Transient Focal Increase in Perihematomal Glucose Metabolism After Acute Human Intracerebral Hemorrhage

Allyson R. Zazulia, MD; Tom O. Videen, PhD; William J. Powers, MD

Background and Purpose—Progressive perihematomal cell death over 3 to 4 days has been described after experimental intracerebral hemorrhage (ICH). We investigated whether progressive perihematomal damage occurs in human subjects by measuring relative changes in regional cerebral glucose metabolism with \(^{18}\)F-fluorodeoxyglucose (FDG) positron emission tomography at multiple time points during the first week after ICH.

Methods—Thirteen subjects with a median hematoma volume of 22 cm\(^3\) were studied 1.0 to 1.8 days after ICH. Normalized mean counts in 5 concentric annular 2-mm-thick perihematomal volumes-of-interest (VOIs) were compared to the initial study. Next, automated searches with 0.5 to 5.0 mL spherical VOIs identified maximum focal changes in normalized counts compared to the initial study.

Results—No annular or focal decrease in perihematomal FDG uptake developed. Instead, FDG uptake significantly increased at session #2 in the first 3 2-mm annular VOIs (9.2% ± 14.2, 7.8% ± 11.3, 5.9% ± 9.0), returning to baseline at session #3. The VOI search identified focal regions of increased perihematomal FDG uptake relative to the contralateral control hemispheres in 6 subjects, which accounted for the annular increase.

Conclusion—Perihematomal glucose metabolism increased transiently in a subset of patients 2 to 4 days after acute ICH. These transient focal increases in glucose metabolism occurring in the brain after acute ICH demonstrate that there are ongoing processes in response to injury that last for days. Although further studies are needed to elucidate their pathophysiology, these processes may be indicative of a prolonged window for intervention to improve neurological outcome.

Key Words: intracerebral hemorrhage • glucose metabolism • fluorodeoxyglucose • positron emission tomography

The primary mechanism of brain injury attributable to intracerebral hemorrhage (ICH) is traumatic when a sudden jet of blood at high pressure disrupts and displaces brain tissue. Experimental data indicate that progressive cell death may occur over 3 to 4 days in the area immediately surrounding the hematoma. In humans, the pathophysiological changes that occur in the hours to days after ICH have been poorly studied, and the importance of secondary brain damage remains controversial. We undertook this study to investigate whether progressive perihematomal cerebral damage occurs in the first week after ICH by measuring relative changes in regional cerebral glucose metabolism (CMRglc) with \(^{18}\)F-fluorodeoxyglucose (FDG) positron emission tomography (PET). FDG is only trapped by living cells. Initially, the area of reduced FDG uptake surrounding the hematoma is a combination of the partial volume effect caused by the hematoma itself and any perihematomal cells that have died. In the absence of hematoma enlargement, progressive perihematomal cell death would be reflected by a progressive increase in the area of reduced CMRglc surrounding the hematoma over this period of time.

Materials and Methods

Subjects

Patients were eligible for inclusion in the study if they suffered a spontaneous, nontraumatic ICH that was evident on computed tomographic (CT) scan, were at least 18 years of age, and could be studied within 48 hours of symptom onset. (Onset was defined as the time the patient was last known to be normal if symptoms were first noticed on waking from sleep or if no accurate history could be obtained.) Patients were excluded if pregnant; if the hemorrhage was thought to be associated with a vascular malformation, aneurysm, or tumor; or if there were plans for immediate surgery. Informed consent was obtained from subjects or their legally authorized representative. The study was approved by the Human Research Protection Office and the Radioactive Drug Research Committee of Washington University.

NIH Stroke Scale (NIHSS) was performed on admission and daily throughout the study period. Physiological data (temperature, blood pressure, and heart rate) were recorded at the time of each PET study. Plasma glucose values were measured within 3 hours before FDG injection. No subject had monitoring of intracranial pressure.

Imaging

Subjects underwent PET and CT scanning of the head at 3 time points after ICH onset: within 48 hours, at 2 to 5 days, and at 5 to 8
days. All subjects were studied using a Siemens/CTI ECAT Exact HR 47 PET scanner (Siemens) located in the Neurology-Neurosurgery Intensive Care Unit (NNICU). The scanner collects 47 simultaneous slices at 3.12-mm intervals comprising an axial field of view of 15 cm. Subjects were placed supine in the PET scanner using a thermoplastic face mask or tape to minimize movement. A physician or NNICU-trained research nurse was present in the scanner room throughout all PET studies.

