



# Flow volume measurement of arterial venous and cerebrospinal fluid in patients with multiple sclerosis

## *Medição do volume de fluxo do líquido cefalorraquidiano e venoso arterial em pacientes com esclerose múltipla*

Serpil Aglamis<sup>1</sup> Murat Gönen<sup>2</sup>

<sup>1</sup>Firat University, Faculty of Medicine, Department of Radiology, Elazig, Turkey.

<sup>2</sup>Firat University, Faculty of Medicine, Department of Neurology, Elazig, Turkey.

Address for correspondence Serpil Aglamis (e-mail: drserpil23@yahoo.com.tr).

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### Abstract

**Background** Multiple sclerosis (MS) is usually described as an autoimmune disease, although the exact mechanism of the disease remains unknown. There have been studies reporting that venous flow abnormalities may be involved in the pathogenesis of MS or many of the associated clinical manifestations.

**Objective** The aim of this study was to evaluate flow volumes of the middle cerebral artery (MCA), transverse sinus (TS), and cerebral aqueduct using phase contrast magnetic resonance imaging (PC-MRI) in relapsing-remitting MS patients and a control group.

**Methods** We included 34 patients diagnosed by the McDonald criteria, revised in 2017, as well as 15 healthy controls matched by age and sex. The MRI scans were performed using a 1.5-T superconducting scanner. Axial T1-weighted, T2-weighted, and PC-MRI sequences were performed for the quantitative investigation of flow volume measurements. Quantitative analyses of flows were performed using flow analyses program PC-MRI angiography software. A circular region of interest was placed manually into the cerebral aqueduct, bilateral MCA, and TS.

**Results** Flow volumes of the cerebral aqueduct and MCA were not statistically significant between the MS and control groups. The flow volumes of the TS for the patient group were lower than those of the control group, and this difference was statistically significant.

**Conclusions** A reduced TS flow volume in MS patients was noted in the present study when compared with the control group, suggesting a relation between venous pathologies and MS. Further studies are needed to understand whether this relation is causal or epiphenomenal.

### Keywords

- ▶ Multiple Sclerosis
- ▶ Magnetic Resonance Imaging
- ▶ Middle Cerebral Artery
- ▶ Transverse Sinuses

### Resumo

**Antecedentes** A esclerose múltipla (EM) é comumente descrita como uma doença autoimune, embora seu mecanismo exato permaneça desconhecido. Há estudos que

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afirmam que anormalidades no fluxo venoso podem estar relacionadas à patogênese da EM ou a muitas das manifestações clínicas associadas.

**Objetivo** O objetivo deste estudo é avaliar os volumes de fluxo da artéria cerebral média (ACM), do seio transversal (ST) e do aqueduto cerebral usando ressonância magnética com contraste de fase (PC-MRI) em com EM recorrente-remitente.

**Métodos** Incluímos 34 pacientes diagnosticados pelos critérios de McDonald, revisados em 2017, além de 15 controles saudáveis pareados por idade e gênero. A ressonância magnética foi realizada usando um scanner supercondutor de 1,5 T. As sequências de PC-RM axiais, ponderadas em T1 e ponderadas em T2 foram realizadas para investigação quantitativa das medidas de volume de fluxo. As análises quantitativas de fluxo foram realizadas usando o software de angiografia PC-MRI do programa de análise de fluxo. Uma região circular de interesse foi localizada manualmente no aqueduto cerebral, ACM bilateral e ST.

**Resultados** Os volumes de fluxo do aqueduto cerebral e da ACM não foram estatisticamente significantes entre o grupo de pacientes e os controles. Os volumes ST do grupo de pacientes foram menores que os do grupo controle, e essa diferença foi estatisticamente significativa.

**Conclusões** No presente estudo, um menor volume de fluxo ST foi registrado em pacientes com EM em comparação ao grupo controle, sugerindo uma relação entre patologias venosas e EM; Mais estudos são necessários para entender se essa relação é causal ou um fenômeno secundário.

