Diffusion-Weighted MRI and Proton MR Spectroscopic Imaging in the Study of Secondary Neuronal Injury After Intracerebral Hemorrhage

Juan R. Carhuapoma, MD; Paul Y. Wang, MD; Norman J. Beauchamp, MD; Penelope M. Keyl, PhD; Daniel F. Hanley, MD; Peter B. Barker, DPhil

Background and Purpose—Cerebral ischemia has been proposed as contributing mechanism to secondary neuronal injury after intracerebral hemorrhage (ICH). Possible tools for investigating this hypothesis are diffusion-weighted (DWI) and proton magnetic resonance spectroscopic imaging (1H-MRSI). However, magnetic field inhomogeneity induced by paramagnetic blood products may prohibit the application of such techniques on perihematoma tissue. We report on the feasibility of DWI and 1H-MRSI in the study of human ICH and present preliminary data on their contribution to understanding perihematoma tissue functional and metabolic profiles.

Methods—Patients with acute supratentorial ICH were prospectively evaluated using DWI and 1H-MRSI. Obscuration of perihematoma tissue with both sequences was assessed. Obtainable apparent diffusion coefficient (Dav) and lactate spectra in perihematoma brain tissue were recorded and analyzed.

Results—Nine patients with mean age of 63.4 (36 to 87) years were enrolled. Mean time from symptom onset to initial MRI was 3.4 (1 to 9) days; mean hematoma volume was 35.4 (5 to 80) cm3. Perihematoma diffusion values were attainable in 9 of 9 patients, and 1H-MRSI measures were obtainable in 5 of 9 cases. Dav in perihematoma regions was 172.5 (120.0 to 302.5)×10^-2 mm²/s and 87.6 (76.5 to 102.1)×10^-2 mm²/s in contralateral corresponding regions of interest (P=0.002). One patient showed an additional area of reduced Dav with normal T₂ intensity, which suggests ischemia. 1H-MRSI revealed lactate surrounding the hematoma in 2 patients.

Conclusions—DWI and 1H-MRSI can be used in the study of ICH patients. Our preliminary data are inconsistent with ischemia as the primary mechanism for perihematoma tissue injury. Further investigation with advanced MRI techniques will give a clearer understanding of the role that ischemia plays in tissue injury after ICH. (Stroke. 2000;31:726-732.)

Key Words: intracerebral hemorrhage ■ magnetic resonance imaging, diffusion-weighted ■ neuronal damage ■ spectroscopy, nuclear magnetic resonance

Patients with intracerebral hemorrhage (ICH) are at increased risk of death and long-term functional disability compared with ischemic stroke victims, despite relatively similar volumes of neuronal tissue at risk of injury.¹ This poor outcome could be related to various factors, such as hemorrhage extension, elevated intracranial pressure with subsequent herniation, or possibly cellular damage that develops over a period of hours or days after the initial damage—(secondary neuronal injury) in the perihematoma tissue, as recent evidence seems to suggest.²⁻⁵

Although early animal studies suggested the existence of an ischemic penumbra that surrounded the hematoma, more recent clinical and experimental investigations have failed to demonstrate consistent presence of neuronal ischemia in remaining viable tissue peripheral to the hematoma.²⁻⁶ For this reason, other nonischemic mechanisms of neuronal injury after ICH, such as thrombin-induced neurotoxicity and inflammation, are now being investigated and may offer new avenues for therapeutic research in ICH patients if validated.⁷

Currently available advanced MRI techniques may enable clarification of mechanisms that mediate injury to perihematoma brain tissue. Diffusion-weighted MRI (DWI) and 1H-magnetic resonance spectroscopic imaging (1H-MRSI) have already proved valuable in the diagnosis and study of the natural history of ischemic stroke.⁸ These tools have enabled us to delineate areas of essentially irreversible injury soon after the ictus and have shown that progression of ischemic tissue to infarction continues beyond the current treatment window.⁹,¹⁰ However, use of these techniques to assess mechanisms of neuronal injury after ICH has been limited, in

Received September 23, 1999; final revision received November 15, 1999; accepted December 2, 1999.

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part because of concerns about magnetic field inhomogeneity generated by the presence of intraparenchymal hemorrhage that limited the study of regions adjacent to blood products.

