at baseline scan to 1.01 ml at the 5-hour follow-up CT scan (29.6% hematoma retraction). Perihematoma hypodensity was visualized in 70% of ICH in goat brains, with an increasing mean hypodensity volume of 0.4 ml in the baseline CT scan to 0.8 ml in the 5-hour follow-up CT scan.

CONCLUSION: Our study demonstrated that substantial hematoma retraction and perihematoma hypodensity occurs in ICH in the absence of any new bleeding or biological activity of surrounding brain. Such observations suggest that active bleeding is underestimated in patients with no or small hematoma expansion and our understanding of perihematoma hypodensity needs to be reconsidered.

Keywords: Intracerebral hemorrhage, perihematoma edema, hematoma retraction, hematoma expansion.

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Correspondence: Address correspondence to Shahram Majidi, MD, Department of Neurology, George Washington University, 900 23rd Street NW, Washington, DC 20037, USA. Tel: 763-496-9283, E-mail: majidis@gwu.edu

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Introduction

A rim of hypodensity around the hematoma can be seen in the computed tomographic (CT) scan obtained within the first few hours after intracerebral hemorrhage (ICH) and it may continue to increase up to 2 weeks after ICH onset.1 The perihematoma hypodensity is thought to be edema secondary to direct mechanical damage, secondary inflammation, and oncotic pressure of the hematoma products.2–4 However, despite being considered a manifestation of tissue injury and reaction, larger magnitudes of perihematoma edema correlate with lower rates of death and disability.5,6 Some authors have postulated that the perihematoma hypodensity is secondary to hematoma retraction and exudation of serum proteins from thrombus.7,8 Hematoma retraction can be seen in ICH patients which is consistent with in vitro thrombus evolution.9,10 However, the magnitude of hematoma retraction and perihematomal hypodensity secondary to retraction and serum exudation is difficult to study in humans and experimental models because of ongoing hematoma expansion due to continuation of hemorrhage from the primary and secondary sites and surrounding tissue reaction.11

In this study, we sought to study the chronological changes in the size of hematoma and perihematoma hypodensity in postmortem ICH models to provide a setting without active hematoma expansion or surrounding tissue reaction.

Methods

The study protocol was reviewed and approved by the Anatomy Bequest Program at the University of Minnesota. One unpreserved human and six goat cadaveric heads were obtained. The human cadaver was approximately 70-year-old man without any known intracranial lesion.
The scalp was removed from the human cadaver head. A small burr hole was made 2 cm lateral to sagittal suture and 2 cm posterior to coronal suture on both sides. A 22 G spinal needle was introduced via the hole into the brain tissue and advanced down to 5 cm deep. The head CT scan was obtained in order to ascertain that the tip of the needle was within the deep brain tissue and not inside the ventricular space. The direction and the depth of the needle could be adjusted if necessary based on CT scan findings. Fresh human blood was obtained from healthy volunteers. A total of 20 cc of fresh whole blood without any anticoagulant was slowly injected into the brain tissue via the spinal needle over 5 minutes on each hemisphere. A baseline non-contrast head CT scan immediately obtained using Philips Scanner Brilliance 256 (Philips Healthcare, Andover, MA, USA) with 2 mm slice thickness. Repeat CT scans were obtained at 1, 3, and 5 hours after hematoma induction.

A similar protocol was followed for the goat heads. The scalp was removed and small burr hole was made 2 cm posterior to the coronal suture separating frontal bones from parietal bone and 1.5 cm lateral to the midline. A 22 G spinal needle was passed via the hole and advanced approximately 3 cm deep into the brain tissue. The head CT scan was obtained to ascertain that the tip of the needle was inside the brain tissue.

For the goat heads; the blood injection was made only into one hemisphere and only 4 cc of whole blood was injected blood due to the smaller brain volume. Following slow injection (over 5 minutes) of fresh blood into deep brain tissue, baseline and follow-up CT scans were obtained immediately after hematoma induction and then at 1, 3, and 5 hours after hematoma induction similar to human cadaver head.

The volumetric measurement of the hematoma and perihematoma edema was done by one of the authors (SM) who was blind to the timing of the CT scans. Analyze 10.0 software (AnalyzeDirect, Inc. Overland Park, KS, USA) was used to measure hematoma and perihematoma hypodensity volumes in the baseline and follow-up CT scans. The pixel thresholding technique was used to select region of interest (ROI) in each slide and then the ROI visually reviewed and its borders manually adjusted to ensure that the whole area of hematoma or perihematoma hypodensity was included. Finally the volume of interest was calculated by automatically sampling all of the selected ROI. The technique has been explained in detail in a previous publication.12

**Results**

In the cadaver head, the baseline hematoma volume was 11.6 ml in the right hemisphere. The hematoma volume gradually decreased in the repeat CT scans and measured as 6.6 ml in the CT scan obtained at 5 hours after hematoma induction, with an estimated 43% reduction in volume (see Figs 1 and 2). There was a slight perihematoma hypodensity in the baseline CT scan with measured volume of 2.03 ml; the volume of hypodensity increased in the repeat CT scans up to 4.6 ml on 5 hours follow-up CT scan (see Fig 3).

Similarly, in the left hemisphere, the baseline hematoma volume was 10.5 ml which decreased to 5.4 ml on the 5 hours follow-up CT scan, with an estimated 48% reduction in volume (see Fig 2). The perihematoma hypodensity volume was 1.6 ml on the baseline CT scan and the volume increased to 4.4 ml on the 5 hours follow-up CT scan (see Fig 3).

