Perihematomal Edema in Primary Intracerebral Hemorrhage Is Plasma Derived

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Background and Purpose—The mechanisms of perihematomal injury in primary intracerebral hemorrhage (ICH) are incompletely understood. An MRI study was designed to elucidate the nature of edema and blood flow changes after ICH.

Methods—Perihematomal blood flow and edema were studied prospectively with perfusion-weighted MRI (PWI) and diffusion-weighted MRI in 21 ICH patients. MRI and computed tomography (CT) images were coregistered to ensure perfusion and diffusion changes were outside of the hematoma. Edema volumes were measured on T2-weighted images. Apparent diffusion coefficient (ADC) values of the edematous regions were calculated.

Results—Mean patient age was 64.2 years (45 to 89), and median National Institutes of Health stroke scale score was 12 (3 to 24). Median time to MRI was 21 hours (4.5 to 110). Average hematoma volume on CT was 26.1 (4 to 84) mL. PWI demonstrated perihematomal relative mean transit time (rMTT) was significantly correlated with hematoma volume ($r = 0.60; P = 0.004$) but not edema volume. Perihematomal oligemia (rMTT $> 2$ s) was present in patients with hematoma volumes of $> 15$ mL (average rMTT 4.6 ± 2.0 s). Perihematomal edema was present in all patients. ADC values within this region (1178 ± 213 × 10^-6 mm²/s) were increased 29% relative to contralateral homologous regions. Increases in perihematomal ADC predicted edema volume ($r = 0.54; P = 0.012$) and this was confirmed with multivariate analysis.

Conclusions—Acute perihematomal oligemia occurs in acute ICH but is not associated with MRI markers of ischemia and is unrelated to edema formation. Increased rates of water diffusion in the perihematomal region independently predict edema volume, suggesting the latter is plasma derived. (Stroke. 2004;35:1879-1885.)

Key Words: intracerebral hemorrhage ▪ magnetic resonance imaging, diffusion-weighted ▪ magnetic resonance imaging, perfusion-weighted

Primary intracerebral hemorrhage (ICH) accounts for 10% to 20% of all strokes worldwide. No medical interventions have been proven effective in the management of acute ICH. Potential therapies include prevention of hematoma expansion and limitation of secondary neuronal injury.

Imaging abnormalities within the perihematomal region have been reported previously, but the extent and mechanisms of cellular injury are incompletely understood. Although perihematomal edema has been described previously, its etiology and significance remain unknown. It has been hypothesized that the perihematomal region is hypoperfused, secondary to microvascular compression, resulting in ischemia and cytotoxic edema. Previous studies of blood flow in acute ICH have yielded conflicting results, and no clear markers of ischemia have been demonstrated. Edema has also been postulated to be vascular in origin, resulting from the oncotic effects of intrahematomal blood clotting. Rational medical therapies require a better understanding of perihematomal edema etiology. This is particularly true of acute blood pressure management because the proposed mechanisms of edema formation support opposing treatment strategies. Specifically, acute blood pressure reduction may theoretically inhibit hematoma expansion. Conversely, hypotension may exacerbate or even invoke cerebral ischemia.

Dynamic-susceptibility perfusion-weighted MRI (PWI) allows the visualization of areas of altered blood flow. Diffusion-weighted MRI (DWI) demonstrates regions of restricted water movement that are associated with bioenergetic failure. DWI can be used to quantify the degree of tissue bioenergetic compromise through calculation of the apparent diffusion coefficient (ADC). We undertook a serial PWI and DWI study of the perihematomal region in ICH. We hypothesized that any observed perihematomal hypoperfusion resulting in ischemia would be associated with decreases in the ADC.
Methods

Patients
Twenty-one patients with primary ICH were imaged within 110 hours of onset. Twelve patients were scanned within 24 hours and reimaged 3 to 5 days after onset. National Institutes of Health stroke scale (NIHSS) scores, blood pressure, and venous glucose levels were obtained before imaging. Patients were recruited prospectively after informed consent was obtained.

