Perilesional Blood Flow and Edema Formation in Acute Intracerebral Hemorrhage
A SPECT Study

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Background and Purpose—Secondary brain injury and edema formation contribute significantly to morbidity and mortality after intracerebral hemorrhage (ICH). The pathogenesis of this process is poorly understood. We sought to characterize alterations in perilesional blood flow that occur during the acute phase of ICH and to determine whether progressive enlargement of edema surrounding ICH is related to increased or decreased perfusion.

Methods—We performed paired consecutive CT and 99m Tc-hexamethylpropylenamine oxime single-photon emission computed tomography (SPECT) scans during the acute (mean, 18 hours) and subacute (mean, 72 hours) phase of ICH in 23 patients. Hematoma and edema volumes were traced and calculated from CT images. SPECT-derived hypothetical flow deficit volumes (FDV) around each hematoma were calculated by measuring a “zero-flow” volume within a large perilesional region of interest (based on percent tracer count loss compared with the contralateral side) and subtracting the corresponding ICH volume. Patients with significant midline shift (>5 mm) or global blood flow reduction were excluded from the analysis.

Results—ICH volume (18 mL) did not change, mean edema volume increased by 36% (from 19 to 25 mL, P < 0.0001), and mean FDV decreased by 55% (from 14 to 6 mL, P = 0.0004) between the acute and subacute phases. Edema volume on the second CT scan correlated positively with FDV on the first SPECT scan (Spearman’s ρ = 0.48, P = 0.02), and with the volume of reperfused perilesional tissue (FDV_acute – FDV_subacute) (Spearman’s ρ = 0.41, P = 0.05). Perilesional edema on CT always corresponded topographically with perfusion deficits on SPECT. In 4 patients, delayed focal hyperemia was identified in more peripheral cortical regions, but these areas appeared normal on CT.

Conclusions—Perilesional blood flow normalizes from initially depressed levels as edema forms during the first 72 hours after ICH, and the eventual extent of edema correlates with the volume of reperfused tissue. These results suggest that the potential for perilesional ischemia is highest in the earliest hours after ICH onset and implicate reperfusion injury in the pathogenesis of perihematoma edema formation. (Stroke. 1998;29:1791-1798.)

Key Words: brain edema ■ cerebral blood flow ■ intracerebral hemorrhage ■ tomography, emission computed ■ tomography, x-ray computed

Intracerebral hemorrhage (ICH) affects approximately 65,000 individuals per year in the United States, and is widely considered the deadliest form of stroke.1 ICH victims experience higher mortality and suffer more severe deficits than any other stroke subtype.2 In contrast to advances in the acute management of subarachnoid hemorrhage and ischemic stroke, no specific therapies have been shown to improve outcome after ICH: treatment is generally supportive, and outcomes remain poor. Specifically, randomized trials of surgical evacuation3,4 and therapies aimed at reducing intracranial pressure5–6 have failed to show benefit in treating ICH.

In recent years, attention has shifted to perilesional brain injury as a potential target for therapeutic intervention in ICH patients. Pathological and experimental studies indicate that a “penumbra” of progressive tissue damage and edema develops in regions immediately surrounding a hematoma7–12 Mechanical injury caused by elevated local tissue pressures, reduction of cerebral blood flow (CBF),13–17 infiltration of plasma,18 and inflammation related to clotting proteins19 and protease induction20 have all been implicated as mediators of this form of secondary injury. Clinical neurological deterioration, which occurs in one third of ICH patients,21 may occur as a direct consequence of this process, or may result indirectly from hyperacute bleeding into the perilesional region or herniation related to brain swelling.

Improved understanding of the pathophysiology of perilesional brain injury after ICH may result in improved treatment strategies. Although perihematoma hypoperfusion in
humans has been demonstrated by both single-photon emission computed tomography (SPECT)\textsuperscript{22,23} and positron emission tomography\textsuperscript{24} during the subacute and chronic phases of ICH, alterations of perilesional blood flow during the acute phase (<24 hours), when ischemia and neurological deterioration are most likely to occur, remain poorly understood. Specifically, the extent to which ICH-related edema is cytotoxic, resulting from circulatory insufficiency due to elevated tissue pressures, or vasogenic and hyperemic in nature, is unknown. Although a short-lived reduction of perilesional CBF to ischemic levels occurs within minutes to hours of hematoma injection in animals,\textsuperscript{7,14,17} cortical hyperemia during the subacute phase of ICH has been documented in both experimental\textsuperscript{17} and clinical studies.\textsuperscript{25,26} We conducted this study to further clarify the relationship between perilesional perfusion and edema formation after ICH.

