Combined Magnetic Resonance Imaging and Proton Magnetic Resonance Spectroscopy of Patients With Acute Stroke

S.R. Felber, MD; F.T. Aichner, MD; R. Sauter, PhD; and F. Gerstenbrand, MD

Background and Purpose: The prospect for a therapeutic window for treatment of ischemic stroke encourages the noninvasive investigation of metabolic changes in acute ischemia. Recently, localized proton spectroscopy became available at 1.5-T magnetic resonance systems. In this study we evaluated the usefulness of combined magnetic resonance imaging and spectroscopy on the diagnosis of acute and chronic infarctions.

Methods: Combined magnetic resonance imaging and spectroscopy investigations were carried out with a 1.5-T system in 16 volunteers, eight patients with chronic infarction (>8 months), and 10 patients with acute ischemic stroke (<8 hours). We used a stimulated echo sequence to acquire localized spectra from image-guided volumes of interest (16–27 ml).

Results: There were no significant interindividual differences of choline, creatine, phosphocreatine, and N-acetyl aspartate resonances in the spectra from volunteers. In chronic infarctions, N-acetyl aspartate was decreased in relation to choline. Acute ischemic infarctions were characterized by decreased N-acetyl aspartate resonances and elevation of lactate.

Conclusions: The study demonstrates the feasibility of proton spectroscopy in stroke patients. Metabolic alterations in ischemic tissue can be monitored and can distinguish acute from chronic lesions. (Stroke 1992;23:1106-1110)

KEY WORDS • cerebral ischemia • magnetic resonance imaging • nuclear magnetic resonance • stroke assessment

Magnetic resonance imaging (MRI) has already improved the early detection of cerebral ischemia. Magnetic resonance (MR) can also be used to observe tissue metabolism in vivo, and magnetic resonance spectroscopy (MRS) has been successfully used to investigate cerebral ischemia in animals. Recently, MRS became available as a whole-body MR system for the examination of patients. In this study we have used combined proton MRI and MRS to examine patients during the acute as well as the chronic stage of middle cerebral artery (MCA) infarction. The purpose was to evaluate the feasibility and usefulness of MRI/MRS in the diagnosis of stroke patients.

Subjects and Methods

Only patients with ischemic infarctions of the MCA territory were chosen for this study. A total of 18 patients underwent a standardized MRI/MRS protocol after informed consent was obtained. Heart rate, electrocardiographic (Sirecust, Siemens), and blood oxygenation (TM 8604, NONIN) values were continuously monitored during the MRI/MRS examination.

We examined eight patients, five men and three women, 47–80 years of age (mean, 57 years), in the chronic stage after stroke (8 months to 6 years). Two patients had suffered complete MCA infarctions, and the others had lesions in the parietal cortex (n=2) and the subcortical white matter (n=4).

Ten patients, five men and five women, 30–79 years of age (mean, 60.3 years), suffering from acute infarction were investigated. All of them showed onset of hemiparesis <8 hours before the MRI/MRS examination (range, 4–8 hours; mean, 5.8 hours) and underwent computed tomographic (CT) scan and duplex sonography of the extracranial vessels. X-ray angiography was performed in five patients. Serial MRI/MRS examinations (on days 1, 6, and 12 after stroke) were obtained for three patients.

Volunteers (nine women, seven men) were examined to optimize the MRI/MRS protocol. They were 21–63 years of age (mean, 41 years) and had no history or symptoms of previous neurological or cardiovascular diseases. Combined MRI/MRS investigations were carried out with a 1.5-T iron-shielded system (Magnetom, Siemens) equipped with a 10 mT/m gradient system and a standard circularly polarized head coil. The imaging protocol consisted of a sagittal T1-weighted multislice spin-echo sequence (repetition time [TR], 550 msec; echo time [TE], 15 msec) and a multislice proton density (PD)/T2-weighted double echo sequence (TR,
FIGURE 1. Localized proton magnetic resonance spectra of the left hemisphere in two healthy volunteers. Resonances are assigned to choline (Ch), creatine/phosphocreatine (Cr/PCr), and N-acetyl aspartate (NAA) as indicated in the spectra. Signals between 3.5 and 4.5 ppm were not interpreted because of possible baseline modulations due to the water suppression pulse.