MRI Protocol
MRI scans were obtained with 1.5-T echo-planar imaging (EPI)-equipped scanners (Signa Horizon SR 120; General Electric) at baseline, 3 to 5, and 30 days after symptom onset. Perfusion-weighted images were obtained using a bolus of gadolinium diethylenetriamine penta-acetic acid (Gd-DTPA [0.2 mmol/kg]) delivered at 5 mL/s with a power injector (Spectris), followed by 15 mL of saline. Thirteen slices (6 mm; matrix 256×256; field of view [FOV] 40×40 cm) were obtained, centered on the hematoma. Diffusion-weighted images were obtained using a multislice spin-echo EPI sequence. Sixteen slices (6 mm; matrix 256×256; FOV 40×40 cm; repetition time/echo time 6000/107 ms) were obtained in 6 orthogonal directions. Diffusion gradient strength was 0 to 22 mT/min, resulting in b values of 0 to 1000 s/mm.

Data Analysis
Postprocessing of raw perfusion images was performed with the software package Stroketool (Digital Imaging Systems). This software was used to plot the change in MRI transverse relaxivity, which is linearly related to Gd-DTPA concentration, over time. Quantitative perfusion indices including relative mean transit time (rMTT), relative cerebral blood flow (rCBF), and relative cerebral blood volume (rCBV) were calculated using single-value decomposition. The tissue concentration time curve was calculated on a pixel-wise basis as a deconvolution of the contrast enhanced images using an arterial input function selected from the contralateral homologous regions. The latter were outlined manually on baseline T2*, DWI b=0, and CT images. A 1-cm region of interest (ROI) was drawn around the boundary of the hematoma (T2*) on PWI maps. Edema volumes were calculated on b=0 images with standardized windowing as the volume of hyperintense signal outside the hematoma boundary (b=0). ROI volume measurements were determined by a single investigator (K.S.B.). PWI and DWI measures were expressed as ratios or delays (rMTT) relative to contralateral homologous regions. The latter were mirror images of the ipsilateral ROIs, reflected 180°. Cerebrospinal fluid was removed using a thresholding technique. On the basis of previous studies, hypoperfusion was defined as rMTT of >2 s relative to the unaffected hemisphere. To assess global perfusion changes, mean PWI indices were measured in the entire hemisphere on slices on which the hematoma was visible.

Statistical Analysis
Analysis was performed using statistical software (Stata Corp). ANOVA and t tests were used to test differences in hematoma volumes on CT and MRI scans. In correlation and regression analyses, hematoma volumes were based on the more accurate CT measurements. All other imaging variables were based on MRI assessment. Relationships were assessed initially with correlation coefficients and tested with Pearson product moments. To determine confounding effects and interactions, a multivariate linear regression model was used to assess the relationship between edema volume, hematoma volume, perihematomal ADC, rMTT, time to MRI, NIHSS, systolic blood pressure, and glucose. The final model included significant variables (P<0.05) and time, a likely confounder.

Results

Baseline Clinical Data
Mean patient age was 64.2 years (range 45 to 89). Median baseline NIHSS score was 12. Median time to baseline MRI was 21 hours (4.5 to 110); 5 patients were scanned within 6 hours. Median time between CT and MRI scan was 6 hours (range 0.5 to 20). Median time to the subacute MRI (n=11) was 4.5 days after symptom onset. Average initial systolic, diastolic, and mean arterial blood pressures were 162±27, 91±15, and 114±19 mm Hg, respectively.

Seventy-one percent of patients were previously diagnosed with hypertension. All but 2 hemorrhages were subcortical (putamen, thalamus and caudate). Three patients were taking warfarin (INR 1.7, 1.8, and 2.1).

Hematoma Volumes
Average hematoma volume on CT was 26.1 mL (range 4 to 84). Apparent hematoma volumes were significantly greater when measured on T2-weighted (36 mL; range 4.8 to 80.5; P<0.001) and susceptibility-weighted images (55.1 mL; range 11.9 to 128.9; P<0.001). Coregistered images demonstrated that the limits of the hematoma on CT scan were consistently within the region of decreased signal on MRI (Figure 1). Hematoma volumes did not change between the acute and subacute scans.