In the present study, we demonstrate the feasibility of DWI and $^1$H-MRSI in the study of perihematoma brain tissue and report our initial results of early (acute and subacute) functional and metabolic profiles of brain parenchyma surrounding ICH. Because the ultimate diagnosis of secondary neuronal damage is based on histopathology, these perilisional brain tissue MRI profiles are interpreted in the present article to be surrogate MRI markers of secondary brain injury after ICH.

Subjects and Methods

Patients

With approval from the Johns Hopkins Hospital’s investigational review board and after informed consent was obtained from patients or their relatives, consecutive subjects with a diagnosis of acute, nontraumatic supratentorial ICH were screened and enrolled in the pilot study. Inclusion criteria were as follows: patients admitted to the NeuroCritical Care Unit at the Johns Hopkins Hospital with new onset of a measurable neurological deficit and a head CT compatible with acute supratentorial ICH. Patient exclusion criteria included any contraindication of MRI, evidence of allergy to gadolinium documented in a previous exposure to the contrast agent, or ICH secondary to known anticoagulation or abnormal prothrombin/partial thromboplastin time. Similarly, the following patients also were excluded: those with ICH due to bleeding into a tumoral lesion that was secondary to traumatic brain injury or due to subarachnoid hemorrhage and those with hemorrhagic infarction and prior ischemic stroke in the same distribution of the current ICH. Women of childbearing age were screened for pregnancy before being considered candidates for the study. All subjects enrolled received standard care for ICH patients with or without secondary IVH. Studies were performed only after patients were deemed clinically stable to be safely transported to the MRI facility. A NeuroCritical Care Unit staff member accompanied every patient during the MRI studies, and continuous neurodynamic, hemodynamic, and respiratory monitoring was performed.

MRI Techniques

All MRI experiments were performed on a 1.5-T General Electric scanner with quadrature head coil that was located in the MRI facilities at Johns Hopkins Hospital. The following MR sequences were recorded: (1) sagittal $T_1$-weighted localization images, (2) axial spin-echo spin density and $T_2$-weighted images, (3) diffusion-echo spin density images, and (4) 2D 1H-MRSI. All sequences (except 1) were recorded in an oblique-axial plane parallel to the anterior-posterior commissure line and at the same slice locations and thickness (5 mm [except the spectroscopic images, which were performed with a 15-mm slice thickness]).

Conventional MR Sequences

Sagittal and axial spin-density images were recorded with standard spin-echo sequences. For $T_1$-weighted images, acquisition parameters were field of view (FOV), 24 mm; 5-mm slice thickness; 1-mm gap; repetition time (TR), 535 ms; echo time (TE), 10 ms; 256×192 matrix; and 1 excitation. For SD/TE/weighted images, parameters were FOV, 24 mm; 5-mm slice thickness; TR, 3000 ms; TE, 30/100 ms; 256×192 matrix; 0.75 excitation; flow compensation; and variable bandwidth.

DWI-EPI

Multi-slice, single-shot, diffusion-weighted EPI of the whole brain was performed. The following parameters were used: FOV, 24 mm; 5-mm slice thickness; TR, 4000 ms; TE, 100 ms; 128×128 matrix; and 1 excitation, with a diffusion time of 40 ms and a diffusion gradient length of 25 ms. Diffusion gradient strengths of 0.1, 1.1, 1.5, 1.9, and 2.2 g/cm were used, which gave b-values of 2, 216.5, 433, 649.5, and 866 mm²/s, respectively, applied sequentially in the x, y, and z gradient directions. Isotropic DWI and images of the average diffusion constant (Dav) were reconstructed as follows:

$$Dav = (D_{xx} + D_{yy} + D_{zz})/3$$

MR Spectroscopic Imaging

$^1$H-MRSI was performed in 5 patients by use of a spin-echo sequence with 2D phase encoding and outer-volume saturation pulses for lipid suppression.11 Four 15-mm-thick slices were recorded, with the following parameters: TR, 2300 ms; TE, 272 ms; FOV, 24 cm; 32×32 circular-phase encoding; 1-kHz sweep width; 256 data points; and 1 excitation. Nominal voxel size was approximately 0.8 cm³. Water suppression was accomplished with a single “CHESS” pulse at a bandwidth of 110 Hz, and extracranial lipid signals were suppressed by use of 8 outer-volume saturation pulses arranged in an octagonal pattern. $T_1$-weighted MR images (TR, 400 ms; TE, 20 ms) were recorded at the same slice locations and thickness (15 mm) for anatomic registration of the MRSI data.

