Normal-appearing White Matter and Venous flow Multiparameter comparison between Multiple Sclerosis and Healthy Control Subjects

Eric Mathew Schrauben[1], Kevin M Johnson[1], Oliver Wieben[1,2], and Aaron Field[3]

[1]*Medical Physics, University of Wisconsin - Madison, Madison, Wisconsin, United States,* [2]*Radiology, University of Wisconsin - Madison, Wisconsin, United States,* [3]*Radiology, University of Wisconsin - Madison, Madison, Wisconsin, United States*

TARGET AUDIENCE: Clinicians and physicists interested in multiparameter quantitative MRI in multiple sclerosis (MS).

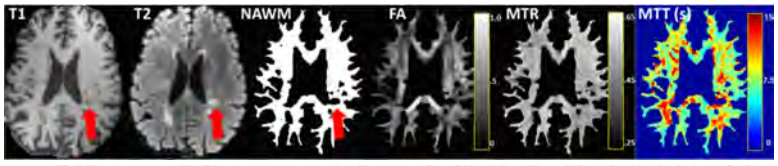
PURPOSE: Several MR-derived biomarkers are able to detect pathology in normal-appearing white matter (NAWM) of patients with multiple sclerosis (MS), making them potentially more meaningful measures of disease status than conventional T1- or T2-weighted lesion load. These include fractional anisotropy (FA) garnered from diffusion tensor imaging, magnetic transfer ratio (MTR)[1], and mean transit times (MTT) from dynamic perfusion data[2]. Chronic cerebrospinal venous insufficiency (CCSVI) is a controversial hypothesis suggesting that venous reflux to the level of the deep cerebral veins induces amplified iron deposition, ultimately resulting in MS[3]. It has generated much interest in the quantification of venous blood flow; 4D flow MRI[4] provides volumetric coverage so that multiple venous structures may be interrogated within a single scan. The purpose of this study was to determine whether MS-related changes in multiparametric MR-derived biomarkers in NAWM would be predicted by venous flow parameters derived from 4D flow MRI in the head, neck, and chest, in MS patients and healthy controls (HC).

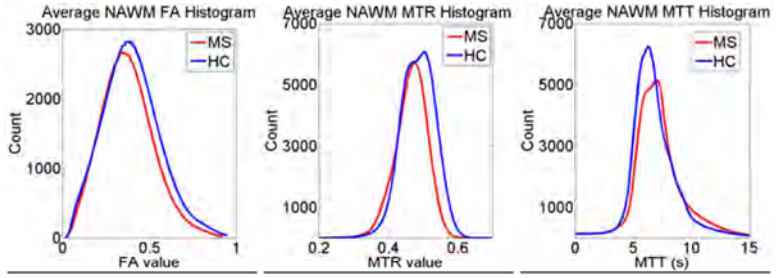
METHODS: *Demographics:* As part of a larger CCSVI study currently underway at our institution, 34 MS patients (Age: 46.7 ± 10.8 yrs, 16M/18F) and 25 age-matched HCs (Age: 44.7 ± 12.1 yrs, 12M/13F) were selected for preliminary analysis. *MR Image Acquisition:* A clinical 3T scanner (Discovery MR750, GE Healthcare, Waukesha, WI) was used to collect the following scans: **1) T1 BRAVO** (TE/TR/α = 3.2ms/8.2ms/12°, resolution = 0.94x0.94x1.5 mm); **2) T2 CUBE-FLAIR** (TE/TR/α = 126ms/6000ms/90°, resolution = 1x1x2 mm); **3) DTI** SE-EPI (25 directions, TR = 7400ms, bvalue = 1000 sec/mm^2, resolution = 0.94x0.94x2.84 mm); **4) MT** on/off 3D GRE (TE/TR/α = 3.2ms/35ms/5°, resolution = 0.94x0.94x1.5 mm); **5) DSC** EPI perfusion (TE/TR/α = 45ms/1500ms/60°, resolution = 1.7x1.7x5 mm); **6) 4D flow** with radial undersampling: **PC-VIPR**[5] head (TE/TR/α = 3.5/9.0/15°, resolution = (0.69 mm)^3 isotropic, Venc = 20 cm/s); **7) PC-VIPR** neck (TE/TR/α = 3.0/7.9/15°, resolution = (0.86 mm)^3, Venc = 40 cm/s); **8) PC-VIPR** chest (TE/TR/α = 2.7/6.9/15°, resolution = (1.25 mm)^3, Venc = 40 cm/s).

	Processing	MRI Scan(s)	Software
NAWM	Lesion Segmentation Lesion volume (mL) Lesion ratio (%)	T1-w, T2-FLAIR	*SPM LST*
NAWM	FA	Diffusion Tensor	*FSL*
NAWM	MTR	3D SPGR MT on/off	*FSL*
NAWM	MTT (s)	DSC-MRI	*FSL*
Flow	Cerebrospinal Veins Total Flow (mL/cycle) Peak Flow (mL/s) Retrograde Flow (%)	4D flow MRI	*Matlab, Ensight*

Table 1. Measured quantitative parameters, MRI acquisitions, and processing software.

