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\(_2\)) exposure, 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/90\(^\circ\)) 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 SpO\(_2\) 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.

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 brain regions, more pronounced in the frontal and right parietal lobes.

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.


Acknowledgement: This study was supported by R01 grants NS076588, NS029029, and NS067015 from National Institute of Health (NIH) as well as Research Grant from National Multiple Sclerosis Society (NMSS).