Evaluation of IVIM in the Spinal Cord of Multiple Sclerosis Patients

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Purpose To evaluate the ability of intravoxel incoherent motion (IVIM), a perfusion-weighted imaging technique, to differentiate microcirculation changes in the spinal cord of patients with multiple sclerosis (MS) compared with healthy individuals.

Methods Fifteen healthy individuals and 15 individuals with MS underwent IVIM magnetic resonance (MR) imaging using a 3 T scanner with 2-D axial gradient recalled echo and 2-D axial diffusion-weighted imaging (DWI) sequences. The MR images underwent segmentation to produce white matter and gray matter regions of interest. IVIM metrics for perfusion fraction, pseudo-diffusion coefficients, water-diffusion coefficients, and signal without diffusion encoding were calculated using DWI data. An unpaired *t* test was performed on these IVIM metrics to compare imaging of healthy individuals with imaging of individuals with MS.

Results No significant differences between images from healthy individuals and individuals with MS were found for any IVIM metric. The lowest *P* values calculated (.082 and .055) were in the white matter region of interest perfusion fraction and pseudo-diffusion measurements. The gray matter region of interest had the highest *P* value.

Discussion The findings in this study are consistent with current perfusion-weighted imaging literature focused on MS in the brain. The gray matter in MS patients in this study showed reduced perfusion compared with healthy individuals.

Conclusion IVIM is a promising imaging technique for the evaluation of the spinal cord in MS patients. It has the potential to provide valuable information on microvascular perfusion and diffusion in the spinal cord, which might be related to disease progression and response to treatment.

Keywords | *multiple sclerosis, spinal cord, magnetic resonance imaging, intravoxel incoherent motion*

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that leads to demyelination and neurodegeneration.[1] MS affects mobility, balance, vision, and cognition, making it the leading cause of nontraumatic disability in young adults worldwide.[2] Despite its global prevalence, little is known of the etiology of MS, and its progression is highly variable. Early and accurate diagnosis of MS is critical and is completed through a combination of reported clinical symptoms and positive radiological findings on magnetic resonance (MR) imaging.[3]

MS is categorized as relapsing-remitting or primary progressive, with most patients being diagnosed with relapsing-remitting MS. Relapsing-remitting MS most commonly affects young people with the average presentation of symptoms occurring when they are aged 30 years with a predominance of cases being diagnosed in women.[3] Relapsing-remitting MS consists of time periods of neurological dysfunction or relapse, followed by periods of remission with no symptoms.[4] Primary progressive MS patients, conversely, show a slow and progressive decline in neurological function.[5] However, patients with relapsing-remitting MS can progress into secondary progressive MS when the disease course switches and no relapses occur, just a steady increase in disability.[5]

The pathogenesis of MS is not completely understood. However, growing evidence shows that a vascular component might contribute to the progression of the

disease.[6-8] Evidence of vascular involvement includes development of MS lesions predominantly around central veins, metabolic dysfunction due to hypoperfusion, and detection of microvascular occlusions, indicating ischemic conditions.[7-9] Advanced MR imaging techniques, including perfusion-weighted imaging (PWI), have been used to better characterize and understand MS.[10] PWI techniques are categorized into contrast- and noncontrast-based techniques. Contrast-based PWI techniques require the administration of gadolinium-based contrast agents to assess perfusion. However, the use of gadolinium-based contrast agents has been scrutinized recently with reports confirming deposition of gadolinium in the brain.[11] This is of special concern in the MS population as they complete serial MR imaging with gadolinium-based contrast agents.[12]

Previous PWI studies in MS have revealed alterations of cerebral perfusion compared with healthy controls. Acute MS lesions have shown increased perfusion when compared with normal-appearing white matter (NAWM).[13-15] This hyperperfusion is thought to reflect the inflammatory process.[16,17] PWI studies of the parenchymal tissue have reported reduced cerebral blood flow and cerebral blood volume in NAWM.[8,17-22] This hypoperfusion in NAWM suggests that perfusion deficits extend beyond MS lesions, and changes in perfusion can serve as a clinically relevant biomarker.[20,23] However, all of the PWI work in MS has been completed in the brain, leaving a gap of information in regards to perfusion changes in the spinal cord caused by the progression of MS.[24]