Transmission scans were acquired using 68Ge,68Ga rotating rod sources. A 10-minute transmission scan acquired before radiotracer injection at 1 of the 3 scan sessions was used to calculate the attenuation correction for all emission scans. A 2-minute transmission scan, performed either immediately before or after each emission scan, was used to coregister images from each study session to the 10-minute transmission scan.

For the emission scans, subjects received a slow intravenous injection of 10 mCi FDG in a peripheral vein and were instructed to rest with their eyes closed until scanning was completed. Lights were kept dim, and noise was kept to a minimum. Fentanyl was used for sedation within 30 minutes of FDG injection in 2 subjects. One received the same dose at approximately the same time after injection on each of the studies. The other received 50 mg on the first study only. Emission data were acquired in 3-dimensional mode for 20 to 30 minutes in 2-frame minutes beginning 30 minutes after FDG injection. Individual frames were aligned to each other to correct for movement between frames using Automated Image Registration software (AIR, Roger Woods, University of California, Los Angeles).5 For each subject, the 10-minute transmission image was coregistered to each individual frame from each of the 3 study sessions and then forward projected to generate a common attenuation correction for each emission frame for all 3 study sessions. Each frame of the emission data was then reconstructed a second time using this common attenuation correction. Finally, single composite images for each of the 3 study sessions were created by summing all coregistered frames during which no significant movement occurred. Emission scans were reconstructed with filtered back projection using measured attenuation and scatter correction with a ramp filter to generate images with 3D resolution of 4.4 mm FWHM.

High-resolution CT images (0.435×0.435×3.0 mm pixels, 120 kV, 170 mAs) were acquired using a Siemens Somatom Plus 4 or Siemens Somatom Plus S CT scanner (Siemens) within 6 hours of each PET scan. CT images were coregistered to one other and to the PET images using AIR.5

Image Analysis
CT images for each subject were examined for changes in hematoma size by comparing the coregistered images and evaluating subtractions images created from them. Hematomas were segmented in the original high-resolution images to measure volume and were then resliced to match the plane of the PET images for FDG volume-of-interest (VOI) analysis. The 3 composite FDG images for each subject were normalized to each other using the whole-brain counts from the first image.

Two image analysis strategies were applied to these coregistered images of normalized PET counts: (1) For each slice containing hematoma, annular VOIs were created by 2-dimensional dilation around the hematoma on study image 1 to yield 5 2-mm-thick concentric rings spanning the 1-cm volume adjacent to the hematoma (excluding CSF spaces). Mean normalized counts in these VOIs from study images 2 and 3 were compared to study image 1 by paired t tests.2 The second analysis used difference images for each subject, subtracting the study 1 image from the study 2 image and the study 1 image from the study 3 image. An automated search with nonoverlapping spherical VOIs of different sizes (0.5, 1.0, 2.0, 3.0, 4.0, and 5.0 mL) was then used to identify in each hemisphere in each difference image the regions of each different size with the highest and lowest values. These correspond to the regions with the greatest increases and decreases in FDG uptake compared to the baseline study image 1. Data from the 13 contralateral hemispheres were used to determine how much variation could be expected because of statistical, biological, and methodological factors independent of the hematoma. For each study session and each sphere size, the mean and standard deviation (SD) of the absolute values of highest and lowest values from the contralateral hemisphere of all subjects were computed. Any change in the hemisphere ipsilateral to the hematoma that was greater than 3 SD above the contralateral mean of these maximum absolute values was considered to be statistically significant.

Because this study was not designed with the intent of measuring quantitative CMRglc, no arterial samples for radiotracer measurement were collected. However, to determine whether the focal increases in FDG uptake we found unexpectedly in half the subjects were explicable by uniform reductions in CMRglc in the rest of the brain, we used the method of Tsuchida et al6 to estimate whole brain CMRglc (excluding the hematoma and 1 cm perihematomal region) in these subjects. This method uses a population-based standardized input function calibrated with injected FDG dose, body weight, and plasma glucose level. We used a value for the lumped constant of 0.81.7

Results
Sixteen subjects with acute ICH were studied as part of this protocol between March 2005 and October 2006. Three were excluded from this report because PET data collected at the first or second study session were not analyzable because of excessive subject movement (n=2) or death before the second study session (n=1). Among the remaining 13 subjects, 12 completed all 3 PET scans and 1 completed the first 2 only.