Spectroscopic Imaging Data Processing

$^1$H-MRSI data were reconstructed by use of 3D Fourier transformation. Before Fourier transformation, a cosine filter was applied in the spatial dimensions. Exponential line broadening was set at 3 Hz zero-filling to 8192 data points, and a high-pass convolution filter was used to remove the residual water signal (50-Hz stop bands were applied in the time domain).12 Absolute quantification of lactate levels was performed as described previously by use of phantom replacement methodology.13 Magnitude spectra were used to reconstruct metabolic images on the basis of integrated signal intensities of the metabolites in regions 3.34 to 3.24 ppm (Cho), 3.14 to 2.94 ppm (Cr), 2.22 to 1.82 ppm (NAA), and 1.55 to 1.15 ppm (lactate). Metabolic images were linear interpolations from the original 32×32-matrix size to 256×256 points. A signal was only assigned to lactate if it had a chemical shift of exactly 1.33 ppm and a scalar coupling of 7 Hz.

Image Analysis

Quantitative image analysis was performed on an Apple Macintosh G3 computer (Apple Computer) using the program NIH Image (version 1.61, Wayne Rasband, NIH, Bethesda, Md). Feasibility of assessment was based on ability to obtain spectroscopic and diffusion data in perihematoma brain regions. Images were evaluated for the presence of obscuration secondary to susceptibility artifact. The hematoma was visualized on conventional $T_1$ MRI in all cases; all cases also exhibited $T_2$ hyperintensity in brain parenchyma surrounding the hematoma. These regions (hematoma and $T_2$ hyperintense rim) were outlined on the low b-value DWI-EPI images manually by 2 investigators (J.R.C., P.B.B.). The low b-value DWI-EPI images are essentially $T_2$-weighted images with the same slice locations and spatial distortions as the high b-value DWI-EPI images. Coordinates of these regions of interest (ROIs) were then transferred to the calculated Dav images for measurement of hematoma and perihematoma diffusion constants. Dav was also measured in identical ROIs in the contralateral hemisphere. Dav images were screened by 2 investigators (J.R.C., P.B.B.) for focal abnormalities beyond the regions identified on $T_1$ MRI.

Statistical Methods

The Stata 6 statistical software package was used for data analysis. A paired t test was used to determine whether a significant difference existed in Dav between perihematoma and corresponding contralateral brain areas, and a 95% confidence interval was calculated for the mean difference.

Results

Between August 1997 and December 1998, 9 consecutive patients were enrolled in this pilot study. The following demographic and clinical characteristics of the study cohort are summarized in Table 1.
Demographic Characteristics
The mean ± SD age of the study cohort was 63.4 ± 17.7 (range, 36 to 87) years, and the men/women ratio was 5:4. Mean time from symptom onset to initial MRI evaluation was 3.4 ± 2.6 (range, 1 to 9) days in all 9 patients. Follow-up MRI studies were obtained in patients 1, 2, and 7 at 6, 9, and 4 days, respectively.

Clinical Features
The cause of ICH was systemic hypertension in 6 patients, probable vascular malformation in 1, and probable amyloid angiopathy in 1 and was associated with cocaine use in 1 patient. The hematoma was located in the basal ganglia or thalamus in 6 patients and was lobar in 3. No blood pressure or ventilatory manipulation was performed immediately before or during the MRI studies. Mean arterial pressure in the study cohort at the time of first MRI study was 102.2 ± 15.2 (range, 85 to 130) mm Hg.

Radiological Features
The initial mean hematoma volume was 35.4 ± 31.4 (range, 5 to 80) cm³ as measured on admission head CT. Values were obtained by use of a method described previously.¹⁴