Perfusion-Weighted Images
Perihematomal rMTT was prolonged, relative to contralateral homologous regions, in 11 of 21 patients (average 4.6±2.0 s; Figure 2). These patients had significantly larger hematoma volumes (37.2±20.3 mL) than those without perihematomal rMTT changes (14.7±7.0 mL; P=0.002). Overall, rCBF in
The perihematomal region was decreased by 7.3±16.2%. In contrast, there were no associated changes in rCBV in any patients (1.5±14.4%; Figure 2). Perihematomal rMTT was correlated positively with hematoma volume ($r=0.60$; $P=0.004$; Figure 2). Although perihematomal rCBF appeared to be correlated inversely with hematoma volume, the relationship was not significant ($r=0.18$; $P=0.43$).

A diffuse prolongation of rMTT throughout the hemisphere ipsilateral to the hematoma (>2 s) was observed in 9 patients (Figure 2). Eight of these patients had hematoma volumes >15 mL. No regions of decreased rMTT or increased rCBF consistent with hyperemia were identified in any patients.

Acute perihematomal rMTT appeared to be correlated inversely with time to MRI, although not significantly ($r=-0.10$; $P=0.66$; Figure 3). In patients reimaged subacutely, the average rMTT (1.8±1.7 s) was not prolonged relative to the contralateral hemisphere. Subacute rMTT was normal (≤2 s) in 6 of 11 patients and decreased, relative to the acute study, in the remaining 5 (Figure 3). No perihematomal rCBF or rCBV changes were observed subacutely.

### T2- and Diffusion-Weighted Images

Perihematomal edema was visible as regions of high signal on T2-weighted (b=0 DWI) images (Figure 4). Edema was visible in all patients. The mean absolute volume of perihematomal edema on acute T2-weighted scans was 29.7±20.9 mL. The mean relative edema volume, calculated as the ratio of absolute edema volume to hematoma volume, was 0.91±0.58.$^{11,17}$ Although high signal was apparent on isotropic DWI images, ADC values within this region (1178±213×10^-6 mm²/s) were increased 29% relative to contralateral homologous regions (Figure 4). Perihematomal relative ADC (rADC [ratio of ADC perihematomal/contralateral homologous regions]) values were correlated positively with the absolute ($r=0.54$;
Perihematomal rADC values were increased in all patients, including those imaged within 6 hours. No regions of decreased ADC, outside the hematoma itself, were identified in any patients.

Perihematomal absolute edema volumes, measured on T2-weighted images, increased an average of 43% on the subacute scans (Figure 4). A single patient who had a surgical hematoma resection showed reduced edema volume on the subacute scan and was excluded from this portion of the analysis. Relative edema values were also increased by 48% on the subacute scans. Absolute ADC values were not significantly different from those seen acutely (1151.0±103.2×10⁻⁶ mm²/s). The positive correlation between rADC and absolute (r=0.79; P=0.002) as well as relative edema volume (r=0.76; P=0.005) was preserved on the subacute studies.

**Multivariate Analyses**

A multiple linear regression model including admission NIHSS, systolic blood pressure, glucose level, hematoma volume (CT), time to MRI, perihematomal rMTT, and rADC was used to determine predictors of edema volume. Univariate regression coefficients for all variables are summarized in the table. The final model consisted of hematoma volume, time to MRI, and rADC, all of which independently predicted absolute edema volume (see Table). In contrast, only rADC predicted relative edema volumes (coefficient 1.65; 95% CI, 0.05 to 2.87; P=0.017). The model also indicated that rMTT was independently predicted only by hematoma volume (coefficient 0.10; 95% CI, 0.03 to 0.17; P=0.011).

**Discussion**

This study indicates that a modest reduction in blood flow occurs in the perihematomal region. This is the first MRI report that oligemia is self-limited, spontaneously normalizing in most patients by 3 to 5 days after symptom onset. The lack of any decrease in CBV is inconsistent with the concept of vascular compression by the hematoma. Furthermore, the reduction in blood flow is not associated with MRI markers of ischemia. Although high signal was observed on DWI, ADC values were elevated rather than decreased as in ischemia. The high signal on DWI represents the presence of water itself, which is heavily T2-weighted. The elevated ADC indicates that perihematomal edema is highly diffusible. Multivariate analysis indicates that the rate of diffusion (rADC) is a strong and independent predictor of both absolute and relative edema volume. PWI changes are unrelated to edema volume. These observations suggest that perihematomal edema is plasma derived.

