Normobaric Hyperoxia Therapy in Acute Ischemic Stroke: Serial Multivoxel MR Spectroscopy and Diffusion/Perfusion MRI

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Introduction: In animal studies of transient focal cerebral ischemia, we and others have shown that 100% oxygen delivered at normal atmospheric pressures (normobaric hyperoxia, NBO) attenuates 48-hour infarct volumes, improves diffusion- and perfusion-MRI (DWI and PWI) parameters of ischemia, and improves neurobehavioral deficits [1-3]. In this pilot human study, we randomized patients with acute (<12 hr) hemispheric ischemic stroke and baseline NIHSS score ≥4, to 8-hr NBO or room air (Controls). Serial DWI/PWI and multivoxel 2D MR-spectroscopic imaging (MRSI) were performed at baseline, 4 hrs (during therapy), and 24 hrs. Preliminary results indicate that NBO transiently improves NIHSS scores, attenuates DWI lesion size, and results in a significantly higher percentage of apparent diffusion coefficient (ADC) voxels showing improvement from 'ischemic' baseline values to 'non-ischemic' values [4]. The objective of the present analysis was to (a) assess whether MRSI parameters improve with NBO, and (b) assess the correlation between ADC and MRSI parameters at baseline, 4 hrs and 24 hrs, in NBO and Control groups.

Methods: DWI images were acquired with FOV 220 mm, 23 slices, thickness 6 mm, gap 1 mm, TR 7.5 s, TE 99 ms, acquisition matrix 128x128, with both *b* 0 s/mm^2 and *b* 1,000 s/mm^2 in 6 diffusion gradient directions, number of averages 3. Isotropic DWI and ADC images were automatically calculated. MRSI was performed with FOV 220 mm, 16x16 phase encoding steps, thickness 10 mm, TE 135 ms, TR 1500 ms. Spectra were processed off-line using the SAGE spectral analysis program to determine quantities of the brain metabolites lactate (Lac), N-acetylaspartate (NAA), creatine (Cr), and choline-containing compounds (Cho). The data matrix was interpolated to 32x32 spectra yielding individual voxel sizes of 7x7x10 mm^3. The same MRS axial slice was selected to generate mean ADC values in corresponding 32x32 voxels. All data analysis was restricted to voxels within hypoperfused regions (identified on PWI). Voxels were further grouped into those lying within visibly DWI-bright regions, or DWI-normal regions. We excluded voxels within ventricles and CSF spaces, or whose MR spectra showed poor signal-to-noise ratio.

Results: Complete data was available in 5 patients (3 NBO, 2 Controls). None received thrombolysis. No patient showed spontaneous reperfusion between baseline and 4 hrs; 2 NBO-patients reperfused between 4 hrs and 24 hrs. As compared to DWI-normal regions, voxels within DWI-bright regions showed increased Lac/NAA ($p<0.001$) and Lac/Cr ($p<0.0001$), decreased NAA/Cr ($p<0.0001$), and no significant difference in Cho/Cr ratios.

(a) Effect of NBO on MRSI: *In DWI-bright regions (Fig. 1)*, NBO therapy resulted in a significant decrease in Lac/NAA (ANOVA, p=0.006 across time points); this decrease was significant from baseline to 4 hrs as well as from baseline to 24 hrs (the latter perhaps related to the combined effect of NBO and spontaneous reperfusion). In contrast, the Control group showed significant increase in Lac/NAA (p=0.008) and Lac/Cr ($p<0.0001$), whereas NAA/Cr tended to decrease (p=0.05) from baseline until 24 hours. *In DWI-normal regions*, no significant changes were observed with NBO therapy for Lac/NAA or Lac/Cr, however, NAA/Cr increased significantly (ANOVA, p=0.006) from baseline until 24 hours.

(b) ADC and MRSI correlations: Spearman Rank correlation analysis was performed for pooled data across all patients at baseline (pre-therapy). There was a negative relationship between ADC values and Lac/NAA (R_s -0.70, $p<0.0001$), Lac/Cr (R_s -0.66, $p<0.0001$), and Cho/Cr (R_s=-0.20, p=0.05). There was a positive correlation between ADC and NAA/Cr (R_s=-0.20, p=0.05). Further studies are ongoing to assess whether or not these correlations change significantly with therapy and over time.

Conclusion: These preliminary data suggest that (1) there are differences in metabolic markers of ischemia measured by MRSI, between hypoperfused brain regions that are DWI-bright (severely ischemic) and DWI-normal. (2) in patients with acute ischemic stroke, early NBO therapy appears to improve brain lactate and NAA within DWI-bright regions. (3) there appears to be a correlation between ADC and MRSI parameters within early time points (less than 12 hours) after stroke symptom onset. Further studies are ongoing to validate these results.

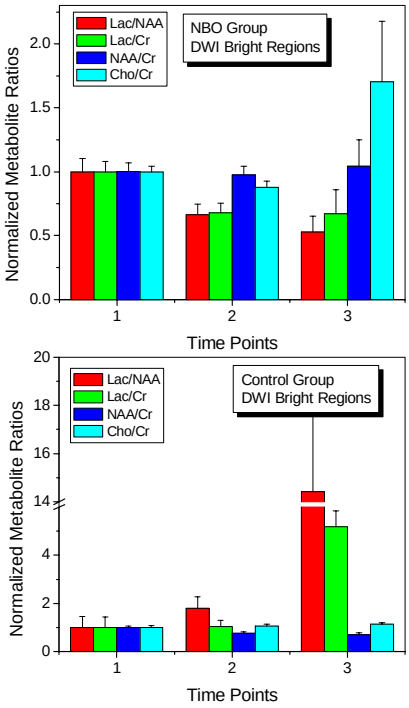

Fig.1: Metabolite ratios measured in the DWI bright regions at different time points. 1: baseline scan; 2: 4 hours later (during therapy in NBO group); and 3: 24 hours later

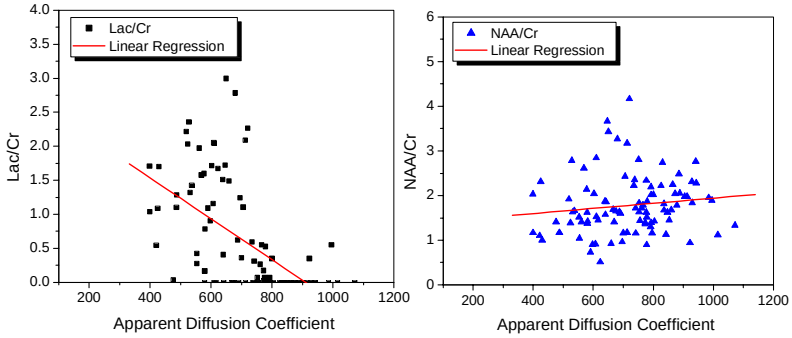

Fig. 2: Spearman Rank correlation analysis between ADC values Lac/Cr and NAA/Cr.

References: [1] Singhal et al. Normobaric hyperoxia reverses MRI diffusion abnormalities and reduces infarct size in experimental stroke. *Neurology* 2002;58:945-52. **[2]** Singhal et al. Effects of normobaric hyperoxia in a rat model of focal cerebral ischemia-reperfusion. *J Cereb Blood Flow Metab* 2002;7:861-8. **[3]** Flynn et al. Eubaric hyperoxemia and experimental cerebral infarction. Ann Neurol 2202;52:566-72. **[4]** Singhal et al. NBO Therapy in Hyperacute Human Stroke: attenuation of DWI abnormalities and improved NIHSS scores. Stroke 2004;35(1):293(P210).