TABLE 1. Results of MRI/MRS in Volunteers and Patients With Stroke

<table>
<thead>
<tr>
<th>Subject group</th>
<th>Cr/PCr:Ch</th>
<th>NAA:Ch</th>
<th>Lac:Ch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volunteers (n = 16)</td>
<td>0.7-1.2</td>
<td>2.3-3.8</td>
<td>No lac</td>
</tr>
<tr>
<td>(1.0)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with chronic infarction (n = 8)</td>
<td>0.7-1.0</td>
<td>1.6-2.3</td>
<td>No lac</td>
</tr>
<tr>
<td>(0.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with acute infarction (n = 10)</td>
<td>0.7-1.0</td>
<td>0.5-1.7</td>
<td>0.2-1.8</td>
</tr>
<tr>
<td>(0.8)</td>
<td></td>
<td>(1.2)</td>
<td>(0.8)</td>
</tr>
<tr>
<td>MCA territory (n = 2)</td>
<td>0.8-1.0</td>
<td>0.8-1.2</td>
<td>1.4-1.8</td>
</tr>
<tr>
<td>Insular cortex (n = 2)</td>
<td>0.8-0.9</td>
<td>0.5-1.0</td>
<td>1.0-1.4</td>
</tr>
<tr>
<td>Parietal cortex (n = 3)</td>
<td>0.8-1.0</td>
<td>1.3-1.6</td>
<td>0.3-0.8</td>
</tr>
<tr>
<td>Internal capsule (n = 3)</td>
<td>0.7-1.0</td>
<td>1.4-1.7</td>
<td>0.2-0.4</td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; Cr, creatine; PCr, phosphocreatine; Ch, choline; NAA, N-acetyl aspartate; Lac, lactate; MCA, middle cerebral artery.

*Peak intensity ratios (mean values in parentheses).

FIGURE 2. Panel A: T2-weighted image of a 67-year-old man examined 5 hours after onset of hemiparesis, showing an area of increased signal intensity in the right parietal cortex. Panel B: Sequential magnetic resonance imaging examination 12 days later demonstrating extension of the abnormal signal into the white matter. Panel C (see next page): Sequential magnetic resonance spectroscopy on days 1 (upper spectrum), 2 (middle spectrum), and 12 (lower spectrum). Lactate (Lac) levels decreased, whereas N-acetyl aspartate levels decreased from day 1 to day 2 and then remained unchanged. Spectra were acquired within 3 minutes (128 NEX) because the patient could not tolerate a longer examination.
was 270 msec to rephase the doublet of lactate (lac)
methyl protons (J, 7 Hz) together with the singlet
resonances and to avoid contributions from short T2
compounds like fatty acids. Spectra were accumulated
for 3–9 minutes (128–384 NEX). The total examination
time for MRI and MRS was <60 minutes. The spectra
were processed in the time domain by a 1–2-Hz line-
broadening Gaussian function and displayed relative to
water (chemical shift, 4.7 ppm).

Results

Figure 1 shows two typical spectra from volunteers.
The resonances were assigned to choline (Ch) ([N-
CH$_3$]) at 3.2 ppm, creatine/phosphocreatine (Cr/PCr)
(N-CH$_3$) at 3 ppm, and the methyl group of N-acetyl
aspartate (NAA) at 2 ppm. There were no signifi-
cant interindividual differences (Table 1).

Localized proton spectra from areas of infarctions
were obtained for all patients. One patient who suffered
from concomitant lower back pain did not tolerate the
entire protocol. Thus, we limited the acquisition time
for the localized spectrum to 3 minutes (128 NEX) and
achieved diagnostic images together with interpretable
spectra within 35 minutes (Figures 2A–2C). The MRI/
MRS examination did not influence heart rate, electro-
cardiographic, or blood oxygenation parameters of the
patients.

Chronic ischemic lesions showed decreased signals
for NAA, Ch, and Cr/PCr. Metabolite levels maintained
higher values if the MRI indicated preservation of

![Figure 3](Image)

**Figure 3.** Panel A: T2-weighted magnetic resonance image
of chronic infarction on the right side showing preservation of
astroglial architecture in a 63-year-old patient. White square
indicates the volume of interest for spectroscopy. Panel B:
Localized proton spectrum showing decreased levels of choline,
creatine/phosphocreatine, and N-acetyl aspartate. There is no
evidence of lactate in the chemical shift at =1.3 ppm.

