

# An Objective Quantification Technique of the Cerebrospinal Fluid (CSF) Flow in the Cerebral Aqueduct, in Patients with Multiple Sclerosis

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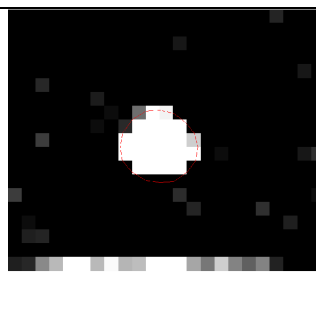
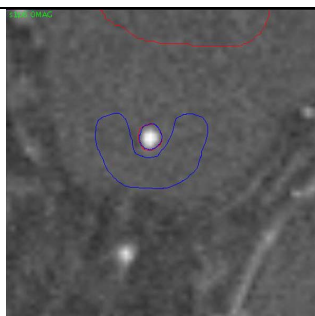
**Introduction:** Multiple Sclerosis (MS) is a neurological disease affecting more than 2.5 million people worldwide. While the involvement and the effect of the MS disease on white matter (WM) and gray matter (GM) has been studied and described extensively, the in vivo fluid-mechanical properties of the lesioned brain in MS patients has been studied to a much lesser extent. The flow behavior of cerebrospinal fluid (CSF) on dynamic MRI studies may yield information regarding CSF production rates and brain elasticity in response to changes in intracranial pressure gradients during systole/diastole in both normal patients and the lesioned brain. We are presenting results of a pilot study in which we employed non-invasive MRI to measure CSF flow in the aqueduct of Sylvius and other standard MRI disease metrics, in MS patients and normal controls (NC). Furthermore, to improve the quantification accuracy for the flow in the aqueduct, an algorithm that uses a semi-automated segmentation of the aqueduct was developed.

**Methods:** Sixteen (16) consecutive relapsing-remitting MS patients and 8 age- and sex-matched NC were scanned on a GE 3T scanner using a peripheral cardiac-gated phase-contrast gradient-echo MR technique with high spatial-temporal resolution (in-plane resolution 0.39x.039mm<sup>2</sup> and 32 phases corresponding to a full cardiac cycle –systole and diastole), on one 4mm thick slice positioned perpendicular on the cerebral aqueduct (Fig 1). Other parameters were TR/TE =40/8ms, FA=20 and Venc=20cm/s. Two independent operators manually outlined the aqueduct region-of-interest (ROI) and background ROI, in two different ways (Fig 2), using the GE ReportCard software v3.6. For consistency and objective quantification of the antegrade (from the 3<sup>rd</sup> ventricle towards the 4<sup>th</sup> ventricle), retrograde (towards 3<sup>rd</sup> ventricle) and net CSF flow rates, a semi-automated minimum area contour change (MACC) program [2] was used to automatically outline the aqueduct in each phase, with sub-voxel accuracy. The calculated outline was fitted to an ellipse and the minor radius was considered to be the radius of the aqueduct  $R_{ph}$  (variable during the cardiac cycle). Because the flow in the aqueduct of Sylvius is laminar [3], and considering the cylindrical shape of the aqueduct, the flow rate for each phase  $Q_{phase}$  can be calculated as half of the product between the peak velocity for that phase  $V_{peak}$  - as reported by the ReportCard software- and the area of the aqueduct,  $A_{ph}=\pi R_{ph}^2$ ; thus,  $Q_{phase}=1/2*V_{peak}*(\pi R_{ph}^2)$ . The antegrade and retrograde stroke volumes (**ASV and RSV**), representing the CSF volume passing through the cerebral aqueduct in the antegrade and retrograde directions during one cardiac cycle (heart beat), were calculated by integrating over the phases with peak velocities in the antegrade and retrograde directions, respectively. The net flow (**NF**) of CSF passing through the aqueduct in the cranial-caudal direction per cardiac cycle was calculated as the flow integral over the 32 phases. The CSF flow quantification technique was validated using the same acquisition sequence used in the study, imaging the flow of a saline solution pushed through a thin tube phantom (Fig 3) by a power injector (manufactured by Medrad), which provided a controlled flow rate of 0.15 (+/- 0.02) ml/sec. Two NC and 2 MS patients were scanned and rescanned within a week, to test reproducibility. In addition to CSF flow measures, lesion volume (LV) and atrophy MRI outcomes were calculated.