#### Palavras-chave

- ▶ Esclerose Múltipla
- ▶ Imagem de Ressonância Magnética
- ▶ Artéria Cerebral Média
- ▶ Seios Transversos

## INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating and degenerative disease of the central nervous system (CNS).<sup>1</sup> The pathogenesis of MS remains unknown; however, multiple factors have been implicated in its etiology, and it is widely accepted that an autoimmune mechanism plays an essential role in the disease.<sup>2</sup> A close relation between MS lesions and the cerebral vasculature has long been recognized; autoreactive lymphocytes cross the blood-brain barrier to initiate an autoimmune response, which eventually leads to neuronal degeneration and tissue damage.<sup>3-5</sup>

Recently, an alternative hypothesis related to the pathogenesis of MS has been proposed, with some authors claiming there is a strong relationship between venous flow abnormalities and MS. A study examining whether cerebrospinal fluid (CSF) flow dynamics are affected in MS patients has been reported; however, there is little evidence supporting venous insufficiency in patients with MS.<sup>6</sup>

The chronic cerebrospinal venous insufficiency (CCSVI) hypothesis introduced by Zamboni et al. suggests that MS is triggered by CCSVI.<sup>4</sup> Zivadinov et al., however, put forward a different hypothesis, suggesting that chronic venous insufficiency is a clinical condition that occurs as a result of MS rather than being its cause.<sup>7</sup> Comparisons of MS patients and healthy controls have revealed that the prevalence of CCSVI varies from 0 to 100% in patients with MS.<sup>8-10</sup>

Studies in literature investigating the relationship between CCSVI and MS report complicated and conflicting results. The CCSVI hypothesis has spurred passionate discus-

sion in the scientific community and has led to an increase in invasive endovascular therapy. The importance of this discussion and its potential impact on treatment strategies necessitates the resolution of the question of whether CCSVI exists in patients with MS.

There are limited studies that have measured cerebral volumes of the artery, vein, and CSF flow in MS patients. The aim of the present study was to evaluate the flow volumes of the middle cerebral artery (MCA), transverse sinus (TS), and cerebral aqueduct, using phase contrast magnetic resonance imaging in relapsing-remitting multiple sclerosis (RRMS) patients and a control group.

## METHODS

### MS patients and controls

We included 34 patients (aged 18–61, mean: 37.1 years) diagnosed by clinically defined RRMS fulfilling the McDonald criteria, revised in 2017, as well as 15 healthy controls (aged 19–49, mean: 33.2 years) matched by age and sex.

This study was approved by the Firat University's Ethics Committee. The patients were recruited from the neurology department of our hospital, and the control group consisted of neurologically normal participants with no other known diseases. The inclusion criteria for the MS patients were a current remission status of the disease and no history of any other neurological disease. All patients and the control group were informed of the study procedures and gave their informed consent.



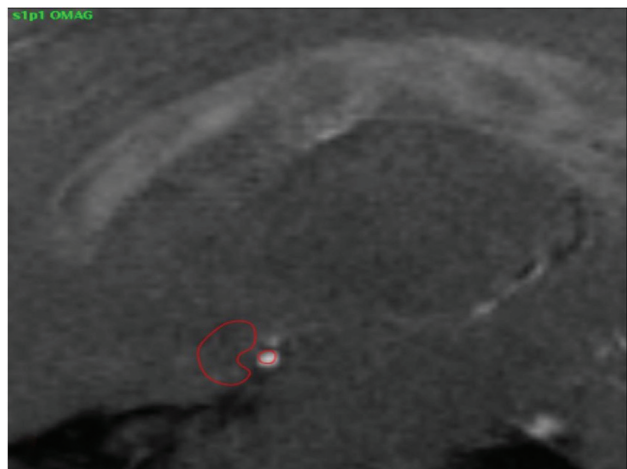
**Figure 1** The CSF flow was performed in the axial plane, which was perpendicular to the cerebral aqueduct.

