Magnetic Resonance Spectroscopy Study of Oxygen Therapy in Ischemic Stroke

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Background and Purpose—Recent studies suggest that normobaric oxygen therapy (NBO) is neuroprotective in acute ischemic stroke.1 In contrast to hyperbaric oxygenation, which has multiple molecular/biochemical effects, NBO’s mechanisms are relatively unknown. We investigated NBO’s metabolic effects on acutely ischemic brain tissues using multivoxel magnetic resonance spectroscopic imaging (MRSI) and diffusion-perfusion MRI (DWI and PWI).

Methods
MRSI was performed in seven patients; one data set was discarded due to poor coregistration and motion artifact. Analyzable data were obtained in 6 patients, including 5 consecutively enrolled in a pilot study of NBO in stroke.2 Detailed patient selection criteria are published;1 eligible patients were obtained in 6 patients, including 5 consecutively enrolled in a pilot study of NBO in stroke.2 Detailed patient selection criteria are published;1 eligible patients were obtained in 6 patients, including 5 consecutively enrolled in a pilot study of NBO in stroke.2 Detailed patient selection criteria are published;1 eligible patients were obtained in 6 patients, including 5 consecutively enrolled in a pilot study of NBO in stroke.2 Detailed patient selection criteria are published;1 eligible patients were obtained in 6 patients, including 5 consecutively enrolled in a pilot study of NBO in stroke.2 Detailed patient selection criteria are published;1 eligible patients were obtained in 6 patients, including 5 consecutively enrolled in a pilot study of NBO in stroke.2 Detailed patient selection criteria are published;1 eligible patients were obtained in 6 patients, including 5 consecutively enrolled in a pilot study of NBO in stroke.2 Detailed patient selection criteria are published;1 eligible patients were obtained in 6 patients, including 5 consecutively enrolled in a pilot study of NBO in stroke.2 Detailed patient selection criteria are published;1 eligible patients were obtained in 6 patients, including 5 consecutively enrolled in a pilot study of NBO in stroke.2 Detailed patient selection criteria are published;1 eligible patients were obtained in 6 patients, including 5 consecutively enrolled in a pilot study of NBO in stroke.2 Detailed patient selection criteria are published;1 eligible patients were obtained in 6 patients, including 5 consecutively enrolled in a pilot study of NBO in stroke.2 Detailed patient selection criteria are published;1 eligible patients were obtained in 6 patients, including 5 consecutively enrolled in a pilot study of NBO in stroke.2 Detailed patient selection criteria are published;1 eligible patients were obtained in 6 patients, including 5 consecutively enrolled in a pilot study of NBO in stroke.2 Detailed patient selection criteria are published;1 eligible patients were obtained in 6 patients, including 5 consecutively enrolled in a pilot study of NBO in stroke.2 Detailed patient selection criteria are published;1 eligible patients were obtained in 6 patients, including 5 consecutively enrolled in a pilot study of NBO in stroke.2

Results—Voxel-based analysis showed excellent correlation between apparent diffusion coefficient values, lactate, and N-acetyl-aspartate levels at all time points. Lactate decreased during NBO and increased post-NBO. N-acetyl-aspartate decreased in patients receiving room air but not in NBO-treated patients.

Conclusion—These data suggest that NBO improves aerobic metabolism and preserves neuronal integrity in the ischemic brain. (Stroke. 2007;38:2851-2854.)

Key Words: diffusion-weighted magnetic resonance imaging ■ neuroprotection ■ oxygen therapy ■ proton magnetic resonance spectroscopic imaging ■ stroke

The results of recent studies suggest that normobaric oxygen therapy (NBO) is neuroprotective in acute ischemic stroke.1 In contrast to hyperbaric oxygenation, which has multiple molecular/biochemical effects, NBO’s mechanisms are relatively unknown. We investigated NBO’s metabolic effects on acutely ischemic brain tissues using multivoxel magnetic resonance spectroscopic imaging (MRSI) and diffusion-perfusion MRI (DWI and PWI).