### Table 1: Clinical and MRI Characteristics of the Study Cohort

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y/Sex</th>
<th>Perihematoma DWI</th>
<th>Perihematoma ¹H-MRSI: Lactate</th>
<th>ICH Volume, cm³</th>
<th>MAP, mm Hg</th>
<th>Time to MRI, d</th>
<th>Cause</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44/F</td>
<td>↑ Dav</td>
<td>+Lac</td>
<td>15</td>
<td>85</td>
<td>3</td>
<td>Probable AVM</td>
<td>R basal ganglia</td>
</tr>
<tr>
<td>2</td>
<td>72/M</td>
<td>↑ Dav</td>
<td>NP</td>
<td>5</td>
<td>95</td>
<td>9</td>
<td>HTN</td>
<td>L basal ganglia</td>
</tr>
<tr>
<td>3</td>
<td>70/M</td>
<td>↑ Dav ↓ Dav</td>
<td>NP</td>
<td>80</td>
<td>95</td>
<td>6</td>
<td>HTN</td>
<td>L basal ganglia</td>
</tr>
<tr>
<td>4</td>
<td>87/F</td>
<td>↑ Dav</td>
<td>NP</td>
<td>72</td>
<td>90</td>
<td>9</td>
<td>Probable AA</td>
<td>L basal ganglia+IVH</td>
</tr>
<tr>
<td>5</td>
<td>87/F</td>
<td>↑ Dav</td>
<td>+Lac</td>
<td>72</td>
<td>105</td>
<td>4</td>
<td>HTN</td>
<td>L basal ganglia</td>
</tr>
<tr>
<td>6</td>
<td>61/M</td>
<td>↑ Dav</td>
<td>−Lac</td>
<td>5</td>
<td>110</td>
<td>2</td>
<td>HTN</td>
<td>L basal ganglia</td>
</tr>
<tr>
<td>7</td>
<td>52/F</td>
<td>↑ Dav</td>
<td>−Lac</td>
<td>35</td>
<td>130</td>
<td>2</td>
<td>HTN</td>
<td>L basal ganglia</td>
</tr>
<tr>
<td>8</td>
<td>62/M</td>
<td>↑ Dav</td>
<td>NP</td>
<td>5</td>
<td>120</td>
<td>2</td>
<td>Cocaine-induced</td>
<td>L thalamus+IVH</td>
</tr>
<tr>
<td>9</td>
<td>36/M</td>
<td>↑ Dav</td>
<td>NP</td>
<td>30</td>
<td>90</td>
<td>2</td>
<td>Cocaine-induced</td>
<td>R parietal lobe+IVH</td>
</tr>
</tbody>
</table>

MAP indicates mean arterial pressure; +Lac, lactate signal present; AVM, arteriovenous malformation; R, right; NP, not performed; HTN, systemic hypertension; L, left; −Lac, lactate signal absent; AA, amyloid angiopathy; and IVH, intraventricular hemorrhage.

### Table 2: Dav in ROIs of Brain Tissue Surrounding ICH

<table>
<thead>
<tr>
<th>Patient No. (Time After ICH, d)</th>
<th>Ipsilateral Dav (×10⁻³ mm²/s)</th>
<th>Contralateral Dav (×10⁻³ mm²/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (3⁴)</td>
<td>137.2±16.5</td>
<td>86.2±7</td>
</tr>
<tr>
<td>1 (6⁴)</td>
<td>169.2±77.2</td>
<td>77.8±4.6</td>
</tr>
<tr>
<td>2 (2)</td>
<td>131.7±1.9</td>
<td>76.5±1.3</td>
</tr>
<tr>
<td>2 (9)</td>
<td>132.7±7.5</td>
<td>93.7±3.8</td>
</tr>
<tr>
<td>3 (6)</td>
<td>302.5±46.5</td>
<td>102.1±8.7</td>
</tr>
<tr>
<td>4 (9)</td>
<td>140.6±14.8</td>
<td>92.5±14.2</td>
</tr>
<tr>
<td>5 (4)</td>
<td>162.0±14.9</td>
<td>88.9±4.2</td>
</tr>
<tr>
<td>6 (1)</td>
<td>140.8±12.8</td>
<td>77.8±0.4</td>
</tr>
<tr>
<td>7 (2)</td>
<td>223.1±42.1</td>
<td>84.9±6.7</td>
</tr>
<tr>
<td>7 (4)</td>
<td>240.0±51.9</td>
<td>90.3±9.6</td>
</tr>
<tr>
<td>8 (2)</td>
<td>120.1±22.6</td>
<td>92.7±21</td>
</tr>
<tr>
<td>9 (2)</td>
<td>194.7±51.9</td>
<td>86.7±11.9</td>
</tr>
</tbody>
</table>