**Subjects and Methods**

**Study Population**

Seventy-two patients with CT-documented ICH admitted to the Columbia-Presbyterian Neurological Intensive Care Unit between February 1993 and April 1996 were assessed for entry into the study. Eligibility was based on (1) supratentorial ICH and (2) hospital admission within 24 hours of onset. If symptoms were present on awakening, onset was judged to have occurred after the patient went to sleep. Exclusion criteria included (1) deep coma (Glasgow Coma Scale score of ≤5); (2) emergency surgical hematoma evacuation; (3) history of cerebral infarction or severe (>70%) carotid stenosis; (4) hemorrhage related to tumor, trauma, coagulopathy, or arteriovenous malformation; (5) pregnancy; (6) age <20 years; and (7) accurate time of ICH onset not available. On the basis of these criteria, 36 of 49 potentially eligible patients were enrolled in the study. The most common reasons for failure to enroll were unavailability of SPECT within the desired time frame because of scheduling or technical problems and lack of informed consent. The study protocol was approved by the hospital institutional review board, and in all cases informed consent was obtained from the patient or a surrogate.

Of the 36 subjects who underwent SPECT scanning, inclusion in the current analysis was limited to enrolled patients with 2 pairs of high quality SPECT and CT examinations, without significant midline shift (>5 mm) or moderate-to-severe global blood flow reduction related to intraventricular hemorrhage on the admission CT. Five patients were excluded because of damage to or loss of archived SPECT data, 4 because of significant midline shift, 2 because of severe intraventricular hemorrhage (IVH)–related global blood flow reduction, and 2 because of failure to obtain a second SPECT scan, leaving 23 patients for inclusion in the present analysis.

Demographic information, past medical history, blood pressure (BP), and medications received were recorded on admission and on the day of each SPECT scan. Patients were evaluated clinically on hospital days 1, 2, 3, 7, 14, and 30 (or at discharge) using the Glasgow Coma Scale\textsuperscript{37} and National Institutes of Health Stroke Scale.\textsuperscript{24} Functional outcome at 30 days or at discharge was assessed using the Glasgow Outcome Scale.\textsuperscript{39}

All patients received standard supportive therapy during the study period: 15 received treatment for elevated BP, 11 were intubated for airway protection, 9 received phenytoin, 6 briefly (<48 hours) received dexamethasone, 3 had a ventricular drain placed, and 2 received mannitol. BP was monitored with an arterial catheter, and labetolol, nicardipine, nifedipine, or enalaprilat was used to maintain mean BP <120 mm Hg during the first 72 hours after onset.

**Imaging Protocol and Acquisition**

The study protocol called for CT and 99mTc-hexamethylpropyleneamine oxime (HMPAO) single-photon emission computed tomography (SPECT) scans to be performed in rapid succession during the acute (<24 hours) and subacute (48 to 72 hours) phases of ICH. In most cases, the initial CT scan was obtained in the emergency department, and the first SPECT scan was obtained as soon as the patient had been stabilized in the neuro-ICU. In some cases, a follow-up CT scan was obtained immediately after the first SPECT to minimize the time interval between the 2 studies. Because SPECT imaging was not available on evenings, weekends, and holidays, protocol violations were allowed, as long as the initial SPECT was performed within 36 hours of ICH onset, and the second SPECT scan was performed 24 to 120 hours after the first study.

CT imaging was performed on a GE 9800 scanner with 5-mm slices oriented parallel to the orbitomeatal line. SPECT imaging was performed using a Picker Prism 3000 3-headed rotating camera equipped with an ultra-high-resolution fan beam collimator (7 to 9 mm full width at half maximum), with image data processed by an Odyssey 750 supergraphics computer (Picker International). The SPECT images were acquired 1 to 2 hours after intravenous injection of 20 to 25 mCi of 99mTc-HMPAO with the patient at quiet rest in the ICU.