### MRI technique

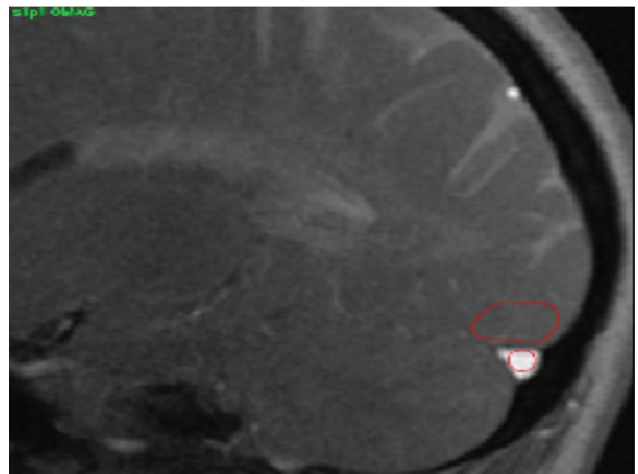
The MRI scans were performed using a 1.5-T superconducting scanner (Signa Excite, GE Healthcare, Milwaukee, WI, USA) equipped with high-speed gradient with an 8-channel head coil. Axial T1-weighted and T2-weighted sequences were performed in all cases for evaluation of the brain.

Phase-contrast (PC) MRI was performed for quantitative investigation of flow volume measurements. For the CSF flow, PC-MRI was performed in the axial plane, which was perpendicular to the cerebral aqueduct (► **Figure 1**). The following parameters were used: TR 16 milliseconds; TE minimum ms; slice thickness 4 mm; flip angle 20°; field of view (FOV) 18 × 18 cm; spacing 1; frequency 256 × 256; velocity encoding (VE) 15 cm/s.

The MCA and TS were quantitatively investigated for arterial and venous flows, respectively. All PC-MRI scans were performed in the axial plane, which was perpendicular to the courses of the MCA and TS. The flow measurements of the MCA and TS were obtained from oblique-sagittal images (► **Figures 2 and 3**). The following parameters were used for the MCA and TS: TR 7.6 and 11.4 milliseconds; TE minimum ms; slice thickness 4 mm; flip angle 20°; FOV 18 × 18 cm;



**Figure 2** The flow measurement of the MCA, from oblique-sagittal image.



**Figure 3** The flow measurement of the TS, from oblique-sagittal image.

spacing 1; frequency 256 × 256; velocity encoding (VE) 20 and 50 cm/s, respectively. Cardiac triggering was performed using finger plethysmography.

### MRI analysis

Quantitative analyses of flows were performed using the flow analyses program PC-MRI angiography software, and PC images were transferred to the Advantage Workstation (GE Healthcare, Milwaukee, WI, USA), software version 2.0. A circular region of interest (ROI) was placed manually in the cerebral aqueduct for measurement of the CSF flow volume (expressed as ml/min). We also placed ROIs into the bilateral MCA and TS for all cases. Thereafter, we measured flow volumes of the MCA and TS. The data of the patient and control groups were recorded and statistically compared.

### Statistical analyses

The Statistical Package for the Social Sciences (SPSS, IBM Corp. Armonk, NY, USA) software, version 22.0, was used to evaluate the data. The Kolmogorov-Smirnov test was used to test the equality of the distribution of variables. Because the age and CSF flow data are normally distributed, the Student *t*-test was performed to evaluate these variables. We also used the Mann-Whitney U-test to compare MCA and TS data because the variables did not show a normal distribution. A *p*-value < 0.05 was accepted as statistically significant.

## RESULTS

We included 34 patients with MS (22 female, 12 male) and 15 normal controls (4 female, 11 male) in the study. The mean ages of the patient group and control group were 37.15 ± 10.89 years and 33.20 ± 10.94 years, respectively. This was not significant (*p* > 0.05).

