Published in final edited form as:

Clin Auton Res. 2019 June ; 29(3): 329–338. doi:10.1007/s10286-018-0555-6.

Abnormal venous postural control: multiple sclerosis-specific change related to gray matter pathology or age-related neurodegenerative phenomena?

Dejan Jakimovski¹, Matthew Topolski¹, Kana Kimura¹, Karen Marr¹, Sirin Gandhi¹, Deepa P. Ramasamy¹, Niels Bergsland¹, Jesper Hagemeier¹, Bianca Weinstock-Guttman², and Robert Zivadinov^{1,3}

¹Buffalo Neuroimaging Analysis Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA;

²Jacobs MS Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, NY, USA;

³Center for Biomedical Imaging at Clinical Translational Science Institute, University at Buffalo, State University of New York, Buffalo, NY, USA

Abstract

Background: Autonomic nervous system dysfunction has been previously observed in multiple sclerosis (MS) patients.

Objective: To assess associations between magnetic resonance imaging-detected neuroinflammatory and neurodegenerative pathology and postural venous flow changes, indicative of autonomic nervous system function.

Methods: 138 patients with MS and 49 healthy controls were scanned using a standardized 3T magnetic resonance imaging protocol. Lesion volume and brain volumes were assessed. The cerebral venous flow (CVF) was examined by color-Doppler sonography in supine and upright position and their difference was calculated as Δ CVF. Based on Δ CVF, subjects were split into absolute or quartile groups. Student's *t*-test, χ^2 -test, and analysis of covariance adjusted for age and sex were used correcting for multiple comparisons.

Results: No differences were found between healthy controls and patients with MS in both supine and upright Doppler-derived CVF, nor in prevalence of abnormal postural venous control. Patients with absolute negative Δ CVF had higher disability score ($p=0.013$), lower gray matter ($p=0.039$) and cortical ($p=0.044$) volumes. The negative Δ CVF MS group also showed worse bladder/bowel function when compared to the positive Δ CVF (2.3 vs. 1.5, $p=0.052$). Similarly, the lowest quartile Δ CVF MS group had higher T1-lesion volume ($p=0.033$), T2-lesion volume ($p=0.032$), and lower deep gray matter ($p=0.043$) and thalamus ($p=0.033$) volumes when compared to those with higher Δ CVF quartiles.

Corresponding Author: Robert Zivadinov, MD, PhD, FAAN, FEAN, FANA, Center for Biomedical Imaging at Clinical Translational Science Institute, Buffalo Neuroimaging Analysis Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, 100 High Street, Buffalo, NY 142013, Phone: 716-859-7040, Fax: 716-859-7066, rzivadinov@bnac.net.

Conclusion: No difference in postural venous outflow between patients with MS and healthy controls was found. However, when the abnormal CVF is present within the MS population, it may be associated with more inflammatory and neurodegenerative pathology. Further studies should explore whether the orthostatic venous changes are an aging or a MS-related phenomenon and if the etiology is due to impaired autonomic nervous system functioning.

Keywords

MRI; multiple sclerosis; ANS; brain atrophy; inflammation; venous flow

Introduction:

Multiple Sclerosis (MS) is a chronic autoimmune-mediated demyelinating disorder of the central nervous system. [1] However, a neurodegenerative component is being increasingly recognized as an important contributor to the disease pathophysiology. [1] Global and regional brain atrophy in MS has been previously associated with both physical and cognitive decline. [2,3] One commonly overlooked pathology within patients with MS is impairment of the autonomic nervous system. The level of autonomic impairment in MS has been associated with clinical measures of disability, such as Expanded Disability Status Scale score, and the measures of cervical spinal cord damage, such as cross-sectional area. [4] High prevalence of patients with MS who present with various levels of autonomic impairment (45%–84%), including cardiovascular, bladder and bowel, sexual and thermoregulatory dysfunction, further corroborate the extensive involvement of autonomic dysfunction in MS. [5] Therefore, a potential link between autonomic dysfunction and both axonal loss and neurodegeneration, which is more prominent in progressive stages of the disease, can be hypothesized.

Studies have shown that a large proportion of patients within the early stages of MS present with autonomic dysfunction, associated with changes in the heart rate variability and lower catecholamine response profiles. [6] In addition to the central vascular autonomic control, questionnaire-based and sudomotor function testing which include sympathetic skin response, thermoregulatory sweat testing, and quantitate sudomotor axon reflex testing may provide better supplementary information on autonomic function. [7,8] Investigating abnormalities of the postural cerebral blood flow changes can potentially provide additional insights into the complex neurodegenerative MS pathophysiology.

Previous reports of differential arterial inflow and venous outflow patterns during changes of the body position in patients with MS have found a high prevalence of abnormal postural control and potentially implied an autonomic dysfunction. [9–11] Moreover, these reports showed that the prevalence of the impairment was higher in progressive patients compared to those with early MS or patients with other neurological diseases. [10,12] The internal jugular veins are the main venous drainage pathway for the brain in the supine position, whereas in the upright position, the jugulars collapse and the flow shifts to the vertebral veins and the vertebral venous plexus. [13–15] The reduction of the size and the flow of internal jugular veins in the upright position occurs as a physiological response to the

opposing gravitational forces, and it allows maintenance of normal cerebral perfusion, resulting in a prevention of excessive orthostatic drainage.

A number of imaging studies have confirmed that the pathways of autonomic control involve the insular, anterior cingulate and infralimbic cortices. [16] Functional MRI studies were able to demonstrate topographical organization of the autonomic signals associated to the right anterior insula and shown that insular cortex is responsible for parasympathetic activity. [17] Similarly, classic autonomic challenges like Valsalva maneuver differentially recruit sympathetic and parasympathetic responses and demonstrate differential lateralization patterns within the anterior and posterior insular cortex. [18] The frontoinsula and cingulate cortex are fundamental regions responsible for maintaining sufficient basal autonomic control. [19] Since widespread cortical networks include pathways responsible for the autonomic control, MS-associated cortical damage may potentially cause autonomic dysfunction and impaired autonomic hemostasis.

The aim of this study was to assess the prevalence of abnormal postural venous control in both patients with MS and in healthy controls, and compare the findings with those in the literature. Additionally, our goal was to employ MRI-derived outcomes in order to understand better the association between abnormal postural venous control and inflammatory and neurodegenerative MS pathology.

