

THE ROLE OF CEREBROSPINAL FLUID DYNAMICS USING PHASE-CONTRAST MAGNETIC RESONANCE IMAGING IN ASSESSMENT OF MULTIPLE SCLEROSIS ACTIVITY

By

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ABSTRACT

Background: Multiple sclerosis (MS) is a chronic complex neurodegenerative disease, targeting the central nervous system (CNS) and widely believed to be autoimmune in nature. Alterations to the normal flow of Cerebrospinal fluid (CSF) in the brain could be a contributing factor to the accumulation of toxic substances in the brain interstitium and may be related to the pathogenesis of neurological disorders such as Alzheimer's disease and MS.

Objective: To evaluate the CSF dynamics and its relation to MS activity using phase-contrast magnetic resonance imaging (PC-MRI).

Patients and methods: This prospective study was performed between April 2020 and October 2020. A total of 45 cases were enrolled in this study divided into three equal groups: MS patients with active plaques-enhanced on MRI (group 1), MS patients with chronic plaques (group 2), and healthy controls (group 3). Quantitatively evaluation of the CSF flow was performed at the level of the cerebral aqueduct by PC-MRI.

Results: Regarding to peak velocity, average velocity, net volume and average flow, there were no statistically significant differences between the three studied groups. Regarding to forward volume, reverse volume and aqueductal area, there were statistically significant differences between the three studied groups.

Conclusion: The forward and reverse CSF flow volumes and aqueductal area were significantly higher in the MS patients. These findings may support the venous theory in MS patients, but may also be explained by atrophy-dependent ventricular dilatation independent of the venous theory in MS patients.

Keywords: Cerebrospinal Fluid Dynamics, Phase-Contrast, Magnetic Resonance Imaging, Multiple Sclerosis Activity.

INTRODUCTION

MS is an inflammatory disease characterized by demyelination centered on the cerebral veins in the white matter (*Filippi et al., 2019*).

The normal CSF circulation depends on the proper balance between CSF

ultrafiltration (from lateral ventricular veins) and venous system clearance from CSF opening at the level of dural sinuses (*Öner et al., 2018*).

Chronic cerebro-spinal venous insufficiency (CCSVI) has been suggested as a new hypothesis for the pathogenesis of MS disease. CCSVI-related MS

hypothesis suggests that significant decrease in CSF flow occurs through cerebral aqueducts secondary to impaired venous outflow from the CNS (Zamboni *et al.*, 2012). The subject of CCSVI has been mired in controversy, with many researchers doubting that it is indicative of any pathology (Beggs *et al.*, 2014). However, there is a growing evidence that restricted cerebral venous outflow is a phenomenon that is more prevalent in patients with MS, even though it is also observed in both healthy individuals and those with other neurological disease (Baracchini *et al.*, 2013).

A great number of demyelinating plaques of different sizes with sharp borders and round, oval or irregular shapes can be seen in MS (Öner *et al.*, 2018).

MRI can support the clinical information for MS diagnosis, allowing an earlier and accurate diagnosis and, consequently, earlier treatment (Filippi *et al.*, 2016).

CSF is predominantly produced by the choroid plexuses of the lateral, third, and fourth ventricles. CSF is eventually cleared to the venous system through arachnoid villi, to the cervical lymphatics through the cribriform plate, and to the recently discovered meningeal lymphatics that line the dural sinuses. Alterations to the normal flow of CSF in the brain could be a contributing factor to the accumulation of toxic substances in the brain interstitium and may be related to the pathogenesis of neurological disorders such as Alzheimer's disease and MS. (Schubert *et al.*, 2019).

PC-MRI is a non-invasive technique that can be used to quantitatively evaluate

CSF flow dynamics (Korbecki *et al.*, 2019).

The aim of this study was to evaluate the CSF dynamics and its relation to MS activity using PC-MRI.

PATIENTS AND METHODS

This prospective study was performed between April 2020 and October 2020 at the Radiodiagnosis Department, New Damietta Hospital, Al-Azhar University and other private center using 1.5 tesla (T) magnetic resonance scanners (Philips Achieva, Netherland and Siemens MGNETOM, Aera respectively).

Inclusion criteria: Age: from 20 to 50 years and no gender predilection. The selection of subjects was done after prior explanation of the aim of the study, and free well-written approval consent was taken. The whole work was done according to the ethical committee, Faculty of Medicine, Al-Azhar University.