Mean initial Dav: 172.5±58.9 (range, 120.0-302.5) (range, 76.5-102.1)

Mean follow-up Dav: 180.6±54.6 (range, 132.7-240.0) (range, 77.8-93.7)

*Preoperative study.
†Postoperative study.
‡P=0.002.
Conventional MRI sequences and DWI studies were performed in every patient at initial investigation; 1H-MRSI was performed in 5 patients. High-intensity signal on T2 MRI was found predominantly in the white matter surrounding the hematoma in every patient studied. Increased Dav values (relative to homologous brain regions in the contralateral hemisphere) that matched areas of high T2 signal intensity were found surrounding the hematoma in every patient, with a mean Dav of 172.5 ± 302.5 (range, 120.0 to 302.5)×10^{-3} mm²/s and 87.6 ± 7.8 (range, 76.5 to 102.1)×10^{-3} mm²/s in the ipsilateral and contralateral ROI, respectively. Using paired t test, the obtained t statistic and P value was 4.65 and 0.002, respectively. The 95% confidence interval for the mean difference was 43 to 127. In addition to T2 high-intensity signal associated with elevated Dav surrounding the hematoma, patient 3 showed an area of reduced Dav in a location superior to the blood clot (51.5 ± 8.9×10^{-3} mm²/s) with corresponding normal T2 signal intensity (Figure 1). Three patients had repeat DWI studies (patients 1, 2, and 7) at 6.3 (range, 4 to 9) days after hemorrhage (Table 2). At 1H-MRSI, patients 1 (after surgical ICH evacuation) and 5 showed incomplete halos of elevated lactate concentration in regions surrounding the hematoma 6 and 4 days after the stroke, respectively (Table 3, Figure 2).

Hematoma mass could not be studied with the application of 1H-MRSI as a result of presence of susceptibility artifacts that interfered with hematoma imaging and data interpretation. In 3 cases, susceptibility effects and T2 shortening precluded reliable Dav measurement of the hematoma mass. However, the blood clot was amenable to study with DWI in patients 2, 3, 4, 6, 8, and 9. In these cases, reduced Dav values were obtained (35.7 ± 14.2 [range, 8 to 47.9])×10^{-3} cm²/s (Figure 3 shows patient 4).

**Discussion**

We report 9 ICH patients studied with functional MRI techniques during the acute and subacute stages of the disease. A primary objective was to assess the feasibility of

<table>
<thead>
<tr>
<th>Patient (time after ICH, d)</th>
<th>Ipsilateral Lac, mmol/L</th>
<th>Lac/Cr</th>
<th>Contralateral Lac, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (3*)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1 (6†)</td>
<td>6.4</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>4 (9)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5 (4)</td>
<td>6.74</td>
<td>1.32</td>
<td>0</td>
</tr>
<tr>
<td>6 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Cr indicates creatine; other abbreviations are as in text and Table 1.

*Preoperative study.
†Postoperative study.

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Dav, T1-, and T2-weighted images; proton MRSI (NAA, lactate); B0 field map; and selected proton spectra from peri-hematoma and contralateral ROI in patient 5 four days after symptom onset. Hematoma is dark on T2-weighted images and shows a large local disturbance of field homogeneity (presumably due to the presence of paramagnetic deoxyhemoglobin). Dav or proton spectra could not be evaluated in the hematoma because of focal-field inhomogeneity. NAA is dark on T2-weighted images and shows increased signal on T2-weighted images, increased Dav, and increased lactate. Lactate is definitively assigned on the basis of a chemical shift of 1.33 ppm and 7-Hz J coupling.

![Table 3](http://stroke.ahajournals.org/)

**Table 3.** Quantitative 1H-MRSI Analysis in ROIs of Brain Tissue Surrounding ICH

<table>
<thead>
<tr>
<th>Patient (time after ICH, d)</th>
<th>Ipsilateral Lac, mmol/L</th>
<th>Lac/Cr</th>
<th>Contralateral Lac, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (3*)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1 (6†)</td>
<td>6.4</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>4 (9)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5 (4)</td>
<td>6.74</td>
<td>1.32</td>
<td>0</td>
</tr>
<tr>
<td>6 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

1. Perihematoma

2. Contralateral

Cr indicates creatine; other abbreviations are as in text and Table 1.