**SPECT and CT Image Analysis**

ICH, ICH plus edema, and IVH volumes, expressed in milliliters, were calculated from CT scans by planimetry. Lesion areas on each slice were calculated separately by an investigator blinded to the results of the SPECT imaging, by tracing the perimeter of the appropriate high- or low-attenuation zone on the CT console; these values were then multiplied by slice thickness to yield single plane lesion volumes, which were summed to yield total lesion volume. Perihematoma edema volumes were calculated by subtracting ICH volume from ICH plus edema volume.

Axial SPECT slices of approximately 10-mm thickness were analyzed by a blinded examiner using Alice imaging software (Hayden Image Processing Group, Boulder, CO) on an Apple computer (Cupertino, CA) with a high resolution monitor. A focal theoretical volume of brain tissue with “zero flow” in the region of each hematoma was calculated according to the method described by Mountz.\textsuperscript{30} With the use of magnified views, a wide region of interest (ROI) surrounding the area of reduced tracer uptake was drawn within the ipsilateral hemisphere on each involved axial slice, and on 1 slice above and below the involved area. A standard ROI was generated from the slice containing the largest area of diminished tracer uptake, but was redrawn on individual slices to avoid areas of no perfusion corresponding to the ventricular or subarachnoid spaces if necessary. No particular effort was made to exclude regions of relative or absolute hyperemia from the ROIs. Mirror ROIs in the contralateral hemisphere were created for each slice by direct translation of the region coordinates across the longitudinal axis. In some cases, contralateral ROIs were repositioned slightly to avoid the ventricular or subarachnoid spaces.

Perilesional “zero-flow” volumes, expressed in milliliters, were calculated by multiplying the ROI volume (identical on both sides) by the percent reduction of tracer counts in the ipsilateral ROI compared with the contralateral ROI, according to the following equation:

\[
V_i = V_p \times \sum_{i=1}^{n} \left| M_i - S/M_i \right| \times P_i
\]

where \(V_p\) is the total volume (mL) of the lesion, \(V_i\) is the volume (mL) of the individual pixel, \(S\) represents the single photon emission counts within the ipsilateral ROI, \(M\) represents the single photon emission counts within the mirrored ROI in the uninvolved hemisphere, and \(P\) is the number of pixels in the ROI. The sum of \(i\) was taken over all scan planes containing an ROI. SPECT-derived flow deficit volumes (FDVs), equivalent to a hypothetical volume of perilesional brain tissue with zero perfusion, were calculated by subtracting CT-derived ICH volumes from the SPECT-derived zero-flow volume. With reference to corresponding CT images, all SPECT scans were also evaluated by 2 blinded radiologists for the...
presence of diaschisis or hyperperfusion, defined as a ≥20% variance in tracer counts compared with adjacent ipsilateral or mirror contralateral regions.

Validation of SPECT Analysis
The main advantage of the Mountz method for assessing perilesional blood flow after ICH is that it does not require coregistration of SPECT and CT images. Theoretically, the SPECT-derived zero-flow volume should always equal or exceed the ICH volume (as long as hyperemia is not present), and the calculated FDV should be independent of the ROI shape or size, as long as the entire area of flow deficit is encompassed. The main disadvantage of this technique, besides the fact that it provides only a relative index of perfusion rather than direct measurement of CBF, is that its accuracy and validity depends on 2 assumptions that can be approximated but not completely guaranteed: (1) the disease process should not affect perfusion in the contralateral hemisphere and (2) the disease process should not produce anatomic distortion that varies the volume of brain tissue contained in the ipsilateral versus contralateral ROI. In addition, the accuracy of the technique is limited by error introduced by Compton scatter and partial volume effects. This phenomenon is more likely to be of significance in smaller than in larger lesions.