There were a total of six goat heads in our experiment. One of the goat heads was removed from the experiment due to the failure in formation of sizeable deep intraparenchymal hematoma on baseline CT scan. Hematoma volume decreased in all five goat brain ICH models on the repeat CT scans (see Figs 4 and 5). The mean ICH volume in the goat brain ICH decreased from 2.02 ml on the baseline CT scan to 1.16 ml on the 5 hour follow-up CT scan. The estimated reduction in hematoma volume was 40% (Fig 4). Perihematoma hypodensity was visualized in three of the goat brain ICH models on baseline CT scan. By 3 hours, perihematoma hypodensity was visible in all the five goat brain ICH models. The mean hypodensity volume was 0.4 ml on the baseline CT scan which increased to 0.8 ml in the 5-hour follow-up CT scan (see Fig 6).

**Discussion**

We found a prominent reduction in hematoma volume (hematoma retraction) which occurred during the first 5 hours after hematoma induction which resulted in up to 48% hematoma volume reduction within the first 5 hours. We also demonstrated that perihematoma hypodensity forms soon after hematoma formation and increases in volume during the first few hours. The changes were observed within the neutral brain, in the absence of cerebral blood flow and perfusion and without any surrounding tissue reaction. Therefore, perihematoma hypodensity seen on the baseline CT scan with increasing volume on follow-up CT scans in cadaveric ICH models contradict the concept of hypodensity being secondary to edema formation. The high magnitude of hematoma retraction seen with one time injection of blood suggests that bleeding must be continuing for...
the hematoma to maintain its baseline volume on follow-up scans in clinical scenarios.

Hematoma retraction has been reported in the previous studies; however, the emphasis in clinical setting is on hematoma growth which can be seen in approximately two third of the patients. In a prospective study of 103 patients with primary ICH, Brott et al demonstrated >33% hematoma growth in 38% of the patients within 24 hours of symptom onset. Of note, 26% of the patients had this significant hematoma expansion between baseline and 1-hour CT scans. Our study demonstrated prominent hematoma retraction within the first 5 hours after hematoma induction which is in contrast to the natural history of ICH in clinical setting. One explanation for this discrepancy could be active bleeding which can obscure the magnitude of clot retraction. Based on our observations, active bleeding is required even for the hematoma to maintain its volume (without any expansion) in clinical settings.

Our finding of occurrence and progression of perihematoma hypodensity in cadaveric ICH models suggests that the hypodense rim surrounding ICH in the first few hours is probably not due to edema and tissue reaction. Perihematoma hypodensity has been generally considered as edema, however its pathophysiology and impact on outcome is not fully understood. Occurrence of cytotoxic edema, mechanical trauma, blood brain barrier disruption and oncotic pressure of hematoma are some of the postulated mechanisms for perihematoma edema. Thrombin mediated inflammatory process has been also shown as possible cause of secondary brain injury and edema formation following ICH. However, there have been observations that suggest that perihematoma hypodensity is independent of surrounding tissue reaction, In a
porcine model of ICH studied by Thiex et al., no correlation was found between the level of inflammation in histopathological analysis and amount of perihematoma hyperintense signal in fluid-attenuated inversion recovery (FLAIR) sequence of MRI. The lack of relationship between volume of hypodensity and clinical outcomes also supports the concept of relatively benign nature of such a radiological finding. In a study of 142 patients with spontaneous ICH, Gebel et al. demonstrated that higher volume of perihematoma hypodensity (adjusted for hematoma volume) resulted in better 3-month functional outcome. Failure of therapeutic studies targeting perihematoma edema in showing any outcome benefits also supports the concept that perihematoma hypodensity in ICH patient may not represent secondary brain injury.
Our study has several limitations which may need to be considered prior to interpretation of our findings. The brains that were used were dead and observations made in such a setting may not exactly correlate with alive brains. The dead brains provided a method to eliminate the role of tissue reaction and study the consequences of whole blood injection within brain parenchyma. The method of whole blood injection into brain parenchyma has been used in previous experimental models and results in histopathological and cranial hemodynamic changes consistent with clinical scenario.26,27 There are differences in biomechanical properties between alive and dead brains and presence of liquefaction and low tissue resistance in dead brains may cause more robust hematoma retraction and perihematoma hypodensity. The relative lack of cerebrospinal fluid and blood within cadaveric skulls may result in greater compliance within the cranial compartment. By using each brain ICH specimen as its own control, we reduced the variation between specimens. We did not perform histological assessment of the perihematoma tissue in our study because reactive changes in the perihematoma region of non-viable brain were not anticipated. The histopathological characteristics of the perihematoma hypodensity seen in the CT scans and erythrocyte morphology and aggregation within the hematoma were not ascertained. Consequently, we would like to emphasize that our findings provide preliminary data regarding chronological changes in hematoma and perihematoma size using a cadaveric model of ICH, such work serves as basis for further studies to better understand the pathophysiology of these findings.

Conclusion
Our study demonstrated that substantial hematoma retraction and perihematoma hypodensity can occur in intracerebral hematomas in the absence of new bleeding or biological activity of surrounding brain. Such observations suggest that active bleeding is underestimated in patients with unchanged hematoma volume on serial CT scans. It also warrants more research to better understand the pathophysiology of perihematoma hypodensity.

References