Venous Oxygenation Mapping in Multiple Sclerosis: A Longitudinal Study

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Introduction: Non-invasive measurement of cerebral venous oxygenation (Yv) helps us in understanding the brain oxygen metabolism in normal and pathological brains. Lu *et al*[1] developed a novel T2-relaxation-under-spin-tagging imaging (TRUST) technique to quantitatively estimate Yv via the measurement of pure blood T2-relaxation time in the lower superior sagittal sinus (a major draining vein). Using positron emission tomography (PET) with a specific tracer of ^{15}O, Sun *et al* [2] demonstrated hypometabolism in both gray matter and white matter regions of MS patients. In a recent study, Ge *et al*[3] observed significant elevated Yv in MS patients compared to healthy subjects, also suggesting considerably reduced oxygen consumption in MS. However, to our knowledge, a longitudinal study evaluating the changes in Yv has not been reported. Therefore, in the present study, we sought to determine the longitudinal changes in Yv using TRUST MRI in MS patients.

Methods: A total of 21 healthy subjects and age matched 17 patients with clinical definite MS (with sporadic episodes of attacks) were recruited and followed-up in this study. All MS patients underwent two scans at 3T MRI system at an interval of approximately 2 years. Axial TRUST slices on sagittal sinus were acquired using single-shot echo planar imaging sequence with the following parameters: TR/TE = 8000/19ms, voxel size = 3.44×3.44×5mm^3, inversion time= 1200ms, tagging slab thickness = 80mm, gap between imaging slab and tagging slab = 20mm as shown in **Fig. 1a** with four different T2-weightings (eTE of 0ms, 40ms, 80ms and 160ms), corresponding to 0, 4, 8 and 16 refocusing pulses in the T2-preparation (τCPMG =10 ms). For each eTE, four pairs of tag and control images were acquired to improve SNR. Data were processed using in-house MATLAB scripts.[1] After pair-wise subtraction between control and tag images, a preliminary ROI was manually drawn on sagittal sinus. Four voxels with highest blood signals in the ROI were chosen as the final mask for spatial averaging (**Fig. 1b**). The venous blood signals were fitted to a mono-exponential function to obtain T2 (**Fig. 1c**). The T2 values were converted to venous oxygenation via a well-established calibration plot [1] for each subject. The T2 and Yv were compared between controls and MS patients. Two tailed paired t-tests were performed to evaluate the changes in the Yv between the baseline and follow-up periods in MS patients.

Results: Compared to healthy controls, MS patients at baseline showed significantly elevations in CPMG T2 (68.24±10.64ms vs 59.65±7.13ms, p=0.01) and Yv (62.1±6.25% vs 58.2±4.08%, p=0.03). Compared to baseline, MS patients showed a significant increase in CPMG T2 at approximately 2-year follow-up time point (68.24±10.64ms vs. 95.46±18.46ms, p<0.001). Similarly, a significant increase in Yv was also observed at follow-up (62.1±6.25% vs. 74.82±6.51%, p<0.001) in MS patients (**Fig. 2**).

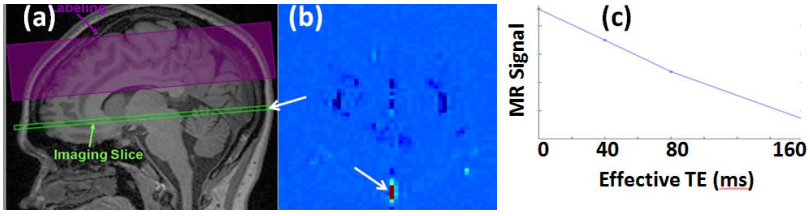

Figure 1. Geometric relationship between the imaging slice (green) and the labeling slab (purple) (a). From lower superior sagittal sinus (arrow), 4 voxels containing the largest difference signals in the eTE=0 image were selected as the mask to compute T2 (b). The signals were fitted to a monoexponential function (c).

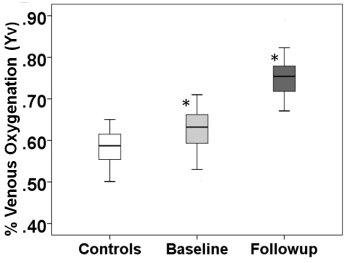

Figure 2. Box and whisker plots demonstrating the variation in Yv from controls and from MS patients at two time points. There was significant higher Yv in MS patients than in controls. Significant elevation in Yv was observed at follow-up period in MS patients. * indicates significant difference (p <0.05).

Discussion and Conclusion: The non-invasive TRUST technique provides a sensitive global measurement for assessing longitudinal variation in oxygen metabolism in patients with MS. Our results suggest that MS patients consume less oxygen content and this oxygen underutilization becomes more prominent with disease progression. Several biochemical studies have shown higher level of nitric oxide (NO) secondary to microvascular inflammation.[4] The increased NO competitively inhibits the binding of oxygen to respiratory complex (cytochrome C oxidase) and inhibits cell respiratory chain function in mitochondria.[5] As a result, histo-toxic hypoxia may develop in which condition even though O2 might be available, but cells and tissues are unable to use it. This impairment of oxygen consumption in MS may have a profound impact on the underlying mechanism of progressive neurodegeneration that is associated with neuronal tissue cellular energy failure.

References: **1.** Lu H. Magn Reson Med. 2008;60:357-63.**2.** Sun X. Ann Nucl Med. 1998;12:89-94.**3.** Ge Y. J Cereb Blood Flow Metab. 2012;32:403-12. **4.** Aboul-Enein F.Acta Neuropathol 2005.109:49-55. **5.** Encinas JM. Curr Neurol Neurosci Rep 2005; 5: 232-8.

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