**Discussion**

This study demonstrates the feasibility of combined
proton MRI/MRS in a clinical setting. The stimulated
FIGURE 4. Panel A: T2-weighted image obtained 4 hours after onset of right hemiplegia. Increase of cortical signal intensity was noted in the left middle cerebral artery territory without major involvement of the adjacent white matter. Chronic white matter changes were present in the contralateral hemisphere. Panel B: Sequential examination 6 days later shows demarcation of the infarction, involving both gray and white matter of the left middle cerebral artery territory. Panel C: Sequential magnetic resonance spectroscopy obtained from the regions indicated by the white squares in panels A and B. Upper spectrum was acquired in the acute stage and exhibits a strong contribution of lactate (Lac) at 1.3 ppm, as identified by $J$ coupling of the methylene protons. N-acetyl aspartate is markedly reduced. Lower spectrum was obtained 6 days later when the true extent of the infarction became visible on magnetic resonance imaging. Lactate had increased further and now exceeds the choline concentration by a factor of 2.8 while N-acetyl aspartate shows further depletion (384 NEX=9 minutes acquired in both spectra).

echo sequence accurately suppressed signals originating outside the VOI. Mobile fat was never present in our spectra even if the VOI was positioned close to the skull (Figure 2). Spectral resolutions of 4–6 Hz were achieved within <10 minutes of the local magnetic field optimization. The examination time for MRI/MRS could be minimized to 30 minutes in a patient with lower back pain. In concordance with previous studies, spectra from the volunteers did not show significant interindividual differences.\textsuperscript{11} In our spectra, signals of physiological lac concentrations were not detected because of the limitations of the signal-to-noise ratio within the time constraints of a clinical examination.

Despite the fact that all of the patients had comparable neurological symptoms, MRI revealed considerable variations in the location and distribution of ischemic lesions. T2-weighted images were most sensitive to acute ischemia and showed signal-intense lesions in all patients. This proved to be necessary for positioning and interpretation of localized MRS.

Although a definite role for the MRS-detectable NAA pool remains to be elucidated, decreased NAA levels have been found in brain tumors and infarctions. Our results in acute and chronic infarctions support the view that NAA is associated with the presence of viable neurons.\textsuperscript{9} Also positron emission tomographic studies that have demonstrated a decreased $^{18}$F-deoxyglucose use in chronic infarction\textsuperscript{12} have also indicated the loss of metabolically active neurons.

$^{31}$P-MR spectra of chronic infarctions have demonstrated a general diminution of phosphate compounds but have otherwise appeared normal.\textsuperscript{7} This suggests tissue loss and normal energy metabolism of the surviv-
ing cells, a finding that is consistent with the absence of lac in our proton spectra of chronic infarctions.

In the acute stage of cerebral infarction, MRS yielded elevations of lac and decreases of NAA levels in all patients. The range of spectral changes varied considerably within the different patients. Partial-volume averaging of normal and ischemic tissue explains these variations in patients with small capsular and parietal infarctions according to the size of the VOI. However, different levels of lac and NAA were also found in spectra of extensive infarctions (Figures 4A–4C). These results indicate that infarctions with a comparable appearance on MR scans were composed of cells in different metabolic states. Lactate may result from anaerobic glycolysis, as has been demonstrated by combined $^3$P- and proton MRS investigations of experimentally induced cerebral ischemia, but is also agonally produced by irreversibly damaged cells. In our protocol, differentiation of the metabolically active lac pool was not possible, but it may be achieved with $^1$Cglucose labeling in the future.\footnote{13}

Because lac is eliminated from the brain by diffusion, increased levels of lac in two serial studies (Figure 4C) support the notion that the VOI included metabolically active cells. In another patient, sequential investigations showed decreased lac levels (Figure 2C), indicating that repeated examinations offer direct insight into the metabolic activity of surviving cells in cerebral infarction.

In this study we did not observe lac in chronic infarctions 8 months to several years after stroke, so the presence of lac contributes to the distinction between acute and chronic ischemic lesions. This is not contradictory to previous reports showing elevated lac levels in the time range of 8 days after transient ischemic attack\footnote{14} and as long as 3 months after stroke.\footnote{8} Magnetic resonance spectroscopy in these lesions was more sensitive than MRI and reflected ongoing metabolic alterations.

In vivo MRS presently does not provide quantification of metabolites because no external standard can be added to the examined tissue. Calculation of relaxation times in volunteers\footnote{15} is helpful in estimating saturation effects, but they may not exactly predict T1 and T2 relaxation changes in ischemic tissue if edema and microhemorrhage are present. Using assumptions that have recently been applied to a patient examined with proton MRS,\footnote{9} we found that lac concentrations ranged from 2 mmol to 30 mmol in our patients.

In conclusion, we have demonstrated an MRI/MRS protocol that can be used by physicians and is tolerable to patients. The combination of MRS and T2-weighted imaging is mandatory for accurate localization and interpretation of the spectra. We have shown that in vivo observation of Ch, Cr/PCr, NAA, and lac offers metabolic information for the differentiation between acute and chronic infarction as well as the normal brain.

References


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Stroke. 1992;23:1106-1110
doi: 10.1161/01.STR.23.8.1106

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

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http://stroke.ahajournals.org/content/23/8/1106

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