The mean CSF flow volumes of the cerebral aqueduct for MS patients and controls were 0.26 ± 0.16 ml/min and 0.32 ± 0.25 ml/min, respectively, and this difference was not significant (*p* > 0.05). The mean flow volume of the TS was 34.65 ± 20.98 ml/min in the MS patient group, and

**Table 1** Mean ages and mean flow volumes of the patient and control groups

Group		Age (years)	FVOAq (ml/min)	FVOS (ml/min)	FVOA (ml/min)
MS	Mean	37.15	0.26	34.65*	19.01
	N	38	31	59	59
	SD	10.89	0.16	20.98	10.67
	Range	43.00	0.65	89.62	59.52
	Median	39.00	0.22	31.80	16.90
Control	Mean	33.20	0.32	53.95*	24.09
	N	15	15	25	24
	SD	10.94	0.25	29.27	13.86
	Range	33.00	0.90	101.50	44.31
	Median	33.00	0.29	51.80	26.05

**Abbreviations:** FVOAq, flow volume of aqueductus of cerebri; FVOS, flow volume of transverse sinus; FVOA, flow volume of middle cerebral artery; SD: standard deviation.

**Notes:** \* $p < 0.05$ .

53.95 ± 29.27 ml/min in the control group, and this difference was statistically significant ( $p < 0.05$ ). The mean flow volumes of the MCA in the MS patient group and the control group were 19.01 ± 10.67 and 24.09 ± 13.86, respectively, but this difference was not significant ( $p > 0.05$ ). The data are summarized in ► **Table 1**.

## DISCUSSION

As in other chronic inflammatory diseases of the CNS, vascular pathology is profound in patients with MS.<sup>11</sup> In chronic MS lesions, extensive enlargement of the perivascular space and vascular fibrosis is common.<sup>12</sup> However, the relation between the blood-brain barrier damage, inflammation, and structural vascular pathology is complex.<sup>13</sup> It is assumed that a chain of events, such as inflammation, demyelination, ischemia, and tissue necrosis following abnormal vascular flow and vasculitis, plays a role in the pathology of MS.<sup>14</sup> Contrasting the hypothesis suggesting that CCSVI triggers the pathology of MS, there have been studies concluding that vascular pathology does not trigger MS.<sup>15–17</sup> A meta-analysis established a strong association between CCSVI and multiple sclerosis, while two recent, large case-control studies could identify no such association.<sup>18–20</sup>

The PC-MRI has a variety of established applications in quantifying blood flow and velocity;<sup>21</sup> it generates a signal contrast between flowing and stationary nuclei by sensitizing the phase of the transverse magnetization to the velocity of motion.<sup>22</sup> Before PC-MRI data are acquired, the anticipated maximum flow velocity must be inserted in the pulse sequence protocol velocity encoding (VENC). To obtain the optimal signal, the flow velocity should be the same as or slightly less than the selected VENC.<sup>23</sup> Velocity and flow are measured with a commercial software that allows users to define the ROI around the vessel lumen.<sup>24</sup>

The cerebrovascular perfusion can be potentially altered due to the close relationship between MS lesions and vascular pathology.<sup>25</sup> Hypoxia-like tissue injury was identified with a suggestion of hemodynamic impairment in relation to lesion

pathogenesis of MS. Brain perfusion in vivo can be assessed with MRI. Whereas enhancing lesions show increased perfusion, chronic MS lesions show decreased perfusion. Ge et al. investigated the perfusion characteristics in MS lesions using dynamic susceptibility contrast MRI (DSC-MRI). They observed reduced blood flow in all MS lesions, prolonged mean transit time, and decreased cerebral blood flow compared with the control group. They concluded that DSC-MRI measurements demonstrate potential for investigating hemodynamic abnormalities in MS lesions.<sup>26</sup> We investigated the flow volume of the MCA using PC-MRI (velocity encoding accepted as 50 cm/s), but we found no statistically significant differences in the MCA flow volumes between the patient group and the control group.