The 13 subjects were studied with PET 1.0±0.3, 2.9±0.8, and 6.7±1.6 days after symptom onset. Age ranged from 43 to 90 years. Six (46%) were female. Twelve (92%) had hypertension, and 1 (8%) was taking warfarin. Hematomas were putamenal (38%), thalamic (46%), or lobar (15%).

Increased to 22.5 cc at the time of the first study; however, there was no increase in hematoma size between any of the 3 study CTs. Subjects 7 and 10 received 80 mg/kg factor VII concentrate 3 hours after symptom onset as part of the FAST (Recombinant Factor VIIa in Acute Haemorrhagic Stroke Treatment) trial. Plasma glucose levels within 3 hours of FDG injection ranged from 88 to 224 mg/dL. The largest change in plasma glucose across scans for any individual subject was 38 mg/dL. Mean arterial pressure remained stable across the 3 studies. No subject had a fever at the time of any scan.

No decrease in mean FDG uptake was observed in any of the sequential 2-mm rings in the 1 cm surrounding the hematoma between the first and second or the first and third study sessions. Instead, there was a significant increase in FDG uptake in the 2-mm rings out to 6 mm from the hematoma at the second study session (P<0.05 by paired t test) that returned to baseline at the third session (Table 1).

The spherical VOI search did not reveal any ipsilateral foci of significantly reduced FDG uptake in the second or third study session compared to the first regardless of sphere size. However, the search did reveal focal areas of increased FDG uptake in the second or third study session compared to the first in 6 of 13 subjects (Figure). Data for the 1 mL spherical search are provided in Table 2, but the same regions were identified regardless of which size sphere (0.5 to 5.0 mL) was used for the search. In each case, the center of the region of focally increased FDG uptake was within 12 mm of the hematoma.
edge. As shown in the figure, the regions included predominantly lobar gray and white matter, though subcortical tissue was involved in at least 2 subjects. Further analysis demonstrated that these regions accounted for the increased FDG uptake in the perihematomal rings discussed above. In the 6 subjects with relative focal increase in perihematomal FDG uptake, the mean uptake in a 6-mm annular VOI significantly increased at the second study by 15.5/11006 10.7% (*P*<0.01), whereas in the 7 without focal increase there was no significant change in the annular VOIs (0.5/11006 5.0%, *P*<0.96).

Subjects with focally increased ipsilateral FDG uptake had significantly larger hematoma volumes (*P*<0.02 by unpaired *t* test) and were less likely to have thalamic ICH location (*χ*² [2 df]=9.78; *P*<0.008) than those without. Timing of the first and second study sessions was similar in those with (23.8±2.6 and 67.3±20.5 hours after ICH onset) and without (23.6±9.3 and 71.8±16.9 hours after ICH onset) increased FDG uptake (*P*=0.67 by unpaired *t* test). Five of the 6 subjects with increased FDG uptake had a third PET scan, which in each case demonstrated the regions of increased uptake to be resolving or at baseline.

Analysis of CMRglc using a standardized input function in the 6 subjects with focal increases revealed that whole brain CMRglc did not significantly change from study 1 to study 2 (7.9±2.8 to 8.9±3.3 μmol/100 g/min).

