Decreased Brain Oxygen Metabolism in Multiple Sclerosis Measured with T2-Relaxation-Under-Spin-Tagging (TRUST) MRI

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Introduction: In multiple sclerosis (MS), mitochondrial ATP production has been shown to be compromised by impaired oxygen uptake due to increased nitric oxide (1) and this mitochondrial hypothesis may have a crucial role in progressive neurodegeneration of the disease. In this study, we have investigated whether there is decreased oxygen metabolism in MS using T2-relaxation-under-spin-tagging (TRUST) MRI (2), which measures the venous sinus blood oxygenation (Yv) and cerebral metabolic rate of oxygen (CMRO2), an index of global oxygen consumption. We have also correlated the changes of oxygen metabolism with brain atrophy, lesion load, and clinical disability in MS.

Methods: Thirty patients (mean age: 38.8, 22~60 years) with relapsing-remitting MS and 30 healthy volunteers (mean age: 37, 20~59 years) were studied at 3T Siemens Tim Trio MR. The mean disease duration for the patient group was 4.8 years (8~167 months) and the mean expanded disability status scale (EDSS) score was 2.3 (range 0~5.5). Routine conventional MRI including T1- and T2-weighted imaging as well as 3D MPRAGE imaging was performed. TRUST MRI was performed in a transverse plane and going through the lower superior sagittal sinus (just above the level of confluence of sinuses) (*Fig 1a*) and it includes labeled (to magnetically tag the venous blood) and control scans acquired at different eTEs for different T2-weightings. The specific imaging parameters of TRUST were as follows: TR/TE/TI=8000/19/1200ms, FOV=230×230mm, matrix=64×64, single-shot EPI, slice thickness=5 mm, four eTEs: 0 ms, 40 ms, 80 ms, and 160 ms. The acquisition time for TRUST is 4 mins & 16 sec. The preprocessing includes pair-wise subtraction to ensure that only blood signal draining into the superior sagittal venous sinus was shown and quantified for T2. Venous blood oxygen saturation (Yv) was computed based on a direct and well-established relationship between T2 and Yv (3,4). Among all subjects, 12 patients and 12 controls also had global cerebral blood flow (CBF) measures in order to calculate CMRO2 using the following equation: $CMRO2=CBF\cdot(Ya-Yv)\cdot Ca$, where arterial oxygen saturation (Ya) was determined by pulse oximetry and Ca is the amount of oxygen molecules that a unit volume of blood can carry, and is well established in hematology literature (5). OEF was also calculated from Ya-Yv. The global CBF (in umol/100g/min) was measured with single slice phase-contrast MRI *(Fig 1b)* using TOF images *(Fig 1c)* as positioning reference to calculate total blood flow from all four feeding arteries (internal carotid and vertebral) *(Fig 1b)* and normalized by total brain parenchyma volume. The imaging parameters and data post-processing procedures for Yv and CMRO2 from TRUST MRI were described in elsewhere [2,6].

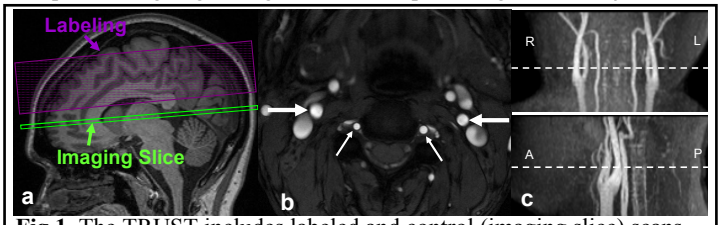

Fig 1. The TRUST includes labeled and control (imaging slice) scans acquired at different eTEs for Yv calculation (a). Phase-contrast MRI (b) was positioned using neck TOF images (c) as reference to calculate the total blood flow of brain based on the bilateral internal carotid arteries (thick arrows) and vertebral arteries (thin arrows) .

Results: *Table 1* showed the comparison of quantitative measurements of T2, Yv, OEF, BPF, global CBF, and CMRO2 in patients and controls. The heart rate, blood pressure, and hematocrit level were all within normal range in patients. There was significantly higher T2 and Yv and lower OEF and CMRO2 in patients compared to age-matched normal controls, suggesting significantly reduced oxygen metabolism or utilization in MS. There was no significant difference of global brain CBF between patients and controls (n=12). There was a positive correlation between Yv and EDSS (n=30, r=0.54, P=0.002) and between Yv and the total lesion volume (n=30, r=0.40, P=0.03). We also found a negative correlation between CMRO2 and EDSS (n=12, r=-0.61, P=0.03) *(Fig 2a)* and between CMRO2 and lesion load (n=12, r= -0.74, P=0.005) *(Fig 2b)*, indicating that patients with higher venous oxygenation level or lower oxygen consumption tend to have higher EDSS and lesion load. There was a significant difference (P=0.03) reduced brain parenchyma fraction (BPF) between patients and controls, implying there is general brain atrophy in MS patients. We did not find any statistical significant correlations between either Yv or CMRO2 with atrophic measures (i.e. BPF) or disease duration.

Table 1: Comparison between MS patients and normal controls

Measurement	Controls	MS Patients	P Value
T2 (ms)	60.1 ± 6.7	71.5 ± 10.3	P < 0.0001
Yv (%)	60.2 ± 4.0	65.9 ± 5.1	P < 0.0001
OEF (%)	37.3 ± 7.4	32.2 ± 5.4	P = 0.0001
BPF (%)	82.8 ± 2.4	81.0 ± 3.4	P = 0.03
Global CBF (ml/min/100g)*	61.1 ± 5.8	57.7 ± 12.9	P = 0.42
CMRO2 (μmol/100g/min)*	180.2 ± 24.8	138.8 ± 35.4	P = 0.003

* The measurements were made in a subgroup (n=12) of patients and controls

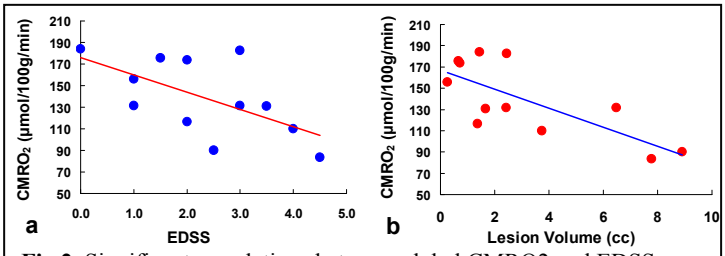

Fig 2. Significant correlations between global CMRO2 and EDSS (R= -0.61, p=0.002) (a) and between CMRO2 and lesion load (r= -0.74, p=0.005) (b) in patients with MS (n=12).

Discussion: The TRUST method presented in this study provides a sensitive global measure for quantifying global oxygen consumption in patients with MS. The results of this study highlighted in vivo the impairment of oxygen consumption in MS, which is correlated with clinical disability and lesion load, but not with brain atrophy. These preliminary results may have a profound impact on the underlying mechanism of progressive neurodegeneration that is associated with tissue cellular energy failure.

References: (1). Encinas JM et al. 2005. Curr Neurol Neurosci Rep 2005:5:232. (2). Lu H and Ge, Y, Magn Reson Med 2008; 60:357-363. (3). Wright GA, et al. J Magn Reson Imaging 1991; 1:275-283. (4). Golay X. et al. Magn Reson Med 2001; 46:282-291. (5) Guyton AC, 2005; Textbook of Medical Physiology. 6. Xu F et al. Magn Reson Med 2009:62:141-148.

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