To address these issues, we excluded patients with significant midline shift or mild-to-severe global reduction of cerebral perfusion related to IVH. We also tested the validity of our technique for estimating perihematoma blood flow in the following ways: (1) we compared the actual volume of phantoms containing gastrografin and 99mTc-HMPAO to estimated volumes measured by CT and the SPECT multislice ROI technique; (2) we tested the hypothesis that in the absence of obvious perilesional hyperemia, SPECT-derived zero-flow volumes would always equal or exceed CT-derived ICH volumes; and (3) we compared the ratio of FDV to ICH volume in patients with large versus small (<10 mL) ICH. We also examined the interobserver reliability of the CT-derived ICH and edema volumes and the SPECT-derived zero flow volumes, with different blinded investigators performing these analyses at different times.

Statistical Analysis
Mean values for normally distributed data were compared using paired and unpaired 2-tailed t tests. Associations between normally distributed continuous variables were tested using Pearson correlation coefficients and Fisher’s r-to-z test for calculation of probability values. Associations between nonnormally distributed data were tested using Spearman’s rank correlation coefficient. To identify factors that influence the extent of perihematoma edema and blood flow, the following variables were screened in a univariate analysis for significant (P<0.05) associations with edema/ICH volume and FDV/ICH volume: age, sex, mean arterial blood pressure, NIH Stroke Scale score; MABP, mean arterial blood pressure; NIHSS, NIH Stroke Scale score; SPECT, single-photon emission computerized tomography. Values are mean±SEM unless otherwise indicated; n=23.

categorical variables), with edema/ICH volume and FDV/ICH volume coded as the dependent variables. Interobserver reliability was evaluated by calculating the mean±SD difference and intraclass correlation coefficient between measurements of ICH volume, IVH volume, edema volume, and FDV obtained by 2 separate observers. Values were considered to be significant at P<0.05.

Results
Demographic and clinical features of the 23 study patients are summarized in Table 1. The mean interval after ICH onset was 18.2 hours (range, 4.0 to 31.5 hours) for the acute-phase SPECT scan; 13.3 hours (range, 2.0 to 36.0 hours) for the acute-phase CT scan; 72.4 hours (range, 29.0 to 137.5 hours) for the subacute-phase SPECT scan; and 71.7 hours (range, 30.0 to 136.0 hours) for the subacute-phase CT scan. The mean interval between the CT and SPECT examinations was 6.7±5.9 hours (range, 1 to 23 hours) during the acute phase, and 2.7±4.6 hours (range, 0 to 22 hours) during the subacute phase.

TABLE 1. Baseline Clinical and Demographic Data

<table>
<thead>
<tr>
<th>Gender, n</th>
<th>7 M, 16 F</th>
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<tbody>
<tr>
<td>Age, y (range)</td>
<td>64±9 (44–76)</td>
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<tr>
<td>Admission MABP, mm Hg (range)</td>
<td>131±24 (73–163)</td>
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<tr>
<td>Admission GCS (range)</td>
<td>11.3±6.6 (7–15)</td>
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<tr>
<td>Admission NIHSS, (range)</td>
<td>17.2±9.1 (1–33)</td>
</tr>
<tr>
<td>ICH location, n (%)</td>
<td></td>
</tr>
<tr>
<td>Putamen</td>
<td>12 (52)</td>
</tr>
<tr>
<td>Thalamic</td>
<td>6 (26)</td>
</tr>
<tr>
<td>Gangliothalamic</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Lobar</td>
<td>3 (13)</td>
</tr>
<tr>
<td>IVH present</td>
<td>11 (48)</td>
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30-Day or discharge GOS, n (%)

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<table>
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<tbody>
<tr>
<td>Independent, good recovery</td>
<td>5 (22)</td>
</tr>
<tr>
<td>Independent, moderate disability</td>
<td>6 (26)</td>
</tr>
<tr>
<td>Dependent, severe disability</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Dependent, vegetative</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Dead</td>
<td>1 (4)</td>
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GCS indicates Glasgow Coma Scale score; GOS, Glasgow Outcome Score; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; MABP, mean arterial blood pressure; NIHSS, NIH Stroke Scale score; SPECT, single-photon emission computerized tomography. Values are mean±SEM unless otherwise indicated; n=23.