*Preoperative study.
†Postoperative study.
use of advanced MR imaging techniques in the presence of intraparenchymal blood. Magnetic properties of blood and associated breakdown products in intraparenchymal hematomas are complex and depend on several factors, which include hemoglobin oxygenation and time after hemorrhage. In particular, deoxyhemoglobin is strongly paramagnetic and can shorten both $T_1$ and $T_2$ relaxation times as well as disrupt magnetic field homogeneity. Thus, it would be reasonable to anticipate sequences that require consistent field homogeneity, such as $^1$H-MRSI and single-shot EPI, to be limited in either hematoma or perihematoma regions because of the presence of deoxyhemoglobin. In all cases examined by use of $^1$H-MRSI, the magnetic field homogeneity within the hematoma was not sufficient to allow detection of interpretable spectra. However, in tissue adjacent to the hematoma ($\pm 1$ cm from the margins of the hematoma), interpretable spectra were obtained in all 5 cases. Although interpretable, $^1$H-MRSI signal in ROIs near the hematoma had larger line widths than spectra from remote brain regions in 1 case.

We did not identify consistent evidence of neuronal ischemic damage in our patient cohort, as defined by the simultaneous presence of surrogate MRI markers of recent cerebral ischemia (reduced Dav values and presence of lactate) in areas surrounding the hematoma. Instead, we found uniformly elevated Dav values that matched regions of increased $T_2$ signal intensity in brain tissue around the blood clot, which suggested the presence of vasogenic edema. In only 1 instance (patient 3) of a large basal ganglia hematoma (80 cm$^3$) was a superimposed region of reduced Dav located superior to the hematoma and associated with normal $T_2$ signal intensity, which indicates additional ischemic injury (cytotoxic edema). Our results therefore suggest that mechanisms other than ischemia might play an important role in secondary neuronal injury after ICH. Inflammation emerges as a probable mechanism, but occasionally ischemia, when present, and may add further to this process.

Recent interest has focused on the presence of secondary neuronal injury in ICH patients. The hypothesis of an ischemic penumbra is the commonly held explanation for the progressive injury occurring with ICH. Most of the evidence for a superimposed ischemic insult originates from animal experiments, but only a few clinical studies support this theory. In 1988, Tanizaki reported his experience with 13 patients studied with $^{133}$Xe inhalation and single-photon emission computed tomography who underwent stereotactic evacuation of the ICH. Dav was measured within 1 week before and after the surgical evacuation of the hematoma. A statistically significant increase in postoperative CBQ on the affected side was noted in the hemispheric CBF ipsilateral to the hematoma in one third of the patients studied, particularly in the region of the thalamus and basal ganglia and in the anterior territory of the middle cerebral artery. Unfortunately, the presence of ischemia in this study could not be definitively established because of the absence of a putative indicator of tissue neuronal anaerobic metabolism.

Reductions in CBF metabolism can also be seen coupled to the presence of decreased neuronal activity and metabolism after acute brain injury. Diringer and coworkers studied 12 patients with ICH using PET and was unable to demonstrate secondary ischemic injury despite pharmacological lowering of the blood pressure. They also described symmetric CBF decrements in both the affected and the contralateral hemisphere associated with decreased oxygen extraction ratio. On the basis of these results, one could hypothesize that the presence of blood or its products produces neuronal injury, dysfunction, or metabolic suppression but not ischemia in regions near the hematoma and perhaps even distant to it.

A competing hypothesis has been suggested on the basis of recognition of the proinflammatory effect that certain blood products have on neuronal tissue. Specifically, there is growing interest in inflammation as a mechanism for secondary brain injury. One of the blood components recognized as playing a major role in the development of acute and perhaps chronic brain injury and neuronal degeneration is thrombin. At the cellular level, several cell lines, such as neurons, glial/ependymal cells, and endothelium, are known to express receptors for this protein in the CNS. Hoff and coworkers studied the effects that blood and its components have on rodent brain tissue and concluded that thrombin induces vasogenic edema as well as direct neurotoxicity.