**Perihematomal Blood Flow**

A previous study assessed perihematomal PWI changes in 32 patients presenting with ICH within 6 hours of onset. A prolongation of rMTT consistent with mild hypoperfusion was seen in 4 patients. Diffuse ipsilateral hemispheric hypoperfusion was also observed in approximately half of the patients. An inverse correlation between time to imaging and rMTT delay was reported, consistent with our observation that perihematomal hypoperfusion normalizes spontaneously. Contrary to our findings, a relationship between hematoma volume and rMTT was not observed. This likely reflects differences in the method of hematoma volume assessment. Given the inaccuracies of hematoma size assessment on MRI, we measured hyperdensities on CT using planimetric techniques, whereas the previous study estimated (ABC/2 method) volume on T2-weighted images. Another PWI study in acute ICH revealed no evidence of decreased perihematomal CBF, although diffuse ipsilateral hypoperfusion was observed. The authors defined the perihematomal region using coregistered CT images. Our coregistration results indicate that the paramagnetic effects of blood extend beyond the CT boundaries of the hematoma. Because the dynamic susceptibility contrast technique relies on the paramagnetic effects of Gd, PWI changes immediately adjacent to the hematoma are unreliable. We therefore defined the perihematomal region using the T2* sequence on
which the PWI maps are based, possibly explaining the discordant results from these 2 studies.

The inability to demonstrate significant hypoperfusion in patients with small hematomas may be a limitation of the PWI technique as described above. It is possible that smaller hematomas are associated with a more restricted zone of perihematomal hypoperfusion, below the resolution of PWI. This is supported by a CT perfusion study of perihematomal blood flow that demonstrated a gradient of decreased rCBF extending from the perimeter of the hematoma.8

Two single-photon emission CT studies of ICH demonstrated decreased blood flow in the region of the hematoma.4,5 Mayer4 reported acute perihematomal hypoperfusion that, as in our study, normalized by 72 hours. One positron-emission tomography (PET) study reported periclot CBF reductions, whereas another showed blood flow was only decreased diffusely in the ipsilateral hemisphere.10,19 Another group demonstrated that reduced perihematomal CBF 5 to 22 hours post ictus was associated with a decreased cerebral metabolic rate of oxygen, suggesting that blood flow changes represent metabolically hypoactive tissue rather than ischemia.6 Similarly, 18F fluoromisonidazole PET, which demonstrates tissue hypoxia, failed to show any abnormalities in ICH.20

The apparently conflicting results of the nuclear medicine and MRI studies may be related to the time periods studied in each series. Assessed together, a pattern of acute CBF reduction and spontaneous resolution subacutely is evident. This is consistent with intact cerebral autoregulatory mechanisms responding to decreased metabolic demands in the perihematomal region. This is supported by another PET study demonstrating that perihematomal hypoperfusion was not exacerbated by pharmacological blood pressure reduction.7

Perihematomal Edema
This study extends the previous observation that perihematomal edema volume increases in the first 24 hours post ictus.2

Figure 4. T2-weighted (T2WI [b=0 DWI]), isotropic DWI, and calculated ADC maps of a putaminal hemorrhage. High signal in the perihematomal region is apparent on the T2-weighted and DWI images because of the presence of edema. ADC values are elevated in this region. Perihematomal edema volumes have increased 3 days later, and ADC values remained elevated. The scatter plot demonstrates a strong positive correlation between acute perihematomal rADC and edema volume (r=0.54; P=0.012);
It appears that edema volume continues to increase in the subacute period. Gebel demonstrated previously that relative edema is independent of hematoma volume and other factors possibly related to edema formation. Our multivariate analysis confirms that relative edema is independent of hematoma volume and time to imaging. For the first time, we have identified a factor that independently predicts not only absolute but also relative edema volume, specifically rADC. In simple terms, our analysis indicates that the volume of perihematomal edema is directly proportional to the rate of diffusion. This is incompatible with a cytotoxic etiology of the edema. The observed rADC–volume relationship is consistent with edema of plasma origin, resulting from the oncotic forces of excess serum proteins associated with hemostasis.