<p>| TABLE 2. CT and SPECT Results |
|---|---|---|</p>
<table>
<thead>
<tr>
<th>Acute Phase</th>
<th>Subacute Phase</th>
<th>P</th>
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<tbody>
<tr>
<td>CT interval from onset, h</td>
<td>13.3±10.9</td>
<td>71.7±22.5</td>
</tr>
<tr>
<td>ICH volume, mL</td>
<td>17.8 (11.4–24.2)</td>
<td>18.3 (11.6–25.0)</td>
</tr>
<tr>
<td>Edema volume, mL</td>
<td>18.6 (12.8–24.4)</td>
<td>25.3 (17.1–33.6)</td>
</tr>
<tr>
<td>IVH volume</td>
<td>3.8 (0.7–5.5)</td>
<td>3.2 (0.9–6.6)</td>
</tr>
<tr>
<td>SPECT interval from onset, h</td>
<td>18.2±7.6</td>
<td>72.4±22.6</td>
</tr>
<tr>
<td>FDV, mL</td>
<td>14.0 (6.7–21.2)</td>
<td>6.3 (2.8–9.8)</td>
</tr>
</tbody>
</table>

ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; SPECT, single-photon emission computerized tomography; FDV, flow deficit volume. Values are mean±SD or mean with 95% confidence intervals in parentheses. Probability values refer to comparisons of acute versus subacute phase by 2-tailed paired t test.

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The timing of the imaging studies; CT-derived ICH, IVH and edema volumes; and SPECT-derived FDVs are shown in Table 2. Among all subjects, ICH volume correlated strongly with edema volume ($r=0.85$, $P<0.0001$) and moderately with FDV ($r=0.36$, $P=0.01$). Mean ICH volume did not change significantly between the acute (18.3±15.5 mL) and subacute (17.8±14.7 mL) phases (95% confidence interval [CI] for ΔICH volume $-1.4$ to $+2.4$ mL). Although the majority of patients showed a mild-to-moderate degree of clot retraction, this was offset by a single patient who experienced an 80% increase in hematoma volume between the acute and subacute periods. As shown in Figure 1, the increase in ICH volume in this patient resulted from the addition of several confluent peripheral hemorrhages into the original low-flow zone surrounding a hematoma.

Mean edema volume increased 36% between the acute and subacute phases (from 18.6±13.5 to 25.3±19.0 mL, $P<0.0001$; 95% CI for Δedema volume $+3.2$ to $+10.2$ mL), and mean FDV decreased by 55% (14.0±16.7 to 6.3±8.0 mL, $P=0.0004$; 95% CI for ΔFDV $-2.9$ to $-12.4$ mL). Accordingly, the edema/ICH volume ratio increased significantly between the acute and subacute phases (1.21±0.41 to 1.79±0.80, $P<0.0001$), and the FDV/ICH volume ratio fell significantly (0.98±0.93 to 0.47±0.61, $P=0.0002$). There were no differences between patients with small (<10 mL, $n=9$) versus large (≥10 mL, $n=14$) hemorrhages with regard to mean percentage change in edema/ICH volume (38% versus 60%, respectively, $P=0.20$) or mean percentage change in FDV/ICH volume (−56% versus −57%, respectively, $P=0.98$).

Edema volume during the subacute phase correlated significantly with FDV during the acute phase (Spearman’s $r=0.48$, $P=0.02$) and with the volume of reperfused perilesional tissue between the first and second SPECT scans (FDV _subacute_ − FDV _acute_) (Spearman’s $r=0.41$, $P=0.05$). Change in edema volume between the first and second CT scans (subacute − acute) did not correlate significantly with FDV during the acute phase (Spearman’s $r=0.35$, $P=0.11$), or with the volume of reperfused tissue (Spearman’s $r=0.34$, $P=0.11$).

