Cerebrovascular reactivity defect in multiple sclerosis

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Purpose: One of the emerging techniques for mapping cerebrovascular reactivity (CVR), which represents potential vascular capacity of regulating cerebral blood flow (CBF) supply, is hypercapnia perfusion MRI [1] with breathing 5% CO_2 as a vascular dilatory stimulus. CVR is an important mechanism for maintaining constant CBF of brain, and the impaired CVR, if exists, may contribute to cellular respiration failure and neurodegenerative processes. Multiple sclerosis (MS) is an inflammatory demyelinating disease with devastating progressive neurodegeneration of poorly understood etiology. In this study, we used psudo-continuous arterial spin labeling (pCASL) [2] to detect whether there is CVR impairment, which might be responsible for neurodegenerative process, in patients with MS during hypercapnia challenge.

Materials and Methods: Nineteen patients with relapsing remitting (RR) MS (9 males and 10 females; mean age, 44.4 years; range, 23 to 65 years) and 19 healthy volunteers (12 males and 7 females; mean age, 40.1 years; range, 20 to 65 years) were studied. Patients with cardiac, pulmonary, and hematologic diseases were excluded and no caffeine was taken within 4 hours prior to MRI in all subjects. The mean disease duration for the patient group was 5.1 years (range 0.67-14 years) and the mean EDSS score was 2.5 (range 0-6). MR imaging was performed on a 3.0T whole body MR scanner with a 12-channel array head coil. CVR was measured with a robust multi-slice pCASL MRI [2] with quantitative CBF (ml/min/100g) maps generated during both room air (baseline) and mild hypercapnia (mixed 5%CO_2, 21%O_2, and 74%N_2) exposure. The following parameters of pCASL were used: TR/TE=3950/17ms, 52 repetitions (i.e. 26 pairs of tag and control images), FOV=22cm, in-plane matrix=64x64, slice thickness=5mm and total axial slices of 32, gradient echo EPI readout, slice-selective gradient=8mT/m, postlabeling delay = 1230ms, label offset = 89mm. The pCASL acquisition time is 3min15sec. End-tidal CO_2 ($EtCO_2$) was recorded continuously during the scan using a capnograph device as an input function. After performing motion correction for the label and control image series separately, CBF calibration was conducted using the standard equation [2]. The CVR (in %CBF/mmHg $EtCO_2$) is calculated of percentage change of CBF per unit of $EtCO_2$ change reflecting the difference between the average recordings of $EtCO_2$ of mild hypercapnia and room air. CVR was computed and compared between patients and controls from global brain parenchyma, gray matter (GM), normal appearing white matter (NAWM), and lesions.

Results: Compared to healthy controls, RR-MS patients showed significantly decreased CVR (%CBF change/mmHg EtCO2) (Figure 1) of whole brain parenchyma (mean: 5.2%±0.6% vs 2.8%±0.5%, P=0.01), global GM (5.3%±0.9% vs 3.1%±0.4%, P=0.01), and global NAWM (5.3%±0.7% vs 3.4%±0.5%, P=0.02) without significant difference of baseline CBF between the two groups. In controls, the mean global GM CBF at baseline and mild hypercapnia were 67.7±9.1 and 98.6±17.9 ml/100g/min, respectively (Figure 2a and 2b). While in patients, the mean of baseline and hypercapnia CBF were 70.6±9.8 and 84.5±12.5 ml/100g/min, respectively (Fig 2c and 2d). There was no significant difference of CBF change in lesions, indicating the normal CVR loss.

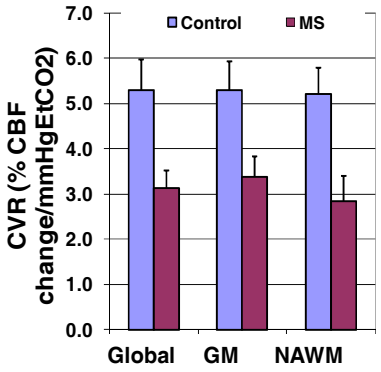

Figure 1. Comparison results of cerebrovascular reactivity or CVR (%CBF change/mmHg EtCO2) based on hypercapnia perfusion MRI between patient and control groups showed significantly reduced CVR in patients of whole brain parenchyma (P=0.01), GM (p=0.01), and NAWM (P=0.02), indicating global defect of blood flow regulation to a vasodilatory stimulus (i.e. 5% CO_2).

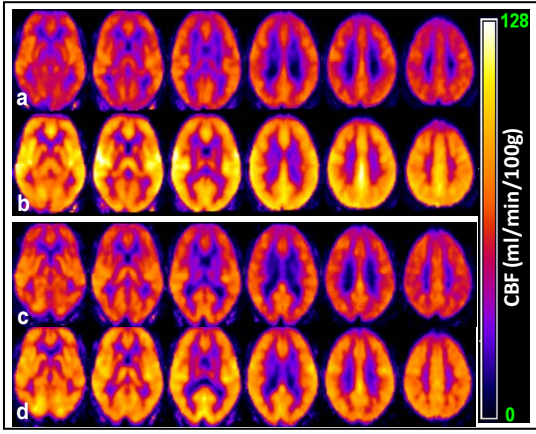

Figure 2. Voxe-by-voxel whole brain CBF maps in controls (a,b) and patients (c,d) at baseline (a,c) and hypercapnia (b,d). The increase of global GM CBF in controls (b vs a) is significantly larger than that in patients (d vs c) (P=0.01), indicating the diffuse defect of CVR in MS.

Conclusions: This is the first study to measure CVR abnormalities in MS. The preliminary data, which showed significant decrease of average global CVR in MS patients compared to controls using pCASL hypercapnia technique, indicate impaired vascular reactivity or response to CO_2. This defect may disturb effective oxygen delivery in MS particularly to the previously active and healthy neurons when increased oxygen demand occurs (i.e. neuronal activity-induced hypoxia), leading to neurodegeneration over time. The impaired CVR is likely due to the vascular habituation effects from chronic and excessive high level of nitric oxide (another potent vasodilator) secondary to repetitive inflammatory activities in MS [3]. These observations may point to a new research target of the link between neuroinflammation and neurodegeneration of this chronic and progressive disease.

References: 1. Aslan S & Lu H. MRM 2010; *2.* Wu WC et al. MRM 2007; 3. Smith KJ & Lassmann H. Lancet Neurol 2002.

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