Intravoxel incoherent motion (IVIM) offers a noncontrast method to study the microcirculatory blood and provide in vivo perfusion information.[25] IVIM also does not require complex tagging strategies or additional hardware like its noncontrast PWI counterpart, arterial spin labeling.[26] IVIM is based on the principle of diffusion-weighted imaging (DWI), which measures the random brownian motion of water molecules in tissue.[27] Furthermore, IVIM also considers the presence of microvascular perfusion, which results in a more complex signal decay that can be modeled using 2 or more diffusion-relaxation components.[27] IVIM can be used to quantify the perfusion fraction (f), which reflects the proportion of blood vessels that are perfused and contribute to the signal decay, and the pseudo-diffusion coefficient, which reflects the combined effects of diffusion and perfusion on the signal decay.[27] IVIM has been shown to be a useful tool for estimating microvascular perfusion in a variety of tissues, including the brain,[28] heart,[29] liver,[30] kidney,[31] and pancreas.[32] Moreover, IVIM studies have shown a correlation between IVIM perfusion metrics and physiologically and pharmaceutically induced changes in perfusion.[33,34] IVIM has shown promise in providing more information about the underlying disease process than have conventional MR imaging techniques and can help to improve the accuracy of diagnosis and disease monitoring.[35] Therefore, advanced MR imaging techniques like IVIM that allow for the evaluation and measurement of changes in perfusion offer a great tool to gain a better understanding of MS and allow for earlier detection.[10]

In patients with MS, the spinal cord often is affected by inflammation and demyelination, leading to axonal damage and neuronal loss.[24] Spinal cord abnormalities are visible on MR imaging in up to 90% of MS patients.[36] One potential advantage of IVIM compared with conventional MR imaging techniques is its ability to provide quantitative information on microvascular perfusion and diffusion in the spinal cord.[26] This might be useful for differentiating between healthy and abnormal tissue, as well as for monitoring the response to treatment.

This study evaluates the ability of IVIM to differentiate microcirculation changes in the spinal cord of MS patients. Given the previous sensitivity of advanced diffusion MR imaging techniques and the implication of altered perfusion kinematics in MS neuroimaging studies, the hypothesis is that IVIM will show hypoperfusion deficits in the spinal cord affected by MS.

Methods

Participants for this prospective cohort study, conducted between November 2021 through November 2022, were recruited via ResearchMatch.[37] Fifteen healthy individuals (10 men, 5 women) with a mean age of 29 years (standard deviation [SD] = 5) and 15 female patients diagnosed with MS with a mean age of 39 years (SD = 6) were enrolled and underwent MR imaging. Institutional review board approval was

obtained from WIRB-Copernicus Group (20193543). Written informed consent from each participant was obtained before scanning; an incentive was provided for participation.

Image Acquisition

All MR imaging examinations were performed on a 3 T scanner (Achieva 3.0T, Phillips) using a 16-channel phased array neurovascular coil. Imaging consisted of 2-D axial T2*-weighted gradient recalled echo (GRE) and 2-D axial echo-planar DWI sequences. T2*-weighted and DWI scans were acquired axially with slice prescriptions centered at the C3 to C4 intervertebral disk level.

Multiecho T2*-weighted GRE scans were acquired to obtain high-resolution anatomical images for visualization of white and gray matter in the spinal cord ($0.65 \times 0.65 \times 5$ mm^3; time to echo, 7.1 ms; repetition time, 753 ms; flip angle, 28°). This sequence nicely shows the classic hyperintense butterfly of the gray matter surrounded by white matter in a healthy spinal cord,[24] which allows for segmentation and coregistration (see **Figure 1**). This sequence also is sensitive to locating hyperintense focal MS spinal cord lesions.[24]

Fat-suppressed multishell sequences ($1.25 \times 1.25 \times 10$ mm^3; time to echo, 65 ms; repetition time, 3000 ms; 96 directions; b values, 0-2855 s/mm^2) were used to perform IVIM calculations. The IVIM technique is sensitive to high fluid velocities such as those found in the nearby pulsatile cerebrospinal fluid.[26] To reduce this effect and other physiological factors, DWI scans were cardiac triggered.

Image Analysis and Processing

Overview of image analysis and postprocessing steps are shown in **Figure 2**. Segmentation, coregistration, and metric extraction were performed using the open-source spinal cord toolbox.[38] Spinal cord segmentation was performed on the T2*-weighted GRE images and DWI using a convolutional neural network[39] to delineate the spinal cord. Using the spinal cord segmentation, a mask was then applied around the spinal cord so T2*-weighted and DWI images could be cropped to remove unnecessary pixels outside of the vertebral column. Motion correction was performed on the DWI volumes.[40] T2*-weighted GRE images underwent additional deep learning segmentation[41] to produce white and gray matter tissue-specific regions of interest (ROIs). The T2*-weighted GRE and DWI images then were coregistered together using a nonrigid registration to allow for the transformations of the anatomical ROIs from the T2*-weighted GRE to the