Variables found to have significant associations with the ratio of edema/ICH volume in a univariate analysis included ICH volume ($r=-0.50$, $P=0.0003$), use of dexamethasone (mean 0.91 [yes] versus 1.70 [no], $P=0.0004$), and time from onset of ICH ($r=0.34$, $P=0.02$). When entered into a multiple regression model ($r=0.63$, $R^2=0.40$, $P<0.0001$), ICH volume (standard coefficient $-0.42$, $P=0.004$) and time from onset (standard coefficient $+0.30$, $P=0.02$) retained their significance, whereas use of dexamethasone (coded yes=1, no=0; standard coefficient $-0.19$, $P=0.17$) did not. Variables found to have significant associations with the ratio of FDV/ICH volume in a univariate analysis included time from onset ($r=−0.42$, $P=0.004$), sex (mean 1.14 [male] versus 0.55 [female], $P=0.02$), and mean BP ($r=0.34$, $P=0.32$). When entered into a multiple regression model ($r=0.62$, $R^2=0.38$, $P=0.0006$), only time from onset retained its significance (standard coefficient $-0.48$, $P=0.001$), whereas sex (coded male=1, female=0; standard coefficient $+0.20$, $P=0.16$) and mean BP (standard coefficient $+0.19$, $P=0.19$) did not.

Perilesional edema on CT always corresponded topographically with perfusion deficits on concurrent SPECT images. A typical patient with a large perihematoma perfusion deficit in

**Figure 1.** A 71-year-old woman with left putaminal hemorrhage. The ICH volume increased by 80%, from 15 mL at 2.5 hours to 26 mL at 11.5 and 29 hours. Notice that the hematoma enlargement resulted from the addition of discrete hemorrhages within the no-flow zone to the periphery of the existing clot. A large perilesional region of no flow is evident on the baseline SPECT obtained at 5 hours, with relative improvement of perfusion at 29 hours; the perihematoma “flow deficit volume” decreased from 39 mL at baseline to 25 mL at follow-up.
the acute phase, and improved perfusion on the follow-up study, is shown in Figures 2 and 3. In 4 patients (17%), including all 3 subjects with lobar ICH, cortical hyperemia was identified in peripheral cortical regions distant from the hemorrhage (Fig 4). Hyperemia of this type was present on both SPECT scans in 1 patient, and appeared only on the second scan in the other 3. In all cases, the hyperemia corresponded topographically with normal-appearing brain tissue on concurrent CT scans. Diaschisis of the contralateral cerebellum was identified in 18 of 23 subjects (78%) on at least 1 SPECT scan. Compared with the initial scan, the severity of contralateral cerebellar hypoperfusion at follow-up was diminished in 12 patients, unchanged in 2 patients, and increased in 4 patients.

SPECT-derived zero-flow volumes equaled or exceeded corresponding CT-derived ICH volumes in all but 6 of 46 paired measurements. In all but 1 of these cases, the extent to which the ICH volume exceeded the zero-flow volume was small, resulting in FDV values ranging from −0.5 to −2.1 mL, and in 3 instances, coexisting hyperperfusion was identified. The volume of a 500-mL brain phantom containing gastrografin or $^{99}$Tc-HMPAO was estimated to be 493 mL (1.4% error) by CT planimetry and 508 mL (1.6% error) by SPECT planimetry. In a subset of 24 CT scans and 29 SPECT scans evaluated independently by 2 different examiners, the intraclass correlation coefficient (and mean±SD difference) was 0.99 (0.0±1.4 mL) for ICH volume, 0.99 (1.0±1.9 mL) for IVH volume, 0.96 (2.9±3.1 mL) for edema volume, and 0.98 (0.7±3.3 mL) for FDV. There was no significant difference in the ratio of FDV/ICH volume in small (<10 mL, n=28) compared with large hemorrhages (≥10 mL, n=18) (0.97 versus 0.57, respectively, P=0.11).

Figure 2. A 69-year-old woman with typical SPECT findings after a 12-mL right thalamic hemorrhage. The SPECT images show improving perihematoma blood flow from the acute to subacute periods; the perilesional “flow deficit volume” fell from 13 mL at 4 hours to 5 mL at 54 hours. The perihematoma edema volume concurrently increased, from 12 to 18 mL, and the ICH volume remained unchanged.

