Impaired Cerebrovascular Reactivity (CVR) in MS Measured with Hypercapnia Perfusion MRI

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PURPOSE: The decreased ability of cerebral blood flow (CBF) modulation in cerebral cortex, secondary to overproduced NO, might be an underlying cause of accumulation of diffuse neuronal/axonal loss and progressive neurological deficits in multiple sclerosis (MS) [1]. CO_2 is a potent vasodilator, and an increase of CO_2 tension in blood (referred as hypercapnia) is known to cause CBF increase. Such hemodynamic changes called cerebral vascular reactivity (CVR) can be measured with arterial spin labeling (ASL) MRI [2]. The objective of this study was to investigate whether there is CVR impairment in MS patients and whether this correlates with lesion load and brain volume change.

MATERIALS AND METHODS: Twenty-one patients with clinically definite relapsing-remitting MS (mean age: 45.86 ± 13.26 years; average EDSS of 2.47) and 20 demographically-similar healthy volunteers (mean age: 39.46 ± 4.37 years) were recruited. MRI imaging was performed on a 3T whole-body MR scanner (Siemens Magnetom Tim Trio; Siemens Healthcare, Erlangen, Germany) using a 12-channel head coil. The quantitative CBF (ml/min/100g) maps were obtained during both room air and hypercapnia (mixed 5%CO_2, 21%O_2, and 74%N_2) exposure conditions with a standard pseudo-continuous ASL (pCASL) sequence [3]. The imaging parameters of pCASL include TR/TE = 3950/17ms, 52 repetitions, FOV=22cm, in-plane matrix =64x64, slice thickness=5mm, postlabeling delay=1230ms, and label location= 89mm below AC-PC line; with 24 slices were collected parallel to the AC-PC line and positioned to cover the entire cerebrum. The balanced labeling method was implemented with mean Gz of 0.6 mT/m and 82 RF blocks (RF GAP=360 µs) for a total labeling duration of 1.47 seconds. The end-tidal CO_2 (EtCO2) of each subject was monitored with a capnograph device; and the second pCASL with CO2 challenge started after the increased EtCO2 reached an equilibrium. $EtCO_2$ was recorded continuously during the scan and was used as a normalization function in the analysis. The CVR was calculated as percentage change in CBF comparing CO_2 inhalation to room-air breathing normalized by changes of EtCO2 ($\Delta EtCO_2$) (%/mmHg). Segmented whole brain grey matter (GM), white matter (WM), and brain parenchymal (global) CVR were quantified. In addition, global cerebral metabolic rate of oxygen (CMRO2), phase-contrast (PC) based CBF and routine T1-, T2-based lesion detection imaging were implemented and analyzed with in-house software [4]. Five hemodynamic imaging features (baseline CBF, hypercapnia CBF, CVR, CMRO2 and PC-CBF) were used to classify MS patients from controls.

RESULTS: At baseline there was significant correlation (r=0.55, P=0.0002) between the CBF measured with ASL and CBF with phase-contrast. And there were significant increases of CBF with CO2 challenge in both groups; and the percentage change of CBF at hypercapnia compared to room air was correlated significantly with the EtCO2 pressure in control group. The global CVR showed a significantly reduction (40%) in MS patients (3.12±0.52 %/mmHg) compared to control (5.16±0.56 %/mmHg) group (P=0.01). The CVR was not statistically different between GM and WM within each group (P>0.7); but CVR was reduced significantly in both WM (P=0.027) and GM (P=0.04) in MS patients compared to controls. The CBF map and CVR changes with different types of lesions were demonstrated in *Figure 1*. As expected as a loss of vasoreactivity, the average CVR of WM lesions from all patients is 0.03%/mmHg, close to zero. The combination of all five hemodynamic measurements could achieve 98% of classification accuracy using the All-Dimensional (AD) tree classifier; with global CVR (together with CMRO2) as the most essential imaging feature among all five measurements for differentiating MS patients from controls. In addition, there were significant correlations between average GM CVR and lesion volumes in MS patients (r=-0.46, P=0.03); and between the global CVR and brain parenchymal ratios in all subjects (r=0.33, P=0.04).