Median NIHSS at the time of study 1 was 16 (range 2 to 31) and remained stable or improved in all but 3 subjects (subject 7, 8, and 11) in whom there was a step-wise increase (18→24→31; 20→24→29; 19→25→37) across the 3 studies. These were the only subjects with at least a 4-point change in NIHSS between the first and second study sessions. There was no correlation between change in NIHSS and change in FDG uptake in a 6-mm annular perihematomal VOI between either the first and second (*r*=0.19, *P*=0.54) or

<table>
<thead>
<tr>
<th>Distance From Hematoma (mm)</th>
<th>PET2-PET1</th>
<th>PET3-PET1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>9.2%*</td>
<td>0.8%</td>
</tr>
<tr>
<td>2–4</td>
<td>7.8%*</td>
<td>0.0%</td>
</tr>
<tr>
<td>4–6</td>
<td>5.9%*</td>
<td>−0.8%</td>
</tr>
<tr>
<td>6–8</td>
<td>3.5%</td>
<td>−1.5%</td>
</tr>
<tr>
<td>8–10</td>
<td>1.4%</td>
<td>−2.0%</td>
</tr>
</tbody>
</table>

*P*<0.05 by paired *t* test.

**Figure.** Coregistered CT and FDG PET images normalized to mean activity in PET 1 from the 6 subjects with a relative increase in perihematomal FDG uptake. PET 1, PET 2, and PET 3 were completed at 23.8±2.6, 67.3±20.5, and 128.0±26.2 hours. PET 2-PET 1 represents the subtraction image of these 2 PET studies superimposed on the CT and demonstrates the region of increased FDG uptake identified by spherical VOI search. For better visualization, the PET images have been filtered to a lower resolution (10 mm FWHM) than was used in the VOI analysis. The color scale is relative, with blue representing the lowest values and red the highest.
first and third study sessions ($r=0.40, P=0.19$). All subjects were continually observed during the period after FDG injection until scan completion. No clinical seizure activity was witnessed at this or any other time during hospitalization. Subject 7 was noted to be less arousable 44 hours after onset of left putaminal ICH (18 hours after first PET). Electroencephalogram (EEG) showed left temporal sharp waves, left hemispheric slowing, and moderate generalized slowing. After the second PET, she was started on phenytoin. Continuous EEG the following day showed only slowing. Mental status progressively deteriorated, and support was withdrawn 11 days after ICH onset. She died 1 week later.

Follow-up MRI was obtained 4 months after ICH in 1 of the subjects with focally increased FDG uptake and showed only the resolving hematoma. No abnormality was detected across several planes in the focal area of increased FDG uptake. Among the 6 subjects with focally increased FDG uptake, 3 were discharged to a rehabilitation hospital, 1 was discharged to an extended care facility, and 2 had care withdrawn and died. Among the 7 subjects without focally increased FDG uptake, 3 were discharged to a rehabilitation hospital, 1 was withdrawn, and died. Among the 6 subjects with focally increased FDG uptake, 6 were discharged to a rehabilitation hospital and 1 to an extended care facility.

**Discussion**

We did not find progressive worsening of relative cerebral glucose metabolism over the first week after ICH. Instead, we found a transient focal increase in perihematomal FDG uptake 2 to 4 days after ICH in 6 of 13 subjects. These localized increases in uptake were striking on visual inspection of the difference images and were confirmed by statistical comparison to the contralateral hemispheres. Hematomas in those subjects with focally increased FDG uptake were larger and were located next to or in cortex. There was no clear clinical correlate to the increase in uptake, although one subject with progressive neurological deterioration had sharp waves on EEG just before the second PET. It was not possible to determine with certainty whether these transient focal increases were associated with worse clinical outcome attributable to the limited outcome data and the association with larger hematoma volume, itself a predictor of poor outcome.

Our results should be considered in the context of several limitations, each of which will be addressed below. First, we used FDG uptake normalized to whole brain counts as a measure of regional cerebral glucose metabolism. FDG is transported across the blood–brain barrier and into brain cells where it is metabolized by hexokinase into FDG-6 phosphate. No further metabolism occurs. Therefore, the rate of FDG uptake into cells can be used as a measure of overall CMRglc but does not provide information about the subsequent metabolic fate of the glucose carbon atoms. In any single scan, the relationship between regional FDG uptake (counts) and regional cerebral glucose metabolism is approximately linear. Effects attributable to variation in the rate constants are small when image acquisition is delayed by 30 to 40 minutes.

Second, our measurements were nonquantitative. It is possible (though pathophysiologically improbable) that the relative increase in perihematomal FDG uptake we observed 2 to 4 days after ICH represents an artifact of a generalized decrease in metabolism that spared the perihematomal area rather than a true local perihematomal increase. Estimates of whole brain glucose metabolism using Tsuchida method support the latter explanation, however. Sequential quantita-
tive FDG studies, although technically challenging to perform, are needed to confirm our interpretation.