Image Processing: All processing was completed by one person uninvolved with data acquisition and with complete blinding to subjects' statuses. Table 1 summarizes biomarkers, as well as MRI scans and software used to generate data. Non-flow data were aligned with the BRAVO image using FMRIB's Linear Image Registration Tool (*FLIRT*). NAWM and lesions were automatically segmented using SPM's Lesion Segmentation Tool (*LST*) with dual inputs of BRAVO and CUBE-FLAIR images. Values of FA, MTR, and MTT in NAWM were computed using FMRIB's Software Library (*FSL*). Example output from this processing is shown in Figure 1 – top with lesion identification (red arrow). For FA, MTR, and MTT in NAWM, a histogram analysis was performed on each subject (Figure 1 – mid), resulting in metrics of peak location, peak count, and full-width at half the maximum (FWHM). In the three station 4D flow MRI exam, parameters were visualized and quantified with *Ensight*[6]. Total flow (mL/cycle), peak flow (mL/s), and percent retrograde flow (%) were measured in the following veins: head – sagittal sinus, left/right transverse sinus, left/right internal cerebral vein, and left/right basal vein; neck – left/right internal jugular vein (IJV) at three locations (Upper, Mid, Lower); chest – azygous vein. *Statistics:* Group differences were assessed on a per-vessel/location basis using two-sample unpaired Student's t-tests. In addition, parameter relationships were assessed using Pearson's correlation analysis with NAWM lesion ratio (%) used as the control variable to tease out differences between groups (MS = 0.81 ± 0.99 %, HC = 0.03 ± 0.07 %, p = 0.0002). False discovery rate control was used to correct for multiple comparisons in NAWM and at different vessel locations[7].





	MS	HC
Count	2917±402	2986±475
Location	0.36±0.03	0.37±0.02
FWHM	0.35±0.02	0.38±0.07

	MS	HC
Count	8570±2843	10598±1953
Location	0.48±0.01	0.49±0.01
FWHM	0.07±0.02	0.06±0.01

	MS	HC
Count	8393±3426	11826±3466
Location	6.69±1.00	6.45±1.10
FWHM	2.16±1.22	1.48±0.46

Figure 1. Top: Example processing results in a patient with MS. Middle: Average histogram distribution in NAWM for MS and HC subjects for FA, MTR, and MTT. Bottom: Average ± std dev results for histogram analysis between groups.

RESULTS: Fig. 1 – bottom shows average (± std dev) histogram values for FA, MTR, and MTT measurements in NAWM between groups. In MS patients, lower peak heights and locations for FA and MTR and prolonged MTTs are observed. Corrected t-test *p-values* in NAWM were significant for Lesion Volume and Lesion Ratio (p = 0.0002; p = 0.0002), MTT peak height and FWHM (p = 0.0003; p = 0.005), FA peak height, FWHM, and peak location (p = 0.002; p = 0.02; p = 0.03), and MTR FWHM (p = 0.01). No significant differences were found between MS and HC for any flow parameters. When correlating with NAWM metrics, only one was statistically significant (FA peak height, r = -0.49, p = 0.004). For MS flow data, no statistically significant correlations with lesion ratio were observed for any metric in any vessel. HC flow data exhibited significant correlation at one location only (right internal cerebral vein peak flow, r = -0.73, p < 0.001).

DISCUSSION and CONCLUSION: In this study groupwise multiparameter comparisons for clinical and research sequences were investigated between patients with MS and age/sex-matched HCs for metrics in NAWM and cerebrospinal flow. In agreement with previous studies[1,2], analysis of diffusion, magnetization transfer, and perfusion based metrics revealed statistically significant differences between these groups. In contrast, no flow parameters derived from 4D flow MRI in 14 cerebrospinal vessel segments showed between-group differences. These results do not support a relationship between MS and impaired venous flow. Further processing of larger group numbers and statistical correlation analysis is warranted to describe combinations of NAWM metrics to distinguish MS patients from HCs.

Acknowledgements: We gratefully acknowledge funding from National MS Society grant #RC1003-A-1 and NIH grant 2R01HL072260, and GE Healthcare for their support.

REFERENCES: **1**. Moll et al. *Ann Neurol* 2011. **2.** Law et al. *Radiology* 2004. **3.** Zamboni et al. *Phlebology* 2010. **4.** Markl et al. *JMRI* 2012. **5.** Johnson et al. *JMRI* 2008. **6.** Stalder et al. *MRM* 2008. **7.** Glickman et al. *J Clin Epidemiol* 2014.