Exclusion criteria: Patients who had cardiac pacemaker, metallic foreign body in their eye, aneurysm clip in brain, any electrically or magnetically activated implants (cochlear implants), severe claustrophobia, excessive motion and uncooperative, bad general condition and contra-indications for the contrast medium, e.g. severe allergic reaction or renal impairment.

A total of 45 cases were enrolled in this study, divided into three equal groups (11 females and 4 males each). Their ages ranged from 20 to 50 years. They were referred from the outpatient clinic of the Neurology Department, Al-Azhar Faculty of Medicine.

- **Group (1):** Patients were referred from neurology department as Relapsing-remitting multiple sclerosis (RRMS) and had active plaques on MRI.
- **Group (2):** Patients were referred from neurology department as RRMS and had chronic plaques on MRI.
- **Group (3) or control group:** Subjects were free from any medical or neurological disease and had normal conventional MRI.

All patients involved in this study were subjected to:

1. Full medical history including: name, age, complaint of the patients, duration of the complaint, history of any disease, previous operations, and any previous radiological examination.
2. Clinical examination (by referring doctor).
3. Laboratory investigations (e.g. serum creatinine).
4. Conventional MRI using routine sequences for brain study and Post-contrast T1-weighted study (in MS cases).
5. PC-MRI.

Patient preparation and positioning:

Patients needed no specific preparation and imaging was carried out with patient in supine position, using standard head coil.

Conventional MRI: Axial T1-weighted, T2-weighted and fluid-attenuated inversion recovery (FLAIR) and sagittal FLAIR. Post-contrast axial T1-weighted study (in MS cases) was done after injection of gadopentate dimeglumine (0.1 ml/Kg). Axial T1-weighted (repetition

time / echo time (TR/TE): 500-600/16ms), fast spin-echo axial T2-weighted (TR/TE: 4490/86ms), axial & sagittal fast FLAIR (TR/TE /TI: 9000/ 14 /2500ms). The slice thickness was 5mm in axial and 3mm in sagittal, matrix size was 128x256 & the field of view (FOV) was 220-240 mm.

Phase contrast MRI Protocol: For axial phase contrast images the following parameters were used: TR ranged from 12 to 17 ms, TE ranged from 7.3 to 10.4 ms, Flip angle=15°, Matrix 256x256 pixels and Slice thickness=5mm.

First step was the cardiac gating. It was performed with MR compatible peripheral pulse transducer applied to the subject's finger. Velocity encoding (VENC) was adjusted for each group, the mean VENC value is 5-8 cm/sec for standard CSF flow imaging. Lower VENC values (2-4 cm/sec) can be helpful in patients with brain atrophy. Higher VENC values (20-25 cm/sec) for hyper-dynamic flow, the velocity direction was encoding in the cranio-caudal direction.

In mid-sagittal image, a localizer was placed perpendicular to the aqueduct of sylvius, the localizer should pass through the aqueduct in the axial plane. Phase contrast images were obtained in one cardiac cycle. A series of phase and magnitude images at different cardiac phases were obtained.

After the data acquisition, all images were transferred to the workstation equipment with Q flow software (on Philips scanner) and Argus flow software (on Siemens scanner). A ROI (region of interest) drawn manually to include all pixels that reflected the CSF flow signals on the phase images after magnification of the images to clarify the flow, after that

the CSF flow parameters were automatically extracted.

Data analysis:

Quantitative analysis: Peak systolic and diastolic velocities were extracted from the mean velocity-time curve. In this curve the area above the baseline represented the diastolic flow with its highest point is the PDV in cm/sec, the area under the baseline represented the systolic velocity with the furthest point from the baseline represented the PSV in cm/sec. Mean velocity (cm/sec) referred to the mean CSF flow velocity. Mean flux (ml/sec) which is the mean CSF flow volume per second. Forward flow volume (ml) that represented the CSF flow volume in the encoding direction, while backward flow volume (ml) represented CSF flow volume moving in the opposite direction and the net volume (ml) is the difference between both. The aqueduct area was represented by the ROI area (cm²) (figure 1).

Statistical analysis of the data: Data were tabulated, coded then analyzed using the computer program SPSS (Statistical package for the social sciences) version 17.0 to obtain:

Descriptive data: Descriptive statistics were calculated in the form of mean + standard deviation (SD), range (minimum-maximum) & frequency (number-percent).

