4D flow MRI assessment of Cerebrospinal Venous blood flow in Multiple Sclerosis Patients and Age/Sex-Matched Controls

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TARGET AUDIENCE: Clinicians and physicists interested in quantitative flow MRI and the role of venous flow in multiple sclerosis (MS).

PURPOSE: The chronic cerebrospinal venous insufficiency (CCSVI) hypothesis by Zamboni et al.[1] posits vascular dysfunction to the level of the deep cerebral veins as a possible mechanism for the cause and/or exacerbation of multiple sclerosis (MS). In comparison with Doppler ultrasound used to diagnose CCSVI, assessment of cerebrospinal venous flow using PC MR has been shown to be reliable[2], is thought to be less user-dependent, and allows for a truly blinded study design. 4D flow MRI[3] provides volumetric coverage so that a number of venous structures may be interrogated with a single scan. The purpose of this study was to compare cerebrospinal venous flow, assessed using 4D flow MRI, between MS patients and healthy controls (HC).

METHODS: <u>*Demographics:*</u> 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 and sex matched HCs (Age: 44.7 ± 12.1 yrs, 12M/13F) were selected for preliminary analysis. <u>*MR Acquisition:*</u> A clinical 3T scanner (Discovery MR750, GE Healthcare, WI) was used to collect 4D flow MRI at 3 stations using a radially undersampled trajectory (PC-VIPR[4]): **1) Head** (TE/TR/θ = 3.5ms/9.0ms/15°, resolution = $(0.69\ mm)^3$ isotropic, Venc = 20 cm/s); **2) Neck** (TE/TR/θ = 3.0ms/7.9ms/15°, resolution = $(0.86\ mm)^3$ isotropic, Venc = 40-70 cm/s); **3) Chest** (TE/TR/θ = 2.7ms/6.9ms/15°, resolution = $(1.25\ mm)^3$ isotropic, Venc = 40 cm/s). Cardiac triggers were recorded for retrospective cardiac gating. <u>*Processing:*</u> All image processing was completed by one person uninvolved with image acquisition and fully blinded to group membership. The image sets were segmented based on the PC angiogram (*Mimics*, Materialize) and exported to advanced visualization software (*EnSight*, CEI). Flow measurements were obtained from reformatted 2D planes manually placed orthogonally to the direction of flow[5]. Figure 1 displays anatomical location of the analysis planes: **1) Head** – superior sagittal sinus, left/right transverse sinus, left/right internal cerebral vein, and left/right basal vein; **2) Neck** – left/right internal jugular vein (IJV) at three stations (Upper, Mid, Lower); and **3) Chest** – azygous vein 2 cm from junction with the superior vena cava. Measured flow parameters were total flow (mL/cycle), peak flow (mL/s), and percent retrograde flow (%). In relation to Zamboni's original criteria for detection of CCSVI using Doppler ultrasound[1], our analysis allows for assessment of directional flow in the cervical and intracranial veins (criteria 1 and 2), anomalies/stenoses of IJVs (criteria 3, Fig. 1C), and blocked outflow in cervical veins (criteria 4). <u>*Statistics*</u>: Group differences were assessed on a per-vessel/location basis using two-sample unpaired Student's t-tests. False discovery rate control was used to correct for multiple comparisons[6].