Materials and Methods:

Subjects:

All participants utilized for this study were part of cardiovascular, environmental, and genetic study in MS (CEG-MS). [20,21] The inclusion criteria consisted of 1) age between 18 and 75 years old; 2) having MRI and Doppler scans completed within 30 days of the clinical examination; 3) MS diagnosis as defined by the 2017 revised McDonald criteria or being a healthy control without any current or prior neurological diseases. [22] The exclusion criteria included: 1) nursing mother or pregnant woman; 2) the presence of a clinical relapse; and/or 3) steroid treatment within 30 days of the MRI scan. The demographic and clinical information was collected by structured questionnaires, physical examination, and by further cross-reference with the medical records. Due to the small number of secondary-progressive and primary-progressive MS patients, they were grouped into a progressive MS group. In order to determine the level of physical disability of patients with MS, an Expanded Disability Status Scale examination was performed by a neurologist. The bladder and bowel functional score was additionally used. The study was approved by the local Institutional Review Board and all participants signed a consent form prior to their participation.

MRI acquisition and analysis:

The MRI scans were obtained using a 3T GE Signa Excite HD 12 Twin Speed 8-channel scanner (General Electric, Milwaukee, WI, USA) with an 8-channel head and neck coil. MRI sequences consisted of an axial 3D-spoiled-gradient recalled T1 weighted image, dual

fast spin-echo T2/proton density, and 2D fluid attenuated inversion recovery. A more detailed description of the MRI acquisition protocol was previously published. [23]

T1 and T2 lesion volume were obtained by a semi-automated edge detection and contouring/thresholding technique. [2] The normalized volumes of whole brain, gray matter, white matter, ventricular cerebrospinal fluid, and cortex were obtained utilizing SIENAX software (version 2.6). [24] Regional tissue-specific normalized volumes of the total deep gray matter and the thalamus, were derived using FIRST. [25] In order to reduce the impact of T1 hypointensities, lesions were filled prior to the tissue segmentation. [26]

Doppler sonography assessment

Extra-cranial neck vessel examination was performed using an echo-color Doppler (ECD Esoate– Biosound My Lab 25 Gold, Genoa, Italy) equipped with a 7.5–10 MHz transducer. During the procedure, patients were seated on an automated reclining chair that allowed positioning in supine (0°) and upright positions (90°). A 3-minute break between repositioning of the patient allowed redistribution of the venous flow. The examination was performed by a blinded technologist who used a standardized scanning protocol. [27] The blood flow within the jugular and vertebral veins was assessed in both supine and upright positions using manual flow calculations. Time average velocity (V_{MT}) was calculated using a manual correction of the Doppler angle, while manually drawn cross-sectional area measurement was performed on color Doppler settings (equation 1). The sites for cross-sectional area measurement were just above the entry of the facial vein (J3) for the jugular veins and at the cervical level of C3-C4 for the vertebral veins. The CVF was calculated by multiplying the V_{MT} over 4 seconds time phase and the manually drawn cross-sectional area on axial view (equation 2).

$$V_{MT} = \Sigma Vi * \Delta T \quad 1)$$

$$Flow = V_{MT} * CSA \quad 2)$$

The total CVF in both supine and upright positions was calculated by adding the individual flow of bilateral internal jugular veins and bilateral vertebral veins (equation 3). Furthermore, for examining the postural changes within the CVF (CVF), the upright CVF was subtracted from the supine CVF (equation 4).

$$CVF = left IJV + right IJV + left VV + right VV \quad 3)$$

$$\Delta CVF = supine CVF - upright CVF \quad 4)$$

Subjects that showed higher upright CVF compared to their supine postural CVF were termed as patients with an “abnormal” postural CVF control (absolute negative CVF). A second analysis was performed based on the lowest quartile cut-off value of the CVF for both the healthy controls (201.9 mL/min) and patients with MS (214.8 mL/min), with the participants split into two respective groups (lowest quartile CVF group and the remaining quartiles group).

Statistical analysis

The statistical analysis was performed using SPSS 25.0 (IBM, Armonk, NY, USA). Clinical, demographic and MRI-derived information was compared using χ^2 -cross tabulation, Mann-Whitney test, and Student's *t*-test, as appropriate. Additionally, an analysis of covariance (ANCOVA) with correction for patients' age and sex was performed. To determine the normality of all variables, both Kolmogorov-Smirnov and Shapiro-Wilk tests were used. For the MRI-derived comparisons, group-specific Benjamini-Hochberg procedure for multiple comparison correction was applied. $P < 0.05$ after Benjamini-Hochberg correction was considered statistically significant using two-tailed test.

Results:

Demographic and clinical characteristics

The demographic and clinical characteristics of the 138 patients with MS and 49 healthy controls are summarized in Table 1. The MS group had mean age of 53.6 ± 10.9 years old, mean disease duration of 20.1 ± 10.6 years, a median Expanded Disability Status Scale score of 3.0 (interquartile range 1.9–6.0), and female ratio of 100/138 (72.5%). The patients were treated with disease-modifying therapies including interferon- β ($n=46$, 33.3%), glatiramer acetate ($n=39$, 28.3%), natalizumab ($n=5$, 3.6%), oral disease modifying medications ($n=13$, 9.4%), other off-label treatments ($n=6$, 4.4%) and 29 patients with MS (21%) were not treated. Additionally, the MS cohort consisted of 88 relapsing-remitting and 50 progressive MS patients. The healthy control group had a female ratio of 36/49 (73.5%) and was 51.4 ± 14.5 years old. There were no significant differences between the both groups regarding their sex ratio nor age.

The demographic and clinical characteristics between the relapsing-remitting and progressive subgroups are summarized in Supplement Table 1. Significant differences between highest and lowest CVF quartiles of PMS patients were seen in sex (27 vs. 11 females; 69.2% vs. 100%; $p=0.046$), disease duration (25.1 vs. 32.6 years, $p=0.026$), as well as a median Expanded Disability Status Scale score (6.0 vs. 6.75, $p=0.021$). There were no differences in terms of the type of disease-modifying therapy use between patients within the higher and lowest quartile (relapsing-remitting, $p=0.781$ and progressive, $p=0.716$).