Analytical statistics:

- Shapiro-Wilk test was applied as a test of normality.
- In the statistical comparison between the different groups, the significance of difference was tested using one of the following tests:

1. Student's t-test (Unpaired): Used to compare between mean of two different groups of numerical (parametric) data.
2. Mann-whitney U test: Used to compare between two different groups of numerical (non-parametric) data.
3. Kruskal-Wallis test: Used to compare between more than two related groups of numerical (non-parametric) data.

P value <0.05 was considered statistically significant.

RESULTS

Regarding to age and gender, there were no statistically significant differences between the three studied groups. Regarding to duration of the

disease, there was a statistically significant difference between the studied groups (Table 1).

Table (1): Demographic data of MS patients & control subjects and comparison between MS patients as regard duration of the disease

Groups		Group (I) (N = 15)	Group (II) (N=15)	Control (N=15)
Parameters				
Age (years)		21 – 50	20 - 50	20 - 49
Mean ± SD		33.9 ± 9.99	33.70 ± 9.40	33.80 ± 7.91
Sex	Male	4 (26.66%)	4 (26.66%)	4 (26.66%)
	Female	11 (73.33%)	11 (73.33%)	11 (73.33%)
Duration of the disease:				
Mean ± SD		3.33 ± 2.28	7.00 ± 3.36	-
P. Value		0.006		

Regarding to peak velocity, average velocity, net volume and average flow, there were no statistically significant differences between the three studied groups.

Regarding to forward volume, reverse volume and aqueductal area there were statistically significant differences between the three studied groups (Table 2).

Table (2): CSF Dynamics in RRMS Patients and Controls.

Parameters	MS patients with active plaques	MS patients with chronic plaques	Controls	p -value
	Mean ± SD (range)	Mean ± SD (range)	Mean ± SD (range)	
Peak velocity (cm/sec)	5.84 ± 1.17 (2.7–6.40)	5.76 ± 1.35 (3.40–8.4)	4.59 ± 1.53 (2.9–7.80)	0.056
Average velocity (cm/sec)	0.52 ± 0.33 (0.08–1.13)	0.31 ± 0.20 (0.03–0.70)	0.41 ± 0.29 (0.05–1.07)	0.143
Forward volume (ml)	0.029 ± 0.013 (0.01–0.06)	0.039 ± 0.020 (0.01–0.08)	0.02 ± 0.01 (0.01–0.04)	0.036*
Reverse volume (ml)	0.024 ± 0.016 (0.00–0.05)	0.029 ± 0.0183 (0.01–0.07)	0.01 ± 0.011 (0.00–0.030)	0.007*
Net forward volume (ml)	0.027± 0.07 (0.00–0.03)	0.014 ± 0.012 (0.00–0.04)	0.009 ± 0.007 (0.00–0.02)	0.559
Average flow (ml/sec)	0.01 ± 0.0136 (0.00–0.04)	0.015 ± 0.0139 (0.00–0.04)	0.013 ± 0.026 (0.00–0.04)	0.272
Aqueductal area (mm2)	4.38 ± 1.66 (1.60–7.40)	5.7 ± 1.88 (2.90–9.00)	3.17 ± 1.9 (1.30–5.20)	0.000*

