Impaired regulation of the blood supply to the brain in multiple sclerosis measured with hypercapnia BOLD MRI

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PURPOSE: Normal neuronal activity is tightly linked to and critically depends on the increase of blood flow for instantaneous supply of oxygen and glucose to the brain. In multiple sclerosis (MS), studies have shown elevated nitric oxide (NO), which is a strong mediator of neurovascular coupling[1] that is responsible for increased blood supply during transient neural activation. Such chronically high NO secondary to repetitive pro-inflammatory cascades [2] in MS may have detrimental effect on brain vascular health (our hypothesis). This study is to investigate whether there is cerebrovascular reactivity (CVR) impairment in MS using mild hypercapnia (by breathing 5% CO_2, another vasodilator) blood oxygen-level dependent (BOLD) MRI [3].

MATERIALS AND METHODS: Fourteen patients with MS (12 relapsing remitting [RR] and 2 secondary progressive [SP] (mean age: 44.0±11.6 years for RRMS and 63.5±2.1 for SPMS) and 16 healthy controls (mean age: 38.3±13.0 years) were recruited for this study. CO_2 is a potent vasodilator, by alternating the inhaled gas between room-air and mild hypercapnia (mixed 5%CO_2, 21%O_2, and 74%N_2) expose, one can modulate blood flow to the brain with resultant BOLD signal changes, similar to a block-design fMRI experiment. The hypercapnia experiment used a standard single-shot EPI BOLD sequence (TR/TE/flip angle =3000ms/30 ms/90º) at 3T MR with a 12-channel array head coil. The scan lasted for 7min32sec in which 140 brain volumes were acquired. The CO_2/air breathing paradigm included 1-min room air breathing interleaved with 1-min CO_2 breathing, repeated three times, Figure 1 showed the hypercapnia apparatus with 5% CO_2 contained within a Douglas bag and delivered to the subject through a two-way non-rebreathing valve and mouthpiece combination. End-tidal CO_2 ($EtCO_2$) was recorded continuously during the scan with a capnograph device and was used as an input function in the analysis. In addition, breath and heart rate, and arterial oxygenation saturation SpO2 are recorded continuously on a laptop. For CVR calculation, post-processing module provided by SPM was used to perform standard voxel-by-voxel GLM analysis on the BOLD images [3]. The CVR (with unit of %BOLD signal change/mmHg $EtCO_2$ change) is estimated [2]. Both regional and whole brain gray matter (GM) CVR were computed for group comparison.

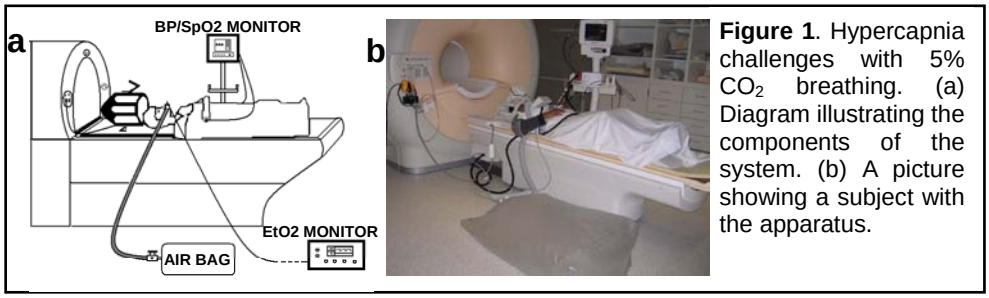

Figure 1. Hypercapnia challenges with 5% CO_2 breathing. (a) Diagram illustrating the components of the system. (b) A picture showing a subject with the apparatus.

RESULTS: As shown in Figure 2, the linear regression between input ($EtCO_2$) and output (BOLD time course) in healthy brains (n=9), which are nicely corresponded to each other, would allow the determination of the CVR with GLM model analysis. There was significantly decreased global GM with averaged CVR of 0.18% (SD: 0.01%) (%BOLD signal change/mmHg $EtCO_2$ change) in patient group as compared to 0.23% (SD: 0.01%) in healthy control group (P=0.008) (Figure 3). Figure 4 showed a representative example of CVR map in a 24-year-old female healthy control and a 23-year-old female RRMS patient, showing reduced CVR in most of brain regions, more pronounced in the frontal and right parietal lobes.

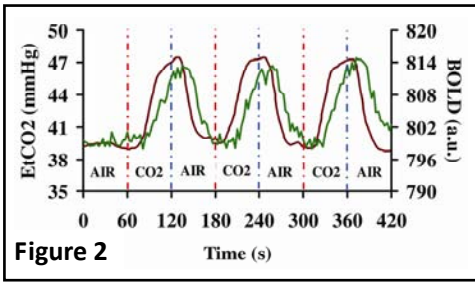

Figure 2

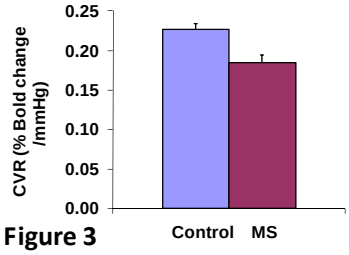

Figure 3

Figure 2.Time course of $EtCO_2$ (red curve) and BOLD (green) response in the healthy brain, showing BOLD response corresponding to $EtCO_2$ waveform, the lags (due to the delay time for blood to travel from lung to brain) can be easily corrected.

Figure 3. Group comparison of CVR (%BOLD signal change/mmHg EtCO2) in patients and controls, showing significantly decreased CVR in patient group (P=0.008).

CONCLUSIONS: The findings of significant decrease of CVR in MS patients suggest an impaired vascular regulation of blood flow supply or defective neurocoupling mechanism, which may affect effective oxygen delivery particularly to the previously healthy and normal neurons and lead to neurodegeneration over time. This is likely due to the chronic presence of a tonically high NO level [4] (even during resting) that desensitizes the vascular smooth muscle with a consequence of decreased CVR and limited blood supply when neurons perform a demanding task (i.e. activity induced hypoxia). These observations may potentially enhance our understanding of the disease pathogenesis/progression regarding neurodegenerative process that is associated with NO hypothesis in MS.

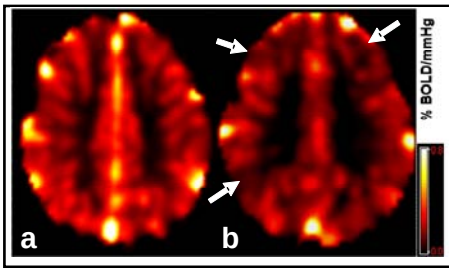

Figure 4. Global GM CVR maps in a RRMS patient (a) and a healthy control (b) showed decreased CVR in different brain regions such as frontal and parietal lobes (arrows).

References: *1.*Iadecola C. Trends Neurosci 1993; *2.* Smith KJ, Lancet Neuro 2002; *3.* Yezhuvath US et al. NMR Biomed 2009; *4*. Encinas JM, et al. Curr Neuro Neurosci Rep 2005.

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