Differences in bilateral internal jugular veins and vertebral veins flow between patients with MS and healthy controls

The venous flow within the bilateral jugular veins, vertebral veins, and total CVF measured in both postural positions of patients with MS and healthy controls is summarized in Table 2. There were no significant differences between patients with MS and healthy controls in their

flow in supine and upright position within the internal jugular veins ($p=0.632$, $p=0.260$), vertebral veins ($p=0.213$, $p=0.293$) nor in total CVF ($p=0.565$, $p=0.391$), respectively.

Differences in MRI-derived outcomes in subjects with “abnormal” postural CVF control

Based on absolute negative postural control of venous flow, the patients with MS were classified as positive (normal) and negative (abnormal) postural venous groups. The differences in demographic, clinical and MRI-derived outcome measures between the positive ($n=124$, 89.9%) and negative ($n=14$, 10.1%) postural venous control in patients with MS are shown in Table 3.

The MS group with abnormal postural CVF control had a significantly higher median Expanded Disability Status Scale score (3.5 vs. 3.0, $p=0.013$), and lower gray matter ($p=0.039$) and cortical ($p=0.044$) volumes, compared to normal postural control group (Table 3). The absolute negative CVF group showed worse bladder and bowel function when compared to the absolute positive CVF (mean 2.3 vs. 1.5, $p=0.052$), but this was not significant. Similarly to the MS group, there were 6 healthy controls (12.2%) that presented with negative CVF status. Although the small sample size limited the analysis, there was no significant difference between negative and positive CVF healthy controls for demographic or any MRI-derived brain volume measures (Table 3).

Differences between subjects with the lowest and higher quartiles CVF

The higher quartiles CVF group of patients with MS, were 68.3% (71/104) female, had a mean age of 53.4 ± 10.9 years old, a disease duration of 19.6 ± 10.9 years, and a median Expanded Disability Status Scale score of 3.0 (interquartile range 1.5–5.25). Among the patients within the higher CVF quartiles group, the ratio of relapsing-remitting to progressive MS patients was 65/39. On the other hand, the lowest CVF quartile had a female ratio of 29/34 (85.3%), was on average 54.2 ± 11.4 years old, had a disease duration of 21.7 ± 12.0 years, and had a median Expanded Disability Status Scale score of 3.0 (interquartile range 2.0–6.5). Similarly, the relapsing-remitting to progressive MS distribution of the lowest CVF quartile was 23/11, respectively. Within the quartile comparison, there were no significant differences observed for sex, age, disease duration, disease course or disability level. All demographic and clinical characteristics of the quartile-based MS groups are shown in Table 3.

Comparably, the higher quartiles of the healthy control group had a ratio of females of 28/37 (75.7%) and was on average 53.8 ± 13.7 years old, whereas the lowest quartile had the average age of 43.9 ± 14.9 years old and had female ratio of 8/12 (66.7%). Participants in the lowest quartile group were generally younger than those in the higher quartile group ($p=0.038$).

MRI-derived outcome measures between lower and higher quartiles CVF for both the patients with MS patients and healthy controls are presented in Table 4. The lowest CVF quartile MS group had significantly higher T1-lesion volume ($p=0.033$), T2-lesion volume ($p=0.032$) and lower deep gray matter ($p=0.043$) and thalamus ($p=0.033$) volumes. Although the small sample size limited the analysis, there were no significant differences in any MRI-

derived outcome measures between the lowest and higher quartiles CVF healthy control groups.

A separate analysis within the relapsing-remitting and progressive MS subgroups was performed. The differences in MRI-derived outflow measures within both subgroups are shown in Supplement Table 2. We found no significant differences between higher and lowest quartiles CVF RRMS subgroups with respect to the volumetric outcomes. The lowest quartiles CVF progressive MS subgroup had significantly lower thalamus volume ($p=0.049$) when compared to the higher quartiles CVF group.

Discussion:

In the present study, there was no difference in the postural control of the venous flow between patients with MS and healthy controls. The inflammatory and neurodegenerative MS pathology was more severe in patients with autonomic impairment, as measured by orthostatic venous dysfunction. Although this impairment was manifested in a similar ratio of healthy controls, patients with MS with abnormal venous postural control (both in terms of absolute and quartile analysis) had longer disease duration, higher clinical disability scores, higher lesion burden, and more gray matter atrophy. The worse bladder and bowel functional scores within patients with abnormal venous postural control provide some concurrent validity of the measure used. Although the small sample size limited meaningful analysis, the healthy controls did not differ in neither demographic nor MRI-derived volumetric measures.

Cerebral venous drainage in supine body posture is mainly attributed to the internal jugular veins, however when positioned upright, the venous drainage shifts and directs through the vertebral venous system. [13,15,28] This gravity-driven increase in jugular resistance and the collapse of the internal jugular veins allow control of the cerebral venous pressure despite the changes of the physical and perfusion forces. [14] The cerebral venous blood flow (referred to as CVF) measured in either supine or upright positions reflects the current and transient state of the venous vascular system, whereas the change of the venous flow prompted by the change in body posture (referred as CVF) provides dynamic information of blood flow control. As proper autonomic nervous system functioning might have an active role in the aforementioned control of orthostatic venous flow, potential MS-associated autonomic system impairment may lead to inadequate outflow change patterns. Similarly to the principles of the orthostatic hypotension diagnosis, inadequate venous blood flow response would yield additional information on the autonomic pathology. These findings are becoming more of interest since it has been shown that not only autonomic dysfunction has been associated with certain MS symptomatology, but also can correlate with future progression of clinical disability. [29]

In addition to the well-described peripheral and brainstem organization of the autonomic nervous system, recent task-based fMRI studies and neurological lesion-damage studies localized the cortical autonomic network to the frontoinsula, anterior cingulate cortices, and midcingulate cortices. [30] The left and right hemispheric networks located in the frontoinsula and cingulate cortex have been shown to be crucial in maintaining basal

parasympathetic and the responsive sympathetic outflow, respectively. [19] Therefore, more advanced gray matter, cortical, and deep gray matter atrophy observed in patients with MS with an inadequate postural response are in line with the localization of autonomic nervous system structures within wide cortical networks. [19] Salient damage to the cortex by cortical MS lesions may result in impairment of the maintenance of autonomic homeostasis as previously shown in stroke patients. [31] Additionally, cortical thinning, a hallmark of the MS neurodegenerative process, may disrupt the autonomic nervous system circuits and contribute to abnormal vascular coupling and perfusion control. In similar fashion, a recent review emphasized the effect of autonomic nervous system and its influence on brain volume. [32] The authors suggested that the constant dynamic changes of brain volume can be a results of cerebral blood volume regulation governed by the autonomic nervous system. [32] Concurrently, the impairment of cerebrovascular reactivity and regulation of the cerebral blood flow have been seen in patients with MS and in the classical settings of autonomic dysfunction in the familial amyloidotic polyneuropathy. [33,34]