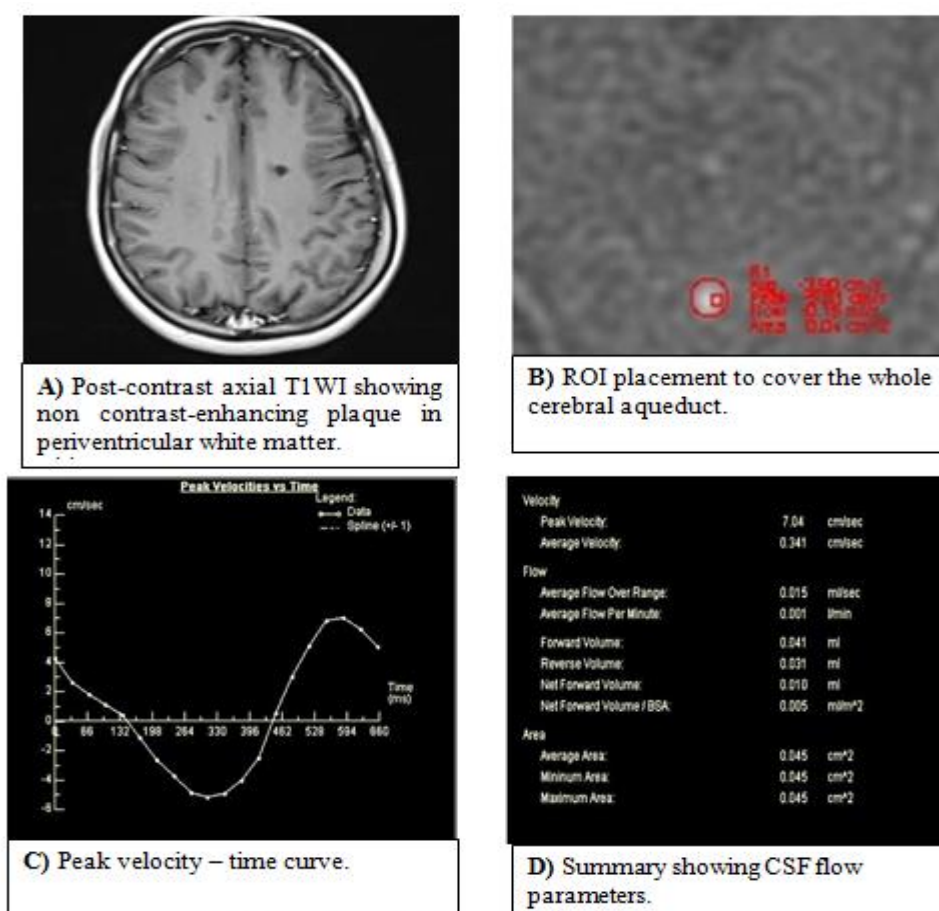


Figure (1): A-D, a case of RRMS with chronic plaques.

DISCUSSION

PC-MRI facilitates accurate and noninvasive evaluation of the flow direction and flow rate of intracranial blood and CSF (Korbecki *et al.*, 2019).

Zamboni *et al.* (2012) reported a strong relationship between CCSVI and MS. They found a significantly higher prevalence of CCSVI in MS patients, as compared to controls, and consequently, a decrease in net CSF flow (mL/beat) passing through the cerebral aqueduct. They concluded that CCSVI has a marked effect especially on intracranial fluid balance in the pathophysiology of brain.

Sundström *et al.* (2010) performed a study to test the hypothesis of CCSVI and,

unlike Zamboni *et al.* (2012), did not detect any difference in internal jugular venous outflow and aqueductal CSF flow between RRMS patients and the control group.

MS patients were divided into 2 groups according to the condition of plaques that were detected on MRI: MS patients with active plaques who exhibit contrast enhancement and those with chronic disease non-enhancement. Therefore, we determined whether PC-MRI contributes to differential diagnosis of active and chronic disease in MS.

If CSF flow is decreased due to impaired extra-cranial venous drainage in MS patients, based on the study of Zamboni *et al.* (2012), we expected lower

CSF flow values in the intense period of active inflammation.

In our results, there were no statistical differences in age and sex between the three studied groups. Likewise, various studies have reported an increase in CSF flow dynamics due to aging (*Sartoretti et al., 2019*).

Our study compared flow speeds in addition to CSF flow volumes passing from the cerebral aqueduct in MS patients. No significant differences were found in terms of peak velocity, average velocity, net CSF flow volume and average flow.

Cranio-caudal (forward) and caudo-cranial (reverse) CSF flow volumes (ml) and aqueductal area were higher in the MS patients with chronic plaques, as compared to patients with active plaques; and of these parameters, reverse volume was statistically significant. In addition, these parameters were higher in MS patients, as compared with the control group.

Increased cranio-caudal and caudo-cranial CSF flow volume and aqueductal area in MS patients could possibly be due to cerebral atrophic changes that may occur at every stage of MS. CSF spaces expand with cerebral atrophy and consequently, CSF flow volumes in a cardiac cycle pass through the cerebral aqueduct.

This idea is supported by *Chiang et al. (2010)* who found a relationship between ventricular morphology and aqueductal CSF flow in healthy subjects and in patients with communicating hydrocephalus. They concluded that aqueductal CSF flow should not be

regarded independently of ventricular morphology.

Zamboni et al. (2012) suggested that impaired CSF dynamics in MS patients contributes to an increase in volumes of the third and lateral ventricles. In addition, reverse volume in the definitive diagnosis of active and chronic period MS disease, was higher in MS patients with chronic plaques. This result can be used in the place of contrast-enhanced MRI.