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Details of the DWI/PWI technique are published.1 MRSI was performed at the end of each serial imaging session, on an axial image coregistered to the DWI image showing the largest hyperintense lesion, using the PROBE-P sequence. MRSI grids were carefully placed to encompass DWI-bright, mismatch, and normal brain regions, avoiding cerebrospinal fluid spaces (Figure 1). Multivoxel spectra were acquired over 6.5 minutes with symmetric 220-mm field of view; 16×16 phase-encoding steps; 10-mm slice thickness; TR/TE=1500/135. DICOM and GE raw data were processed on a SUN-Blade100 workstation (Sun Microsystems) using the SAGE spectral analysis program (General Electric) for preprocessing, which includes 1.25-Hz spectral apodization, internal water-referencing, and spatial-zero-filling before Fourier transformation. Spatial-zero-filling resulted in 32×32 spectra yielding individual voxel sizes of 7×7×10 mm3 (0.5 mL).

Quantities of lactate (Lac), N-acetyl-aspartate (NAA), creatine, and choline-containing compounds were determined using the software package LCModel.2 Metabolites are reported with respect to the sum-of-all-metabolites (Sum). Data analysis was restricted to voxels in the ischemic hemisphere. Voxels with low signal-to-noise ratio, or contaminated by cerebrospinal fluid, were excluded. MRSI voxels were classified according to location as DWI-bright, mismatch, or normal. Co-registered images were used to generate a mean apparent diffusion coefficient (ADC) value for each MRSI voxel.

Analysis
Pearson correlation was used to determine the relationship between ADC and spectroscopic markers. Although we collected data on Lac/Sum, NAA/Sum, creatine/Sum and choline/Sum, analysis was restricted to Lac/Sum and NAA/Sum because these are more relevant to NBO’s effects. Temporal changes were determined using analysis of variance. Student or paired t tests were used for comparisons between time points. P<0.05 was considered statistically significant.
Results
We studied 4 NBO-treated patients (mean age 70±23 years) and 2 who received room air (control subjects, mean age 65±23 years). The median time interval from baseline to subsequent scans was similar (NBO, 4.6 hours and 24.7 hours; control subjects, 4.5 hours and 24.1 hours). At baseline, there was no significant difference in mean DWI lesion volumes (NBO, 42.5 mL, control subjects, 56.3 mL; \( P = 0.75 \)) or mean PWI lesion volumes (NBO, 200 mL, control subjects, 213 mL; \( P = 0.9 \)). Median National Institutes of Health Scale scores changed from baseline to 4 hours to 24 hours as follows: NBO group, 16 to 12 to 13.5; control subjects, 17.5 to 19.5 to 19.5. Reperfusion (>50% reduction in PWI lesion volume\(^1\)) occurred by 4 hours in one control subject and by 24 hours in 2 NBO patients.

At baseline, voxel-by-voxel analysis showed significant correlation between ADC and NAA/Sum (\( R = 0.68, P < 0.001 \)) and Lac/Sum (\( R = -0.69, P < 0.001 \)). These correlations remained significant (\( P < 0.001 \)) at 4 hours (ADC versus NAA/Sum, \( R = 0.42 \); versus Lac/Sum, \( R = -0.46 \)) and at 24 hours (ADC versus NAA/Sum, \( R = 0.54 \); versus Lac/Sum, \( R = -0.66 \)). In addition, we calculated the average of all within-subject voxels and correlated mean values. Despite small patient numbers, there was excellent correlation (Figure 2) between mean ADC and MRSI markers at baseline (ADC versus NAA/Sum, \( R = 0.90, P = 0.015 \); ADC versus Lac/Sum, \( R = -0.88, P = 0.021 \)). These correlations persisted at 4 hours (ADC versus NAA/Sum, \( R = 0.85, P = 0.033 \); ADC versus Lac/Sum, \( R = -0.84, P = 0.037 \)) and tended to correlate at 24 hours (ADC versus NAA/Sum, \( R = 0.77, P = 0.07 \); ADC versus Lac/Sum, \( R = -0.81, P = 0.048 \)).