A previous study demonstrated that patients with MS and healthy controls had initially an equal supine internal jugular vein flow, however, while switching into the upright position, patients with MS did not re-direct the venous flow to the vertebral plexus and had sustained higher internal jugular vein flow indicative of a supine posture. [35] The authors hypothesized that this finding might reflect an ANS autonomic dysfunction and orthostatic dysregulation. [35] Similarly, recent findings also showed that the negative CVF status can differentiate patients with MS versus healthy controls. [9] The same research group also proposed a CVF cutoff value of 503.24ml/min as a sensitive and specific differentiation between patients with MS and patients with other neurological diseases. [12] However, in this study, the absolute delta CVF was calculated by measuring cross-sectional areas in different tracts of the internal jugular veins and vertebral veins (distal vs. proximal tracts) and different quantity of CVF was considered. Furthermore, similar findings reported that negative CVF was present in 52.9% of relapsing-remitting and 75.9% of progressive MS versus only 13.4% of healthy controls. [10] Contrary to their findings, we did not detect differences in the prevalence of abnormal CVF between the patients with MS and healthy controls. The lowest quartile cut-off value of the CVF was not significantly different (201.9mL/min and 214.8mL/min for healthy controls and patients with MS, respectively). In comparison to the aforementioned studies, we used an older cohort of patients with MS and healthy controls. The significant age-dependent decline of both sympathetic and parasympathetic responses have been previously characterized and may have influenced our findings. [36]

Based on previous arterial studies, the Valsalva maneuver (a profound but transient change in cerebral and systemic blood flow) can cause changes in the blood pressure that are subdivided in four main phases. The fourth phase of the maneuver has a characteristic arterial flow overshoot mechanism which exceeds the baseline value. [37] The process of overshoot contributes to an active autonomic regulation and can be successfully inhibited by pharmacological interventions. [38] Furthermore, a Doppler sonography study using the Valsalva maneuver showed a similar phase IV venous overshoot mechanism which was larger when compared to the arterial one by factor of >100%. [39] Additionally, due to the lack of temporal delay when compared to the arterial contra-part, the venous overshoot can

possibly implicate an active involvement of venoconstriction. [39] As mentioned previously, these findings of active venoconstriction coincide with the discovery of smooth muscle cells within the wall of the sinus bridging veins, which are generally considered absent in the wall of the cerebral venous system. [39,40] All these findings point to an active venous outflow control regulated by autonomic nervous system.

After averaging the Doppler flow measures, we did not detect any differences neither in blood volume nor in postural flow patterns between healthy controls and patients with MS. Our flow data confirms the previously described discrepancies in the bilateral venous flow, potentiating the right-sided dominance manifested in both groups. [41–43] The two-fold disparity of venous flow detected in the supine versus upright position suggests an alternative upright venous drainage pathway. The partial increase of venous flow in the vertebral veins while positioned upright does not provide sufficient explanation of the decreased internal jugular vein venous outflow seen both in healthy controls and patients with MS. A recent description of the structural and functional features of a central nervous system lymphatic vessels may provide the missing link in the puzzle of venous, interstitial, and cerebrospinal fluid drainage. [44]

This study is not without limitations. Due to the unavailability of arterial flow measures acquired from different postural positions, we utilized the orthostatic venous flow data in order to derive a measure of orthostatic vascular control. Although the venous postural flow patterns have some concurrent validity to their arterial counterpart, a direct use of arterial postural measures is critically warranted. Furthermore, the limitations of venous Doppler blood flow assessments are substantially greater than arterial flow measures and are elsewhere comprehensively discussed. [45] Fingolimod, a disease-modifying therapy for MS, can cause changes of the heart rate (bradycardia) and atrioventricular block, however these symptoms usually subside during the first month of treatment or when the treatment is discontinued, and only a few patients were treated with this drug in the present study. [46] Finally, the study utilized an exclusion criteria for patients with MS that received corticosteroid infusions 30 days before the study entry since it can additionally cause perturbations within the catecholamine levels that would result in changes of autonomic functioning. [29]

The study does not provide information of whether the presence of abnormal postural venous outflow may be a result of MS-derived neurodegeneration, overall aging effect, or if it precedes brain atrophy. Due to the similar healthy control prevalence and the aging profile of the population used, the current results suggest that this finding is not an MS-specific phenomenon. However, prospective age- and sex-matched studies with baseline flow characteristics and use of validated autonomic nervous system tests/questionnaires may clarify these findings.

Conclusion:

There were no differences in the postural venous outflow between patients with MS and healthy controls. This study did not corroborate the previously reported high level of abnormal postural venous control in patients with MS. However, we found that if present,

the abnormal postural venous flow may be associated with higher inflammatory and neurodegenerative pathology in patients with MS. The potential link between postural venous blood flow control with the MS pathophysiology and autonomic nervous system impairment, if any, remains largely unknown.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References:

1. Reich DS, Lucchinetti CF, Calabresi PA (2018) Multiple Sclerosis. *N Engl J Med* 378 (2):169–180. doi:10.1056/NEJMr1401483 [PubMed: 29320652]
2. Zivadinov R, Bergsland N, Dolezal O, Hussein S, Seidl Z, Dwyer MG, Vaneckova M, Krasensky J, Potts JA, Kalincik T, Havrdova E, Horakova D (2013) Evolution of cortical and thalamus atrophy and disability progression in early relapsing-remitting MS during 5 years. *AJNR Am J Neuroradiol* 34 (10):1931–1939. doi:10.3174/ajnr.A3503 [PubMed: 23578679]
3. Zivadinov R, Havrdova E, Bergsland N, Tyblova M, Hagemeyer J, Seidl Z, Dwyer MG, Vaneckova M, Krasensky J, Carl E, Kalincik T, Horakova D (2013) Thalamic atrophy is associated with development of clinically definite multiple sclerosis. *Radiology* 268 (3):831–841. doi:10.1148/radiol.13122424 [PubMed: 23613615]
4. de Seze J, Stojkovic T, Gauvrit JY, Devos D, Ayachi M, Cassim F, Saint Michel T, Pruvo JP, Guieu JD, Vermersch P (2001) Autonomic dysfunction in multiple sclerosis: cervical spinal cord atrophy correlates. *J Neurol* 248 (4):297–303 [PubMed: 11374094]
5. Kodounis A, Stamboulis E, Constantinidis TS, Liolios A (2005) Measurement of autonomic dysregulation in multiple sclerosis. *Acta Neurol Scand* 112 (6):403–408. doi:10.1111/j.1600-0404.2005.00446.x [PubMed: 16281924]
6. Habek M, Crnosija L, Lovric M, Junakovic A, Krbot Skoric M, Adamec I (2016) Sympathetic cardiovascular and sudomotor functions are frequently affected in early multiple sclerosis. *Clin Auton Res* 26 (6):385–393. doi:10.1007/s10286-016-0370-x [PubMed: 27448576]
7. Illigens BM, Gibbons CH (2009) Sweat testing to evaluate autonomic function. *Clin Auton Res* 19 (2):79–87. doi:10.1007/s10286-008-0506-8 [PubMed: 18989618]
8. Hale LA, Nukada H, Du Plessis LJ, Peebles KC (2009) Clinical screening of autonomic dysfunction in multiple sclerosis. *Physiother Res Int* 14 (1):42–55. doi:10.1002/pri.416 [PubMed: 19107708]
9. Monti L, Menci E, Olivelli M, Cerase A, Bartalini S, Piu P, Marotti N, Leonini S, Galluzzi P, Romano DG, Casasco AE, Venturi C (2011) Quantitative Colour Doppler Sonography evaluation of cerebral venous outflow: a comparative study between patients with multiple sclerosis and controls. *PLoS One* 6 (9):e25012. doi:10.1371/journal.pone.0025012 [PubMed: 21966398]
10. Marchione P, Morreale M, Giacomini P, Izzo C, Pontecorvo S, Altieri M, Bernardi S, Frontoni M, Francia A (2014) Ultrasonographic evaluation of cerebral arterial and venous haemodynamics in multiple sclerosis: a case-control study. *PLoS One* 9 (10):e111486. doi:10.1371/journal.pone.0111486 [PubMed: 25360597]
11. Mancini M, Lanzillo R, Liuzzi R, Di Donato O, Ragucci M, Monti S, Salvatore E, Morra VB, Salvatore M (2014) Internal jugular vein blood flow in multiple sclerosis patients and matched controls. *PLoS One* 9 (3):e92730. doi:10.1371/journal.pone.0092730 [PubMed: 24675965]
12. Monti L, Menci E, Piu P, Leonini S, Arrigucci U, Bellini M, Zandonella A, Galluzzi P, Casasco A (2014) A sonographic quantitative cutoff value of cerebral venous outflow in neurologic diseases: a blinded study of 115 subjects. *AJNR Am J Neuroradiol* 35 (7):1381–1386. doi:10.3174/ajnr.A3864 [PubMed: 24610905]
13. Valdueza JM, von Munster T, Hoffman O, Schreiber S, Einhaupl KM (2000) Postural dependency of the cerebral venous outflow. *Lancet* 355 (9199):200–201

14. Cirovic S, Walsh C, Fraser WD, Gulino A (2003) The effect of posture and positive pressure breathing on the hemodynamics of the internal jugular vein. *Aviat Space Environ Med* 74 (2):125–131 [PubMed: 12602443]
15. Gisolf J, van Lieshout JJ, van Heusden K, Pott F, Stok WJ, Karemaker JM (2004) Human cerebral venous outflow pathway depends on posture and central venous pressure. *J Physiol* 560 (Pt 1): 317–327. doi:10.1113/jphysiol.2004.070409 [PubMed: 15284348]
16. Cechetto DF (2014) Cortical control of the autonomic nervous system. *Exp Physiol* 99 (2):326–331. doi:10.1113/expphysiol.2013.075192 [PubMed: 24121283]
17. Goswami R, Frances MF, Shoemaker JK (2011) Representation of somatosensory inputs within the cortical autonomic network. *Neuroimage* 54 (2):1211–1220. doi:10.1016/j.neuroimage.2010.09.050 [PubMed: 20884359]
18. Macey PM, Wu P, Kumar R, Ogren JA, Richardson HL, Woo MA, Harper RM (2012) Differential responses of the insular cortex gyri to autonomic challenges. *Auton Neurosci* 168 (1–2):72–81. doi:10.1016/j.autneu.2012.01.009 [PubMed: 22342370]
19. Guo CC, Sturm VE, Zhou J, Gennatas ED, Trujillo AJ, Hua AY, Crawford R, Stables L, Kramer JH, Rankin K, Levenson RW, Rosen HJ, Miller BL, Seeley WW (2016) Dominant hemisphere lateralization of cortical parasympathetic control as revealed by frontotemporal dementia. *Proc Natl Acad Sci U S A* 113 (17):E2430–2439. doi:10.1073/pnas.1509184113 [PubMed: 27071080]
20. Zivadinov R, Ramasamy DP, Vaneckova M, Gandhi S, Chandra A, Hagemeyer J, Bergsland N, Polak P, Benedict RH, Hojnacki D, Weinstock-Guttman B (2017) Leptomeningeal contrast enhancement is associated with progression of cortical atrophy in MS: A retrospective, pilot, observational longitudinal study. *Mult Scler* 23 (10):1336–1345. doi:10.1177/1352458516678083 [PubMed: 27811339]
21. Jakimovski D, Marr K, Mancini M, Caprio MG, Gandhi S, Bergsland N, Paunkoski I, Hagemeyer J, Chandra A, Weinstock-Guttman B, Zivadinov R (2017) Global and regional brain atrophy is associated with low or retrograde facial vein flow in multiple sclerosis. *Veins and Lymphatics* 6 (3). doi:10.4081/vl.2017.6976
22. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K, Galetta SL, Hartung HP, Kappos L, Lublin FD, Marrie RA, Miller AE, Miller DH, Montalban X, Mowry EM, Sorensen PS, Tintore M, Traboulsee AL, Trojano M, Uitdehaag BMJ, Vukusic S, Waubant E, Weinshenker BG, Reingold SC, Cohen JA (2018) Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 17 (2):162–173. doi:10.1016/S1474-4422(17)30470-2 [PubMed: 29275977]
23. Zivadinov R, Raj B, Ramanathan M, Teter B, Durfee J, Dwyer MG, Bergsland N, Kolb C, Hojnacki D, Benedict RH, Weinstock-Guttman B (2016) Autoimmune Comorbidities Are Associated with Brain Injury in Multiple Sclerosis. *AJNR Am J Neuroradiol* 37 (6):1010–1016. doi:10.3174/ajnr.A4681 [PubMed: 26892983]
24. Smith SM, Zhang Y, Jenkinson M, Chen J, Matthews PM, Federico A, De Stefano N (2002) Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *Neuroimage* 17 (1):479–489 [PubMed: 12482100]
25. Patenaude B, Smith SM, Kennedy DN, Jenkinson M (2011) A Bayesian model of shape and appearance for subcortical brain segmentation. *Neuroimage* 56 (3):907–922. doi:10.1016/j.neuroimage.2011.02.046 [PubMed: 21352927]
26. Gelineau-Morel R, Tomassini V, Jenkinson M, Johansen-Berg H, Matthews PM, Palace J (2012) The effect of hypointense white matter lesions on automated gray matter segmentation in multiple sclerosis. *Hum Brain Mapp* 33 (12):2802–2814. doi:10.1002/hbm.21402 [PubMed: 21976406]
27. Caprio MG, Marr K, Gandhi S, Jakimovski D, Hagemeyer J, Weinstock-Guttman B, Zivadinov R, Mancini M (2017) Centralized and Local Color Doppler Ultrasound Reading Agreement for Diagnosis of the Chronic Cerebrospinal Venous Insufficiency in Patients with Multiple Sclerosis. *Curr Neurovasc Res* 14 (3):266–273. doi:10.2174/1567202614666170718095203 [PubMed: 28721810]
28. Schreiber SJ, Lurtzing F, Gotze R, Doepp F, Klingebiel R, Valdueza JM (2003) Extrajugular pathways of human cerebral venous blood drainage assessed by duplex ultrasound. *J Appl Physiol* (1985) 94 (5):1802–1805. doi:10.1152/jappphysiol.00782.2002 [PubMed: 12524376]