**Results:** Average CSF aqueductal flow measurements for the MS and NC groups are shown in **Table 1**. The average intra- and inter-rater reproducibility for the peak ante- and retrograde velocities (**APV and RPV**) was better than 1%. Using the MRI-based quantification technique presented here, the flow measured in the thin tube phantom was 0.147ml/s, which falls within the range of 0.13-0.17ml/s specified by the manufacturer of the power injector. For the 2MS and 2NC subjects, the average net CSF flow scan-rescan variability was 10.9% when using our quantification technique and it was 24% when using the ReportCard software with manual outlining. The **NF** was significantly lower in MS patients than in NC ( $p=0.038$ ). In MS patients, T1-LV was strongly correlated with CSF **RPV** ( $r=0.85$ ,  $p<0.001$ ) and **APV** ( $r=-0.71$ ,  $p=0.002$ ), CSF **RSV** ( $r=0.71$ ,  $p=0.002$ ) and **ASV** ( $r=-0.64$ ,  $p=0.008$ ). T2-LV was also related to CSF **RPV** (0.64,  $p=0.007$ ) and **RSV** (0.58,  $p=0.019$ ). Lower net CSF flow rate was related to progression of gray matter ( $r=-0.63$ ,  $p=0.009$ ), whole brain and cortical atrophy ( $p<0.037$ ).

**Discussion:** There is an intrinsic difficulty associated with accurate measurements of net CSF flow through the cerebral aqueduct. Namely, because the small net degree of CSF movement in the cerebral aqueduct is superimposed on a large-amplitude biphasic flow regulated by the arterial pulse, most estimation errors are likely to be associated with obtaining a small quantity from the subtraction of two large numbers. Thus, more accurate estimates of **ASV** and **RSV** will improve the measurement accuracy of **NF**. Manual definition of the aqueduct was shown to result in very large variations in measured CSF production/flow rate [3] and we address this problem via the semi-automated MACC segmentation technique in concert with the assumption of laminar flow through the cerebral aqueduct.

**Conclusions:** CSF flow quantification using semi-automatic segmentation of the cerebral aqueduct via the MACC technique significantly reduces the variability associated with manual outlining of the cerebral aqueduct. In addition, our pilot study provides preliminary evidence that net CSF flow in the cerebral aqueduct is significantly lower in MS patients than in NC. In MS patients, robust correlations between higher LVs, advanced atrophy, and altered flow rate measures were found. A larger study is underway at our institution.



CSF Outcome	MS (16)	NC (8)
APV (cm/s)	-10.3 (4.9)	-8.4 (1.9)
RPV (cm/s)	8.3 (3.2)	6.3 (2.3)
ASV (uL)	-43.2 (27.9)	-33.4 (11.7)
RSV (uL)	39.4 (21.7)	22.8 (10.8)
NF (uL)	-3.9 (13.3)	-10.6 (6.2)

**Fig 1:** Sag T2 image used to prescribe the acquisition plane (green line), perpendicular on the aqueduct.

**Fig 2:** Manually drawn aqueduct and background ROIs, using GE ReportCard software.

**Fig 3:** Sub-voxel precision, automatically calculated MACC outline shown for thin tube phantom used for validation.

**Table 1:** Average (SD) antegrade (APV and ASV) and retrograde (RPV and RSV) peak velocities (in cm/s) and stroke volume (in uL) and net flow (NF) in 16 MS patients and 8 NCs.

**References:** [1] Freedman et al, Arch Neurol 62: p865, 2005 [2] Wack et al, Mult Scler 14: p671, 2008 [3] Huang et al, Radiology 233 (2): p603, 2004