On qualitative MRSI maps, lactate was observed predominantly within DWI-bright regions, although some lactate was also observed in mismatch regions. Changes in lactate paral-

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**Figure 1.** Top, DWI MRI, mean transit-time map, and MRSI grid overlaid on coregistered DWI. MRSI voxels are classified as DWI-bright (pink), mismatch (blue), or normal. Bottom, Representative spectra from the red-highlighted MRSI voxel classified as DWI-bright.

**Figure 2.** Correlation between ADC and Lac/Sum and NAA/Sum levels at baseline.
leled the changes in DWI lesion size. Temporal changes in mean Lac/Sum values and mean NAA/Sum values in both groups are depicted in Figure 3. Although these changes proved significant (analysis of variance) when individual voxels were treated as independent, these changes were not statistically significant when within-subject voxels were averaged, likely because of the small patient numbers. Nevertheless, subject-level changes and changes within different brain regions were meaningful. Both control subjects showed progressive increases in Lac/Sum and decreases in NAA/Sum; the changes were greater in DWI-bright as compared with mismatch regions. In all NBO-patients, mean Lac/Sum decreased during therapy and further decreased posttherapy in the 2 patients with reperfusion, suggesting that NBO’s beneficial effects may not be sustainable with persistent hypoperfusion. NAA/Sum did not decline in NBO-treated patients (change from pre- to post-therapy was +1% in the NBO group; −25% in control subjects).

The change in mean Lac/Sum from baseline to 4 hours (during therapy) tended to be different ($P=0.09$) between NBO and control groups and occurred mainly in DWI-bright regions ($P=0.058$) rather than mismatch regions ($P=0.43$). The change in mean NAA/Sum from baseline to 4 hours was significantly different ($P=0.049$) between NBO and control groups and occurred mainly in DWI-bright regions ($P=0.046$) rather than mismatch regions ($P=0.47$).

Figure 3. Top, Qualitative maps showing serial lactate changes. Bottom, Temporal changes in lactate and NAA in control and NBO groups.
Discussion
Monitoring signal levels of Lac and NAA by MRSI provides important information about the state of acutely ischemic brain tissues and may be useful in assessing prognosis. This first study of serial multivoxel MRSI with DWI/PWI in hyperacute ischemic stroke provides important insights into the temporal evolution and correlation of ADC and MRSI markers. MRSI marker levels correlated strongly with ADC values at multiple time points after stroke, extending previous observations and demonstrating that DWI abnormalities reflect disturbed cerebral metabolism.

Our primary objective was to investigate NBO’s metabolic effects. We found that NBO reduced brain lactate and preserved NAA (a marker of neuronal integrity and mitochondrial function), suggesting that NBO improves aerobic metabolism and restores mitochondrial function either from direct effects on tissue oxygenation or indirectly from alterations in cerebral hemodynamics. The control group data are consistent with previous studies showing increased lactate with reduced NAA in T2-hyperintense infarcted regions and increased lactate with normal NAA in perifarct regions. Furthermore, the observed abnormalities in lactate and NAA in mismatch regions are consistent with published data showing increased lactate and reduced NAA outside ADC or DWI lesion boundaries, including in the early stages after stroke.

The small number of patients is a limitation of our study. A major strength, however, is that each patient was carefully studied with 3 parameters of stroke-related injury (MRSI markers, DWI abnormalities, National Institutes of Health Stroke Scale scores), each measured before, during, and after therapy. All 3 parameters improved during NBO and worsened after NBO. These preliminary results strengthen our contention that NBO, by resuscitating acutely ischemic tissues, may be useful in extending the narrow time window for stroke thrombolysis.

Acknowledgments
We thank Vallent Lee for his help with data analysis. We are grateful to Eng Lo, PhD, F. S. Buonanno, MD, and our residents, fellows, nurses, and MRI technicians for their assistance with this study.

Sources of Funding
Supported in part by NIH grants R01 NS38477 (A.G.S.), R01 NS051412 (A.B.S.), P50 NS051343 (W.J.K.), and R01 NS050041 (R.G.G.).

Disclosures
None.

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Stroke. 2007;38:2851-2854; originally published online August 30, 2007;
doi: 10.1161/STROKEAHA.107.487280
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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