29. Racosta JM, Kimpinski K (2016) Autonomic dysfunction, immune regulation, and multiple sclerosis. *Clin Auton Res* 26 (1):23–31. doi:10.1007/s10286-015-0325-7 [PubMed: 26691635]
30. Critchley HD, Harrison NA (2013) Visceral influences on brain and behavior. *Neuron* 77 (4):624–638. doi:10.1016/j.neuron.2013.02.008 [PubMed: 23439117]
31. Sposato LA, Cohen G, Wardlaw JM, Sandercock P, Lindley RI, Hachinski V, Panel ISTER, the ISTCG (2016) Effect of Right Insular Involvement on Death and Functional Outcome After Acute Ischemic Stroke in the IST-3 Trial (Third International Stroke Trial). *Stroke* 47 (12):2959–2965. doi:10.1161/STROKEAHA.116.014928 [PubMed: 27895298]
32. Racosta JM, Kimpinski K (2016) Autonomic function and brain volume. *Clin Auton Res* 26 (6): 377–383. doi:10.1007/s10286-016-0380-8 [PubMed: 27568208]
33. Azevedo E, Castro P, Santos R, Freitas J, Coelho T, Rosengarten B, Panerai R (2011) Autonomic dysfunction affects cerebral neurovascular coupling. *Clin Auton Res* 21 (6):395–403. doi:10.1007/s10286-011-0129-3 [PubMed: 21796357]
34. Marshall O, Chawla S, Lu H, Pape L, Ge Y (2016) Cerebral blood flow modulation insufficiency in brain networks in multiple sclerosis: A hypercapnia MRI study. *J Cereb Blood Flow Metab* 36 (12):2087–2095. doi:10.1177/0271678X16654922 [PubMed: 27306754]
35. Doepp F, Paul F, Valdueza JM, Schmierer K, Schreiber SJ (2010) No cerebrocervical venous congestion in patients with multiple sclerosis. *Ann Neurol* 68 (2):173–183. doi:10.1002/ana.22085 [PubMed: 20695010]
36. Low PA, Opfer-Gehrking TL, Proper CJ, Zimmerman I (1990) The effect of aging on cardiac autonomic and postganglionic sudomotor function. *Muscle Nerve* 13 (2):152–157. doi:10.1002/mus.880130212 [PubMed: 2314419]
37. Tiecks FP, Lam AM, Matta BF, Strebel S, Douville C, Newell DW (1995) Effects of the valsalva maneuver on cerebral circulation in healthy adults. A transcranial Doppler Study. *Stroke* 26 (8): 1386–1392 [PubMed: 7631342]
38. Schroeder C, Heusser K, Tank J, Diedrich A, Luft FC, Jordan J (2009) The Valsalva maneuver: screening for drug-induced baroreflex dysfunction. *Clin Auton Res* 19 (1):32–38. doi:10.1007/s10286-008-0508-6 [PubMed: 19011931]
39. Stolz E, Rusges DA, Hoffmann O, Gerriets T, Nedelmann M, Lochner P, Kaps M (2010) Active regulation of cerebral venous tone: simultaneous arterial and venous transcranial Doppler sonography during a Valsalva manoeuvre. *Eur J Appl Physiol* 109 (4):691–697. doi:10.1007/s00421-010-1411-0 [PubMed: 20213466]
40. Vignes JR, Dagain A, Guerin J, Liguoro D (2007) A hypothesis of cerebral venous system regulation based on a study of the junction between the cortical bridging veins and the superior sagittal sinus. Laboratory investigation. *J Neurosurg* 107 (6):1205–1210. doi:10.3171/JNS-07/12/1205 [PubMed: 18077958]
41. Ciuti G, Righi D, Forzoni L, Fabbri A, Pignone AM (2013) Differences between internal jugular vein and vertebral vein flow examined in real time with the use of multigate ultrasound color Doppler. *AJNR Am J Neuroradiol* 34 (10):2000–2004. doi:10.3174/ajnr.A3557 [PubMed: 23721896]
42. Magnano C, Belov P, Krawiecki J, Hagemeyer J, Beggs C, Zivadinov R (2016) Internal Jugular Vein Cross-Sectional Area Enlargement Is Associated with Aging in Healthy Individuals. *PLoS One* 11 (2):e0149532. doi:10.1371/journal.pone.0149532 [PubMed: 26895434]
43. Buch K, Groller R, Nadgir RN, Fujita A, Qureshi MM, Sakai O (2016) Variability in the Cross-Sectional Area and Narrowing of the Internal Jugular Vein in Patients Without Multiple Sclerosis. *AJR Am J Roentgenol* 206 (5):1082–1086. doi:10.2214/AJR.15.14689 [PubMed: 26958902]
44. Absinta M, Ha SK, Nair G, Sati P, Luciano NJ, Palisoc M, Louveau A, Zaghloul KA, Pittaluga S, Kipnis J, Reich DS (2017) Human and nonhuman primate meninges harbor lymphatic vessels that can be visualized noninvasively by MRI. *Elife* 6:e29738. doi:10.7554/eLife.29738 [PubMed: 28971799]
45. Marr K, Jakimovski D, Mancini M, Carl E, Zivadinov R (2018) Jugular Venous Flow Quantification Using Doppler Sonography. *Ultrasound Med Biol*. doi:10.1016/j.ultrasmedbio.2018.04.010