The rate of CSF formation in humans is approximately 0.3 to 0.4 ml/min. It originates from the choroid plexus, ependymal lining of the ventricles, parenchyma of the brain, and the spinal cord.<sup>27</sup> The absorption of the CSF happens through the arachnoid villi into the great dural sinuses and true lymphatic vessels;<sup>28</sup> its flow is pulsatile and synchronous with the cardiac cycle, so using cardiac gating can provide increased sensitivity of the image.<sup>29</sup> Because very little CSF liquid truly circulates, pulsatile flow can be measured by PC-MRI.<sup>30</sup> Reliable flow quantification is reported to be feasible if the diameter of the aqueduct lumen is greater than 1.5 mm.<sup>2,31</sup> Zamoni et al. found a net CSF flow in the cerebral aqueduct to be reduced in MS patients with CCSVI. They concluded that a significant relationship exists between the decline in net CSF flow and CCSVI severity.<sup>32</sup> In a study of 40 patients with MS and 40 healthy controls, Gorucu et al. found significantly higher CSF flow volumes in the MS patients compared with the controls.<sup>5</sup> In contrast, Sunderström et al. incorporated both contrast-enhanced MRI venography and PC-MRI venography and found no statistically significant difference in the CSF flow parameters between patients with MS and the normal control group.<sup>33</sup> We also found no statistically significant difference in the CSF flow parameters between patients with and without MS. Beggs et al. investigated the CSF dynamics in the cerebral aqueduct in CCSVI-positive and negative healthy individuals,



and concluded that CSF flow was increased in the CCSVI-positive group compared with the negative group.<sup>34</sup>

The idea of a vascular etiology can be traced back to the original description of a perivenular predilection of MS lesions, based on observations in dogs, in whom the injection of obstructing agents into the venous sinuses caused an MS-like condition.<sup>35</sup> Putnam et al. also claimed that using anticoagulant dicumarol produced favorable results in RRMS patients.<sup>36</sup> Blinkenberg et al., however, found little evidence for anatomic or hemodynamic abnormalities of cervical venous drainage in patients with MS when compared with healthy controls, and claimed that CCSVI-like changes were not a pathological condition.<sup>6</sup> Jurkiewicz et al. evaluated the prevalence of extracranial venous system anomalies in MS patients and found anomalies of the extracranial venous system in 10 MS patients (47.6%) and 13 controls (68.4%). These measurements were not statistically significant.<sup>37</sup> McTaggart et al. evaluated the possible differences in the extracranial venous drainage of MS and healthy individuals. They concluded that patients with MS have a greater internal jugular vein (IJV) flattening, and a trend toward more non-IJV collaterals than control groups.<sup>38</sup> Our study differed from other studies in the literature by the following points: we conducted our measurements at the intracranial levels and flow volumes were measured from the cerebral aqueduct, MCA, and TS using PC-MRI.

In the present study, the flow volume of TS was significantly lower in MS patients than in the control group. It has been suggested that hemodynamic changes in the venous system of MS patients may be a functional epiphenomenon of microvascular disorder.<sup>39</sup> Although there have been studies that do not show vascular pathology to be the cause of MS, the possibility that venous pathologies are a cofactor in the development of MS cannot be excluded. For people with susceptibility to MS, CCSVI is likely to promote the development of the disease.<sup>40</sup>

In conclusion, complicated and conflicting results have been recorded in literature regarding the relationship between CCSVI and MS. A reduced TS flow volume in MS patients was noted in the present study when compared with the control group, suggesting a relationship between venous pathologies and MS. Further studies are needed to understand whether the relationship between venous pathologies and MS is causal or epiphenomenal.

#### Authors' Contributions

SA: planning and design of the study, the analysis of the data, and the writing of the article; MG: responsible for the selection of patients in accordance with the inclusion criteria.

#### Conflict of Interest

The authors have no conflict of interests to declare.

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