Increased cranio-caudal and caudo-cranial CSF flow volume (ml) in MS patients can be explained by the venous hemodynamic impairment in MS patients mentioned by *Zamboni et al. (2012)*. Although we did not investigate this phenomenon in our study, we suggest that it causes a mild deficit in CSF reabsorption through the sinuses and an increase in the above parameters. Another finding supports this hypothesis: the CSF regurgitant fraction was found to be slightly higher in the MS patients than the control group; however, this difference was not statistically significant

Gorucu et al. (2011) reported that the net CSF flow volume showed no significant differences between MS patients and controls. In the present study, the net CSF flow volume (ml) and average flow (ml/sec) parameters evaluated with PC-MRI, were not found to be statistically significant between MS patients and the control group.

Although cranio-caudal (ml) and caudo-cranial CSF flow volume (ml), and aqueductal area (mm²) were higher in MS patients, the fact that peak systolic and diastolic velocities were not significantly different between MS patients and controls may be seen as controversial. But

peak systolic or peak diastolic velocities (cm/s) are not the only parameters used in calculation of CSF flow volume (ml) (*Oner et al., 2017*).

This study is not without limitations: First the number of the enrolled individuals was relatively small and, therefore, further studies should extend our findings using a larger sample size. Also, we did not evaluate the venous outflow abnormalities and the ventricle volumes, which is a limitation of our study. In addition, PC-MRI may result in errors in quantitative measurements, due to non-linear gradients, partial volume effects, and errors in placing ROI (*Demirtaş et al., 2020*).

Lastly, the effect of altered CSF pulsatility on long term neurologic outcomes is unknown, and only longitudinal studies will be able to provide further insight on this important question.

CONCLUSION

The forward and reverse CSF flow volumes and aqueductal area were significantly higher in the MS patients. The altered cerebral flow physiology may be used to differentiate active versus chronic disease. These findings may support the venous theory in MS patients, but may also be explained by atrophy-dependent ventricular dilatation independent of the venous theory in MS patients.

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دور ديناميكيات السائل النخاعي باستخدام التصوير بالتباين الطوري للرنين المغناطيسي في تقييم نشاط مرض التصلب المتعدد

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خلفية البحث: التصلب المتعدد هو مرض تنكسي عصبي معقد مزمن يستهدف الجهاز العصبي المركزي ويعتقد على نطاق واسع أنه من أمراض المناعة الذاتية في الطبيعة. يمكن أن تكون التغييرات في التدفق الطبيعي للسائل النخاعي في الدماغ عاملاً مساهماً في تراكم المواد السامة في النسيج الخلاقي في الدماغ، وقد تكون مرتبطة بالاضطرابات العصبية مثل مرض الزهايمر والتصلب المتعدد.

الهدف من البحث: تقييم ديناميكيات السائل النخاعي وعلاقته بنشاط التصلب المتعدد باستخدام التصوير بالتباين الطوري للرنين المغناطيسي.

المرضى وطرق البحث: تم إجراء هذه الدراسة بين أبريل 2020 وأكتوبر 2020. شملت 45 حالة مقسمة إلى ثلاث مجموعات متساوية (مرض التصلب العصبي المتعدد مع لويحات نشطة معززة في التصوير بالرنين المغناطيسي (المجموعة 1)، مرض التصلب المتعدد مع لويحات مزمنة (المجموعة 2) ومجموعة مقارنة (المجموعة 3). وقد تم إجراء التقييم الكمي لتدفق السائل النخاعي على مستوى القناة الدماغية بواسطة التصوير بالتباين الطوري للرنين المغناطيسي.

نتائج البحث: فيما يتعلق بالسرعة القصوى ومتوسط السرعة والحجم الصافي ومتوسط التدفق ، لم تكن هناك فروق ذات دلالة إحصائية بين المجموعات الثلاث. فيما يتعلق بالحجم الأمامي والحجم العكسي ومنطقة القناة كانت هناك فروقاً ذات دلالة إحصائية بين المجموعات الثلاث.

الاستنتاج: كانت أحجام تدفق السائل النخاعي الأمامي والخلفي ومنطقة القنوات المائية أعلى بشكل ملحوظ في مرضى التصلب المتعدد. وقد تدعم هذه النتائج النظرية الوريدية لدى مرضى التصلب المتعدد، ولكن يمكن تفسيرها أيضاً من خلال التوسيع البطيئ المعتمد على الضمور المستقل عن النظرية الوريدية في مرضى التصلب المتعدد.

الكلمات الدالة: ديناميكيات السائل النخاعي، التباين الطوري، التصوير بالرنين المغناطيسي، نشاط مرض التصلب المتعدد.