The consistently elevated Dav and $T_2$ signal intensity in the perimeter of the hematoma in our study cohort appears consistent with the notion of vasogenic edema as an indicator of the inflammatory response induced by the hematoma. Kuroiwa and coworkers have demonstrated the relationship between increased Dav with the presence and severity of blood brain barrier breakdown associated with vasogenic brain edema in a feline cold cortical lesion model. Similar DWI profiles of elevated Dav were independently reported in humans by Ay and coworkers and Schaefer and coworkers on the vasogenic edema induced by posterior leukoencephalopathy syndrome and eclampsia, respectively. However, in the present cohort, delayed DWI expression of ischemic injury cannot be entirely excluded. Apparent diffusion coefficient (ADC) values are well known to be able to “normalize” and even “supranormalize” 9 to 10 days after the original ischemic insult, although the precise time that this process takes to occur has not been uniformly established in humans. Nevertheless, we consider this to be a less likely occurrence in the present study, on the basis of our current
knowledge of the time course of ADC progression after human focal ischemic injury. Six of 9 patients in our cohort were studied within the initial 48 hours, 1 of them within the first 24 hours after the stroke; all the DWI studies in these and the remaining 3 patients showed significant Dav elevation surrounding the hematoma region. Although cerebral ischemia can induce heterogeneous ADC values in human ischemic stroke, including rapidly progressing early Dav reduction followed by its supranormalization in nearly 8% of the ischemic tissue within the first 10 hours after injury,44 early blood-brain barrier breakdown is presented here as an alternative mechanism for the uniformly observed Dav elevation in our patient cohort.

Lactate, the end product of anaerobic glycolysis, is widely recognized as a reliable indicator of tissue ischemia, as seen in human stroke.45 Nevertheless, anaerobic glycolysis induced by nons ischemic mechanisms can also be observed in areas of vasogenic edema as demonstrated by Mun-Bryce and coworkers46 after they studied the effects of blood on the surrounding brain tissue with H-MRSI in a collagenase rat model of ICH. Similar experience with lactate elevation in areas of vasogenic edema has been reported in the absence of energy failure by other authors.47,48 Our findings of lactate signal in areas that surround the blood clot in only 2 patients (surrounding the surgical site in patient 1) do not support a prominent role of ischemia as a predominant mechanism of secondary neuronal injury. Furthermore, the presence of Dav increased rather than reduced Dav argues against the presence of ischemia as the cause for lactate generation.

We found the blood clot itself to be amenable to study with DWI in 6 of 9 cases. Although the hematoma in some cases appeared dark on low b-value images, sufficient signal was present to allow reliable Dav determinations (Figure 3). The reduced Dav values obtained are likely the result of the different stages of dehydration of blood clots in these patients. Nevertheless, presence of islets of remaining, marginally perfused brain tissue cannot be entirely excluded. This occurrence has been reported in a canine model of ICH by Qureshi and coworkers.3

Limitations of this study include assessment of patients beyond the hyperacute period, when greatest potential for meaningful intervention could be anticipated. However, given the demonstrated feasibility of assessment in the acute and subacute stages when paramagnetic properties of the hemorrhage are more pronounced, assessment in the hyperacute period should not be limited as a result of magnetic field inhomogeneity. Also, the limited sample size restricts our ability to exclude definitively that ischemia plays a central role in secondary tissue injury.

In summary, we have demonstrated the feasibility of MRI assessment of perihematoma viable brain tissue with DWI and H-MRSI. In our pilot population, we did not find evidence of widespread ischemia. Our preliminary results suggest that inflammation surrounding the hematoma, and perhaps ischemia in isolated cases, may develop during the acute and subacute stages (72 to 96 hours) of the disease process in ICH patients. If so, the precise onset and progression and the presence of a subsequent late inflammatory and delayed cell death process remain to be explored. The definition, identification, severity grading, and understanding of the temporal evolution of these pathologic mechanisms are necessary steps to first design and later assess supportive treatments and directed management in ICH patients. New, advanced MRI techniques may help in the achievement of these goals.

Acknowledgments

Dr Carhuapoma is supported in part by the David A. Dana Research Prize in Neurosciences Critical Care, Johns Hopkins University School of Medicine, and by the Daland Fellowship for Clinical Research Award from the American Philosophical Society. Dr Barker is supported by an Established Investigator Award from the American Heart Association. Dr Beauchamp is supported by a grant from the American Roentgen Ray Society. We thank Dr Aziz Uluğ and Dr Peter van Zijl for the DWI sequence and Dr Jeff Duyn (NIH) for the MRSI sequences.

References


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Stroke. 2000;31:726-732
doi: 10.1161/01.STR.31.3.726
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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