Figure 3. Overlay of the 2-hour CT and 4-hour SPECT images depicted in Figure 2, demonstrating a large region of no perfusion surrounding the hematoma.
Discussion

To clarify the role of blood flow alterations in the pathogenesis of ICH-related brain injury, we performed SPECT imaging in 23 patients during the acute (mean 18 hours) and subacute (mean 72 hours) phases of hemorrhage. Perilesional blood flow tended to normalize from initially depressed levels as edema formed during the first 3 days after ICH, and the eventual extent of edema correlated with the size of the initial perfusion deficit and the volume of reperfused tissue. Hyperemia suggestive of breakthrough of autoregulation also occurred in more distant cortical regions in some patients, but was not related to edema formation. Our results suggest that the potential for perihematoma ischemia is highest in the earliest hours after ICH onset, and implicate reperfusion injury in the pathogenesis of perilesional tissue damage after ICH.

Intraparenchymal bleeding sets into motion a process of secondary brain injury that contributes substantially to morbidity and mortality after ICH. In the Stroke Data Bank, one third of patients evaluated approximately 12 hours after the onset of supratentorial ICH experienced neurological deterioration, and the strongest predictor of clinical worsening was hematoma volume, implicating perilesional brain injury caused by large established hemorrhages as the primary cause of late clinical deterioration after ICH.15 Worsening in this setting may result from primary tissue injury or brain tissue shifts related to cerebral edema.

Early hematoma expansion, which occurs in 30% of patients initially scanned within 3 hours of onset, is the main cause of clinical deterioration during the hyperacute phase of ICH.31–34 The pathogenesis of this process is poorly understood, but does not appear to be related to extreme hypertension. Of the 5 patients in the present study who were scanned within 3 hours of onset, hematoma expansion occurred in 1, and it was clearly related to the addition of several confluent hemorrhages to the periphery of the existing clot in the perilesional low-flow zone (Fig 1). It seems plausible that early ICH enlargement results primarily from secondary bleeding into necrotic and congested perilesional tissue rather than continued bleeding at the initial site of arteriolar rupture. This contention is supported by histopathologic studies, and may explain the association of irregular multifocal clot morphology with early hematoma expansion found by 1 team of investigators. Hence, both early and late deterioration after ICH may be considered manifestations of perilesional brain tissue injury.

The results of the present study add to our current understanding of the pathogenesis of perihematoma brain injury, which has been gleaned primarily from experimental models. A primary reduction of CBF to ischemic levels occurs in brain regions immediately adjacent to any acute intraparenchymal mass lesion.15,16 This initial decrease in CBF is related to microvascular compromise from local tissue compression and is short-lived, resolving within minutes to hours. Edema from this type of damage is minimal.15 A more peripheral zone of tissue necrosis and edema after ICH is associated with tissue congestion, blood-brain barrier disruption, and secondary hemorrhages from capillaries and venules. Whether this process is associated with prolonged ischemia in humans (via a mechanism analogous to venous infarction) is a point of controversy, although histological damage of this type has been observed to progress for up to 30 hours in experimental models.30

Figure. A 73-year-old woman with an 11-mL right putaminal ICH. The follow-up SPECT image shows delayed hyperperfusion in the overlying cortex of the posterior temporal lobe (arrows), with no corresponding abnormality on CT scan. This phenomenon may represent excessive vasodilation in normal adjacent brain tissue as flow recovers within the perihematoma zone. At follow-up, the ICH volume was unchanged, the edema volume had increased from 15 to 22 mL, and the “flow deficit volume” fell from 13 to 5 mL.
The majority of ICH-related edema, however, appears to result from leakage of serum proteins and vasogenic edema fluid from the clot into adjacent tissues. Within 8 hours of onset, this edema is interstitial in nature, and results from the accumulation of osmotically active substances and movement of water across an intact blood-brain barrier into the extracellular space. Over the next 24 to 48 hours, however, activation of the coagulation cascade and induction of proteolytic enzymes leads to an inflammatory response, resulting in direct cellular toxicity, blood-brain barrier disruption, depressed metabolic activity, and a secondary reduction in CBF. Blood has consistently been shown to result in direct cellular toxicity, blood-brain barrier disruption, activation of the coagulation cascade and induction of pro-inflammatory response or at biochemical events associated with neuroprotective therapy targeted either at the initial inflammatory response or at biochemical events associated with reperfusion injury. Reperfusion of injured tissue in this fashion may contribute substantially to the formation of edema, and suggests a possible role for neuroprotective therapy targeted either at the initial inflammatory response or at biochemical events associated with reperfusion injury.