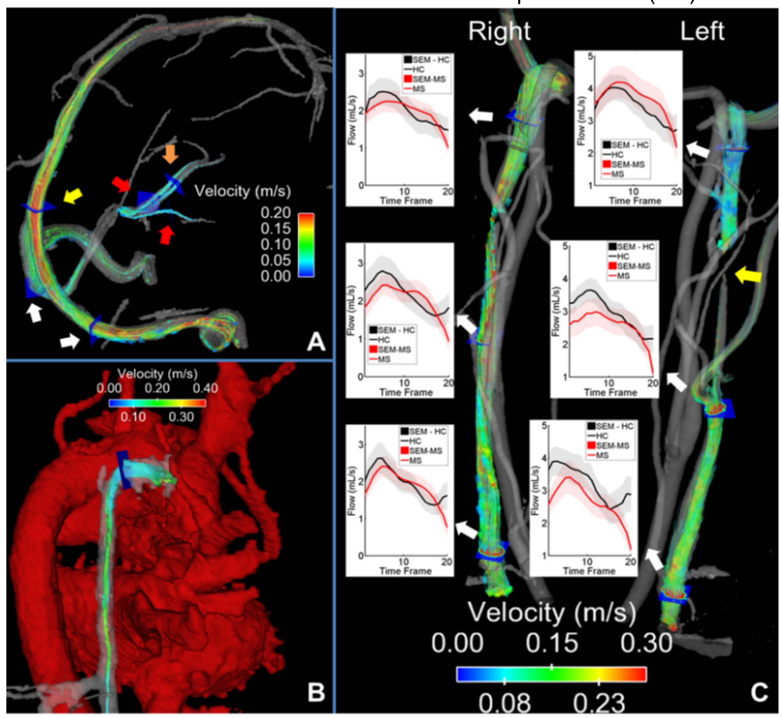

Figure 1. Measurement locations and example velocity streamline visualization within the cerebrospinal vasculature. A – superior sagittal sinus (yellow arrow), left/right transverse sinus (white), left/right internal cerebral vein (orange), left/right basal vein (red); B – azygous vein with heart vasculature in red; C – left/right IJV at upper, mid, and lower stations. Inset shows average flow waveforms (± standard error of the mean, SEM) at these measurement locations between MS and HC. Note the apparent left IJV stenosis observable with 4D flow MRI (yellow arrow).

RESULTS: Figure 1C displays average flow waveforms (± standard error) over the cardiac cycle for each group at measurement locations within the internal jugular vein. Table 1 summarizes total flow (mean ± std dev) between groups. No statistically significant differences between the MS and HC were observed for any measurement location, for any tested parameter.

DISCUSSION and CONCLUSION: This preliminary analysis compares flow parameters from HC with those from patients with MS. No differences between the two groups were identified. IJV flow has been shown to have high interscan variability in healthy subjects[2], potentially preventing small between-group flow alterations from being detected without large sample sizes. However, in the intracranial veins, which are necessarily the conduit by which a venous flow disturbance would be transmitted to the brain, flow is much less variable[2] and still no differences were detected. These negative results do not support a relationship between altered cerebrospinal venous drainage and MS.

Total Flow (mL/cardiac cycle)

	Head							Neck - Internal Jugular Vein						Chest
	Superior Sagittal	Left Transverse	Right Transverse	Left Internal Cerebral	Right Internal Cerebral	Left Basal	Right Basal	Left Upper	Left Mid	Left Lower	Right Upper	Right Mid	Right Lower	Azygous Vein
MS	3.2 ± 1.3	2.2 ± 1.7	3.2 ± 1.9	0.3 ± 0.1	0.3 ± 0.1	0.2 ± 0.2	0.3 ± 0.2	1.7 ± 1.5	1.8 ± 1.5	1.5 ± 1.1	2.8 ± 2.6	2.1 ± 1.9	2.2 ± 2.1	3.2 ± 2.0
HC	3.4 ± 2.3	2.1 ± 1.9	4.1 ± 2.9	0.4 ± 0.2	0.4 ± 0.2	0.2 ± 0.2	0.3 ± 0.2	2.1 ± 2.7	2.6 ± 3.7	2.2 ± 2.5	3.3 ± 2.4	2.9 ± 1.8	3.4 ± 2.9	3.4 ± 1.5

Table 1. Total flow measurements (mean ± std dev) between HC and MS across all selected locations. No statistically significant differences were observed for any parameters or locations.

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References: **1**. Zamboni et al. *Phlebology* 2010. **2.** Schrauben et al. *AJNR* 2014. **3.** Markl et al. *JMRI* 2012. **4.** Johnson et al. *JMRI* 2008 **5.** Stalder et al. *MRM* 2008. **6.** Glickman et al. *J Clin Epidemiol* 2014.