Third, determination of a change in cerebral glucose metabolism was made relative to the initial scan, which was performed on average 24 hours after ICH onset. We cannot exclude the possibility that we missed a decrease in FDG uptake occurring within the first 24 hours and that the relative increase in perihematomal FDG uptake at 2 to 4 days represents a recovery from hyperacute hypometabolism; however, this scenario would require that a second delayed process be invoked to explain the subsequent fall in FDG uptake seen at 1 week.

Fourth, we explicitly assumed that the lumped constant value (ratio of the net extraction of FDG and glucose) did not change regionally or temporally. In adults, the lumped constant has been shown to change appreciably only in tumors or under conditions in which glucose delivery becomes rate limiting for glucose metabolism, eg, during ischemia and hypoglycemia.12–14 We have previously shown that perihematomal ischemia is not present after acute ICH.15 None of the subjects experienced hypoglycemia over the study period. One subject required fentanyl for sedation during the time of the initial study was performed on average 24 hours after ICH onset. We cannot exclude the possibility that we missed a decrease in FDG uptake occurring within the first 24 hours. Recent studies in traumatic brain injury (TBI) have demonstrated regional hyperglycolysis primarily at the edge of focal lesions17,18 and suggest metabolic stress as a possible cause of progressive neuronal injury. Hyperglycolysis in animal models occurs immediately after injury and then resolves, whereas in humans it has been reported up to several weeks after injury.19 Our finding of perilesional increased FDG uptake 2 to 4 days after ICH is remarkably similar to that reported in human TBI. Bergsneider et al17 observed focal hyperglycolysis adjacent to focal mass lesions in 5 of 28 patients studied 3 to 14 days after injury. Three had EEGs on the day of PET, including 1 showing nonconvulsive focal status epilepticus corresponding to the site of increased FDG uptake adjacent to a traumatic ICH and another showing bilateral seizure activity not corresponding to the site of FDG uptake.

Physiopathological explanations for the transient focal increase in perihematomal FDG uptake we found in nearly half our subjects are speculative.

Both activated macrophages and activated neutrophils take up FDG.20 Increases in microglia/macrophages begin 3 to 5 days after ICH but persist to at least 14 days.21 Thus, the time course is wrong for the changes that we observed. Perihematomal neutrophil infiltration peaks at 2 to 3 days after experimental ICH,4 but data on the time course and extent of neutrophil infiltration from human postmortem studies are mixed.21,22 Therefore, although activation of macrophages is unlikely to account for the transient perihematomal increase in FDG uptake, the role of neutrophil infiltration is uncertain.

Cerebral microdialysis in humans and in experimental models of ICH has demonstrated increased extracellular glutamate.23,24 Blockade of posttraumatic and post-ICH hyperglycolysis in animal models by glutamate receptor antagonists is consistent with glutamate-mediated hyperglycolysis.25,26 However, the time course of the increase in glutamate after ICH (peaking within hours) does not correspond well to the transient increase in FDG uptake we observed.

Increased FDG may be seen when seizures occur within 5 minutes of radiotracer injection.27 Although none of our subjects had clinically evident seizure activity, the finding in one of the left temporal sharp waves on EEG 2 hours before her second PET scan raises the possibility of nonconvulsive seizure activity as a mechanism of the focally increased FDG uptake. The cortical localization of the increased uptake in 5 of the 6 subjects would be consistent as well. Nonconvulsive seizures may occur in more than one-quarter of patients with acute cortical or subcortical ICH.28,29 Because glutamate receptor antagonists have anticonvulsant properties, an epileptic etiology would be consistent with animal data showing suppression of hyperglycolysis by glutamate receptor antagonists.30 EEG data were available for only 1 of our subjects, though, so we cannot determine whether the presence of increased FDG uptake correlated with epileptiform activity.

These transient focal increases in cerebral glucose metabolism after acute ICH demonstrate that there are ongoing processes in response to injury that last for days. Although further studies are needed to elucidate their pathophysiology and clinical significance, these processes may be indicative of a prolonged window for intervention to improve neurological outcome.

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Disclosures

None.
References


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