In a previous report of 7 patients studied an average of 51 hours after the onset of hemorrhage with Tc-HMPAO SPECT, Sills and colleagues have convincingly demonstrated that regions of reduced perfusion surround ICH in humans. Our findings extend this observation by demonstrating that perilesional blood flow is lowest during the first 24 hours after ICH and that it normalizes as edema forms during the next 2 to 3 days. Possible mechanisms to explain this pattern of blood flow reduction in our patients include (1) a hydrostatic mechanism, with normalization of perfusion occurring as elevated local tissue pressures normalize; (2) recovery of depressed local cerebral metabolic activity, which might result from direct injury or deafferentation, with a coupled normalization of CBF; and (3) resolution of vasoconstriction or leukostasis induced by inflammatory mediators released from the blood clot. All 3 factors may play a role, although their relative importance in humans is unknown.

Among our study population as a whole, ICH volume correlated strongly with edema volume (r=0.85, P<0.0001) and moderately with the extent of perfusion deficit (FDV, r=0.36, P=0.01). In a multiple regression analysis, time from ICH onset emerged as the primary determinant of the relative extent of perihematoma edema and blood flow; longer time intervals correlated with smaller perfusion deficit (FDV)–to–ICH volume ratios, and larger edema to ICH volume ratios. An independent association was also found relating smaller hematomas to increased edema–to–ICH volume ratios, which may reflect a minimum radius of perihematoma plasma protein leakage that occurs with smaller bleeds. The tendency for edema to increase and FDV to decrease over time was independent of hematoma size; percentage changes in edema/ICH volume and FDV/ICH volume between the acute and subacute periods were similar in patients with small (<10 mL) versus larger hemorrhages.

We have documented reduced perilesional blood flow during the acute phase of ICH, but cannot conclude that these areas were ischemic. Concurrent measurements of metabolic rate, tissue energy stores, and perfusion reserve would be required to document that CBF is insufficient to meet the metabolic needs of brain tissue surrounding a hemorrhage. However, if perilesional ischemia does occur after ICH, as has been suggested by positron emission tomography studies, our results indicate that this process is most severe within the earliest hours and improves progressively with time. To be effective, anti-ischemic or neuroprotective therapy after ICH should probably be initiated as soon as possible after onset. Similarly, it seems likely that the potential for aggravation of ischemia from lowering of blood pressure is highest within the earliest hours after ICH. Further studies are needed to determine whether a penumbra of ischemic perilesional tissue of significant size occurs in the immediate hours after ICH.

We identified delayed cortical hyperemia in 4 of the 23 patients that we studied, including all 3 subjects with lobar hemorrhage. These regions corresponded topographically to normal-appearing brain on concurrent CT scans (Fig 4), which suggests that this phenomenon is not a direct cause of edema formation after ICH. Cortical hyperperfusion occurring 2 to 3 days after onset has also been described in a rodent model of ICH and in pre-CT era studies of human patients using xenon inhalation techniques. Our results indicate that significant heterogeneity of flow can occur after ICH, with low flow near the hematoma and hyperperfusion in healthy overlying cortical regions. Vasodilation of pial arteries and arterioles in the periphery of the injury zone might occur as efforts are made to restore flow to ischemic regions in the immediate vicinity of the hematoma. Alternatively, this phenomenon may reflect a local inflammatory response or a disorder of autoregulation associated with amyloid angiopathy or intracranial hemorrhage in general.

In summary, we found that perilesional blood flow normalizes from initially depressed levels as edema forms during the first 72 hours after ICH and that the eventual extent of edema correlates with the volume of reperfused tissue. These results suggest that the potential for perilesional ischemia is highest in the earliest hours after ICH onset, and implicate reperfusion injury in the pathogenesis of perihematoma edema formation.

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