CONCLUSIONS: We had shown a large decrease of global CVR in MS and a loss of vasoreactivity in most lesions; as well as a tight correlation between GM CVR and lesion load. This suggests that the impaired cerebrovascular response at hypercapnia condition reflecting hemodynamic deficits could be measured with ASL; and this process is related to WM lesion volume (inflammation) in MS patients.

References [1] Rocca et al J NeuroImaging 2007. [2] Bulte et al NeuroImage2012. [3] Wang et al MRI 2008. [4] Ge et al JCBFM 2012.

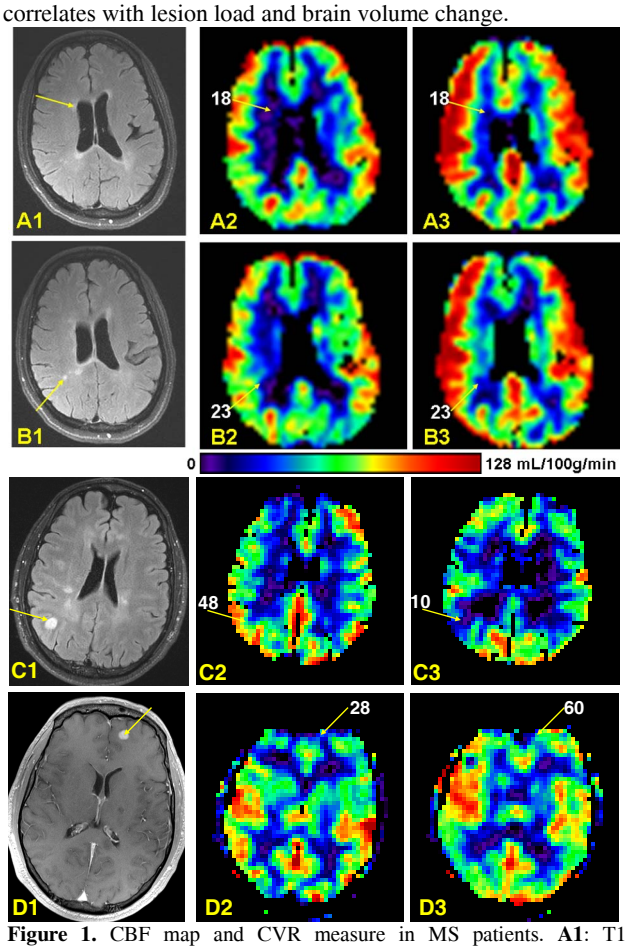

Figure 1. CBF map and CVR measure in MS patients. **A1**: T1 hypo-intense/T2 hyper-intense lesion on the FLAIR image of a MS patient. A2: CBF map at the baseline room air condition for this patient and A3: CBF map at hypercapnia condition for this patient showed relatively increases of CBF in both cortical gray matter and certain white matter regions. The arrows showed the lesion with low CBF (18 mL/100g/min) at baseline and no changes of CBF at the CO2 condition (zero CVR for hypo-intense lesion). **B1**: T1 iso-intense/T2 hyper-intense lesion on the FLAIR image of this MS patient. B2: CBF map at the baseline condition and B3: CBF change in response to hypercapnia with a zero CVR for the iso-intense lesion as well. **C1**: T1 hypo-intense/T2 hyper-intense gray matter (GM) lesion on the T1 FLAIR image of a second MS patient. C2: CBF map at baseline and C3: CBF map at hypercapnia condition for this patient showed some decreases of CBF in cortical gray matter compared to room air. The arrows showed a GM lesion that had low CBF (48 mL/100g/min) at baseline and dramatically decrease of CBF (10 mL/100g/min) at hypercapnia condition; with a negative CVR =-7%/mmHg (normalized with $\Delta EtCO2$=11mmHg). **D1**: T1 enhanced lesion on the post-Gd contrast image of this second MS patient. D2: CBF map at baseline and D3: CBF change in response to hypercapnia condition for this patient showed some increases and decreases of CBF in both gray matter and white matter regions. The arrows showed an enhanced lesion with low CBF at room air but a largely increased CBF at hypercapnia condition (from 28 to 60 mL/100g/min); with a relatively high CVR=10%/mmHg compared to other brain regions, indicating a pathological highly-active inflammatory process.