46. Hilz MJ, Intravooth T, Moeller S, Wang R, Lee DH, Koehn J, Linker RA (2015) Central Autonomic Dysfunction Delays Recovery of Fingolimod Induced Heart Rate Slowing. PLoS One 10 (7):e0132139. doi:10.1371/journal.pone.0132139 [PubMed: 26147106]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1.

Demographic and clinical characteristics of healthy controls and patients with multiple sclerosis.

Demographic and clinical characteristics	HC group (n=49)	MS group (n=138)	p value HC vs. MS
Female, n (%)	36 (73.5)	100 (72.5)	0.892
Age in yrs, mean (SD)	51.4 (14.5)	53.6 (10.9)	0.334
Disease duration, mean (SD)	-	20.1 (10.6)	-
RRMS/PMS	-	88/50	-
EDSS, mean (IQR) median	-	3.6 (1.9–6.0) 3.0	-
Bladder/Bowel FS, mean (IQR) median	-	1.6 (0.0–3.0) 1.0	-
Absolute negative CVF, n (%)	6 (12.2)	14 (10.1)	0.682
Lower quartile CVF cut-off, mean ml/min	201.9	214.8	0.987
Disease-modifying therapies (DMT), n (%)			
Interferon- β	-	46 (33.3)	-
Glatiramer acetate	-	39 (28.3)	-
Natalizumab	-	5 (3.6)	-
Oral medications	-	13 (9.4)	-
Other off-label treatments	-	6 (4.4)	-
No disease-modifying therapy	-	29 (21.0)	-

Legend: MS – multiple sclerosis, SD – standard deviation, RRMS – relapsing-remitting multiple sclerosis, PMS – progressive multiple sclerosis, EDSS – Expanded Disability Status Scale, FS – functional score, IQR – interquartile range. χ^2 cross tabulation, and Student's *t*-test were used accordingly. P-value lower than 0.05 was considered as significant.

Oral medications included dimethyl fumarate (5), fingolimod (5) and teriflunomide (3). Similarly, off-label treatments included intravenous immunoglobulins (4), methotrexate (1), and mitoxantrone (1).

Table 2.

Flow measurements for bilateral internal jugular veins, vertebral veins and total cerebral venous flow in healthy controls and patients with multiple sclerosis.

	HC (n=49)		MS (n=138)		Supine p-value	Upright p-value
	Supine	Upright	Supine	Upright		
Right IJV	541.6 (317.4)	152.8 (190.6)	497.6(352.9)	159.5 (193.4)	0.442	0.836
LeftIJV	295.1 (218.0)	92.4 (156.5)	372.7(317.6)	139.9(247.1)	0.062	0.209
Total IJV	836.8 (362.9)	245.3 (257.9)	870.3 (437.6)	299.5(298.5)	0.632	0.260
Right VV	14.3 (14.6)	51.9 (56.5)	17.1(24.2)	40.4 (46.9)	0.452	0.164
LeftVV	7.5 (8.1)	39.9 (46.9)	10.8(13.5)	37.9(7.1)	0.114	0.788
Total VV	21.8 (18.8)	91.9 (86.9)	27.8(31.9)	78.4(73.1)	0.213	0.293
CVF	858.6 (362.3)	337.2 (254.4)	898.1(429.1)	377.9 (294.7)	0.565	0.391

Legend: MS – multiple sclerosis, HC – healthy control, IJV – internal jugular vein, VV – vertebral vein, CVF – cerebral venous flow. Student's *t*-test was used to compare the flow between MS and HCs. P-value lower than 0.05 was considered as significant.

Data are reported as mean (standard deviation). All flow measurements are expressed in mL/min.

Table 3.

Differences in MRI and clinical outcomes measures between subjects with abnormal (negative) and normal (positive) CVF in patients with multiple sclerosis.