Three DWI studies in acute ICH patients have been reported. Consistent with our results, the majority of patients studied showed evidence of elevated ADC values in the perihematomal region. However, a total of 11 patients have been shown to have reduced ADC areas of restricted diffusion were not associated with decreased CBF in these studies. It should be noted that the lack of consistently demonstrable diffusion restriction does not rule out the possibility of bio-energetic compromise in the perihematomal region. This simply reflects the overwhelming influence of the plasma-derived edema on ADC.

The possibility that ischemia is present in some patients, particularly those with elevated intracranial pressure, has not been ruled out. It has been suggested that an early decrease in ADC or prolonged rMTT may be predictive of poor clinical outcome. Regardless of any possible effect on outcome, our study demonstrates that perihematomal edema itself is unrelated to hypoperfusion.

A limitation of this study is the lack of outcome data. It was planned as an investigation of acute and subacute edema changes, aimed at determining etiology. Given the small sample size, it is unlikely that meaningful outcome measures could be obtained. A recent study indicated that within 24 hours of symptom onset, higher relative edema volumes are actually predictive of a favorable outcome. This implies that higher rADC values may also predict good outcomes, although longer-term studies will be required to investigate this possibility.

Another weakness of this study is the large time interval in which patients were studied. We attempted to compensate for this by including time to imaging in our multivariate analyses. Although this indicated that time to imaging did not affect the initial rADC, it is possible that the early hypoperfusion we observed is associated with ischemic signatures hyperacutely. The relatively long interval between CT and MRI also raises the possibility of interim hematoma growth, particularly in the <6-hour patients. Thus, we may have underestimated true hematoma volume in some patients. Finally, it remains possible that ischemia is present in the limited portion of the perihematomal region that cannot be assessed with MRI. This is supported by experimental studies indicating ischemia secondary to space-occupying lesions is limited to a very thin region around the mass. However, we would submit that these potential changes are of limited clinical significance, relative to the much larger volumes that are amenable to study with MRI.

Conclusions and Implications for Management of ICH
This study supports the hypothesis that perihematomal edema is plasma derived. Although cytotoxic edema was not identified, it is unknown whether manipulation of blood pressure can invoke ischemia. Although the prospect of acute blood pressure reduction in ICH with a view to prevention of expansion is attractive, we would suggest a cautious approach. It would be prudent to undertake a study of perihematomal edema and blood flow changes using surrogate endpoints such as rADC and rMTT after blood pressure reduction.

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References

Univariate Analyses

<table>
<thead>
<tr>
<th>Perihematomal Edema Volume Covariates</th>
<th>Regression Coefficient (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perihematomal rADC</td>
<td>59.89 (17.36–102.42)</td>
<td>0.021</td>
</tr>
<tr>
<td>Hematoma volume (CT)</td>
<td>0.68 (0.30–1.06)</td>
<td>0.002</td>
</tr>
<tr>
<td>Time to MRI</td>
<td>8.84 (0.31–17.99)</td>
<td>0.074</td>
</tr>
<tr>
<td>Perihematomal rMTT</td>
<td>3.27 (0.42–6.12)</td>
<td>0.037</td>
</tr>
<tr>
<td>NIHSS</td>
<td>1.59 (0.26–2.92)</td>
<td>0.030</td>
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<tr>
<td>Systolic blood pressure</td>
<td>0.19 (0.16–0.54)</td>
<td>0.294</td>
</tr>
<tr>
<td>Glucose</td>
<td>2.67 (1.49–6.83)</td>
<td>0.225</td>
</tr>
</tbody>
</table>

Multivariate Analysis

| Perihematomal rADC                   | 52.43 (27.11–77.75)             | <0.001 |
| Hematoma volume (CT)                 | 0.76 (0.54–0.98)                | <0.001 |
| Time to MRI                          | 6.55 (1.51–11.59)               | 0.021 |

Time was normalized with a log transform.


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