MRI and clinical outcome measures	HC group (n=49)	Positive	CVF (n=43)	Negative	CVF (n=6)	BH-corrected p value	MS group (n=138)	Positive	CVF (n=124)	Negative	CVF (n=14)	BH-corrected p value
Female, n (%)	36 (73.5)	32 (74.4)		4 (66.7)		0.687	100 (72.5)	88 (71.0)		12 (85.7)		0.242
Age in yrs, mean (SD)	51.4 (14.5)	51.6 (14.7)		49.6 (14.3)		0.755	53.6 (10.9)	53.2 (10.9)		56.9 (10.7)		0.229
Age at disease onset, mean (SD)	-	-		-		-	20.1 (10.6)	19.5 (10.2)		25.1 (12.9)		0.059
EDSS, mean (SD)	-	-		-		-	88/50	81/43		7/7		0.258
EDSS, mean (IQR) median	-	-		-		-	3.6 (1.9–6.0) 3.0	3.4 (1.5–5.0) 3.0		4.9 (2.5–6.75) 6.5		0.013
Bladder/Bowel FS, mean (IQR) median	-	-		-		-	1.0 (0.0–3.0) 1.0	1.5 (0.0–3.0) 1.0		2.3 (1.0–3.0) 1.0		0.052
BL-LV	-	-		-		-	2.5 (6.0)	2.6 (6.1)		3.6 (5.3)		0.746
BL-LV	0.6 (1.4)	0.6 (1.5)		0.7 (1.4)		1.000	15.0 (18.5)	13.9 (17.8)		24.2 (23.2)		0.137
GMV	771.6 (63.4)	772.9 (64.6)		762.1 (58.4)		1.000	733.2 (61.2)	738.1 (59.8)		689.7 (57.3)		0.039
WMV	752.5 (46.2)	753.5 (44.9)		744.7 (58.7)		1.000	713.6 (44.3)	714.4 (45.6)		706.7 (31.6)		0.800
BBV	1524.0 (99.9)	1526.4 (99.5)		1506.8 (110.6)		1.000	1446.8 (92.5)	1452.5 (93.1)		1394.4 (71.9)		0.95
LVV	627.4 (54.7)	627.9 (55.9)		623.7 (48.8)		0.992	595.4 (48.8)	599.4 (47.7)		559.9 (45.6)		0.044
LVV	36.4 (16.4)	36.3 (16.4)		37.4 (17.3)		1.000	532.3 (26.3)	52.1 (25.9)		62.9 (28.9)		0.287
DGM	60.0 (4.8)	60.1 (16.5)		59.9 (6.1)		1.000	54.1 (7.0)	54.6 (6.9)		50.0 (6.9)		0.065
Thalamus	20.1 (1.9)	20.2 (1.9)		19.7 (1.8)		1.000	17.9 (2.5)	18.1 (2.4)		16.4 (2.4)		0.060

Legend: HC- healthy control, MS – multiple sclerosis, EDSS – Expanded Disability Status Scale, FS – functional score, GMV – gray matter volume, WMV – white matter volume, WBV – whole brain volume, CV – cortical volume, LVV – lateral ventricular volume, DGM – deep gray matter. χ^2 cross tabulation, Student's *t*-test and analysis of covariance (ANCOVA) corrected for age and sex was used. P-value lower than 0.05 after Benjamini-Hochberg correction was considered as significant. Unless otherwise stated, data are reported as mean (standard deviation). Volumes are reported in milliliters.

Table 4.

Differences in MRI and clinical outcomes measures between the lowest quartile and higher quartiles in healthy controls and patients with multiple sclerosis.

MRI and clinical outcome measures	HC group (n=49)	Higher Quartiles (n=37)	Lowest quartile (n=12)	p value	MS group (n=138)	Higher quartiles (n=104)	Lowest quartile (n=34)	BH-corrected p value
Female, n (%)	36 (73.5)	28 (75.7)	8 (66.7)	0.377	100 (72.5)	71 (68.3)	29 (85.3)	0.054
Age in yrs, mean (SD)	51.4 (14.5)	53.8 (13.7)	43.9 (14.9)	0.038	53.6 (10.9)	53.4 (10.9)	54.2 (11.4)	0.727
Disease duration, mean (SD)	-	-	-	-	20.1 (10.6)	19.6 (10.9)	21.7 (12.0)	0.318
RRMS/PMS	-	-	-	-	88/50	65/39	23/11	0.605
EDSS, mean (IQR) median	-	-	-	-	3.6 (1.9–6.0) 3.0	3.5 (1.5–5.25) 3.0	3.9 (2.0–6.5) 3.0	0.294
Bladder/Bowel FS, mean (IQR) median	-	-	-	-	1.6 (0.0–3.0) 1.0	1.4 (0.0–3.0) 1.0	1.9 (0.0–3.0) 1.0	0.336
T1-LV	-	-	-	-	2.5 (6.0)	1.8 (3.8)	5.2 (9.9)	0.033
T2-LV	0.6 (1.4)	0.7 (1.5)	0.4 (0.9)	1.000	15.0 (18.5)	12.0 (13.9)	24.1 (26.6)	0.32
GMV	771.6 (63.4)	768.9 (59.2)	779.6 (77.2)	1.000	733.2 (61.2)	738.7 (60.6)	716.4 (60.6)	0.058
WMV	752.5 (46.2)	750.5 (45.1)	758.3 (51.2)	0.993	713.6 (44.3)	714.2 (45.4)	711.7 (41.5)	0.860
WBV	1524.0 (99.9)	1519.5 (92.7)	1537.9 (122.9)	1.000	1446.8 (92.5)	1452.8 (93.8)	1428.1 (87.2)	0.188
CV	627.4 (54.7)	624.6 (51.3)	635.9 (65.7)	1.000	595.4 (48.8)	599.8 (48.3)	581.9 (48.4)	0.068
LVV	36.4 (16.3)	37.9 (17.2)	31.8 (13.3)	1.000	532.3 (26.3)	50.5 (24.7)	61.5 (29.6)	0.054
DGM	60.0 (4.8)	59.9 (4.6)	60.5 (5.6)	1.000	54.1 (7.0)	54.9 (6.8)	51.7 (7.2)	0.043
Thalamus	20.1 (1.9)	20.0 (1.9)	20.3 (1.9)	1.000	17.9 (2.5)	18.2 (2.4)	17.0 (2.5)	0.033

Legend: HC- healthy control, MS – multiple sclerosis, EDSS – Expanded Disability Status Scale, FS – functional score, GMV – gray matter volume, WMV – white matter volume, WBV – whole brain volume, CV – cortical volume, LVV – lateral ventricular volume, DGM – deep gray matter, χ^2 cross tabulation, Student's *t*-test and analysis of covariance (ANCOVA) corrected for age and sex was used. P-value lower than 0.05 after Benjamini-Hochberg correction was considered as significant. The low quartile cut-off value of the CVF for the groups are 201.9mL/min and 214.8mL/min (HC and MS, respectively). Unless otherwise stated, data are reported as mean (standard deviation). Volumes are reported in milliliters.