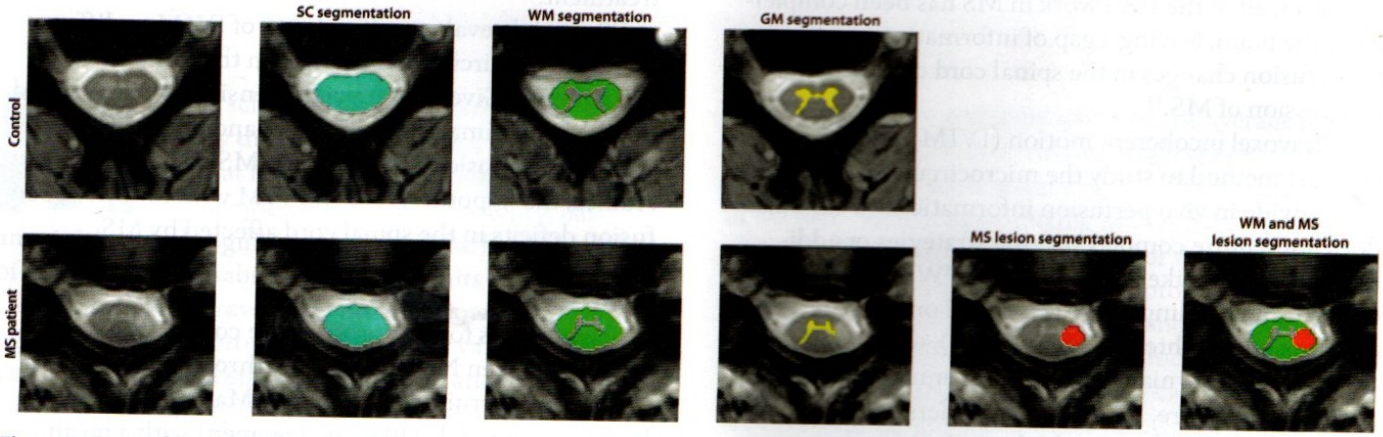

Figure 1. *Example of spinal cord (SC; blue) and white matter (WM; green) and gray matter (GM; yellow) segmentation on high-resolution anatomical T2*-weighted gradient recalled echo (GRE) imaging for control (ie, healthy individuals; top row) and multiple sclerosis (MS) patients (bottom row). T2*-weighted GRE, WM and GM segmentation of the control participants shows the classic anatomical butterfly contrast between WM and GM. T2*-weighted GRE imaging depicts a lateral MS lesion in the MS patient that has affected the WM and GM. To further highlight lesion infiltration, MS lesion segmentation was performed (red) and overlaid with the WM segmentation. Images courtesy of the authors.*

Figure 2. *Schematic of analysis pipeline showing input sources (ie, imaging types) and corresponding postprocessing steps. Postprocessing for diffusion-weighted images (DWI) consisted of spinal cord segmentation followed by motion correction (MOCO) using the spinal cord toolbox. MOCO, DWI were then analyzed via the intravoxel incoherent motion (IVIM) toolbox for IVIM parameter estimation using the 1-step fitting model to calculate IVIM perfusion fraction (f_{IVIM}), pseudo-diffusion coefficient (D*), and water-diffusion coefficient (D). High-resolution anatomical T2*-weighted GRE images underwent spinal cord segmentation to produce SC, GM, and WM regions of interest (ROIs). Finally, warping fields were computed to coregister the MOCO, DWI and T2*-weighted GRE images to allow for extraction of the IVIM metrics from the ROIs. Images courtesy of the authors. Abbreviation: CSF, cerebrospinal fluid.*

DWI and then ultimately to the IVIM parametric maps (see **Figure 3**).[42]

IVIM calculations were performed using the open-source IVIM toolbox,[26] a 1-step fitting model.[43] The 1-step fitting model was chosen because it has shown better parameter estimation performance compared with the 2-step model for noisy and high signal:noise ratio data.[26] IVIM metrics for perfusion fraction, pseudo-diffusion coefficient, water-diffusion coefficient in tissue, and signal without diffusion encoding (S_0, b value = 0 s/mm²) were computed on the motion-corrected DWI data. Individual perfusion fraction, pseudo-diffusion coefficient, water-diffusion coefficient in tissue, and signal without diffusion encoding maps were generated for each patient. To enable the extraction of the spinal cord, the white and gray matter aggregate ROI values, warping field used in the coregistration of the T2*-weighted GRE, and DWI motion correction were applied to the IVIM parametric maps. To increase the signal:noise ratio, IVIM parametric maps were averaged for vertebral levels C2 to C4.

IVIM in the spinal cord has shown poor reliability when analyzed at the single-subject and single-slice level.[26] Similarly, calculation of IVIM metrics has been shown to be dependent on signal:noise ratio. Therefore, an atlas averaged cross-sectional analysis was conducted to determine spinal cord, white matter, and gray matter differences in IVIM-derived indices between the healthy and MS groups. An unpaired t test was performed using Minitab Statistical Software version 18 (Minitab, LLC) on the mean perfusion fraction, pseudo-diffusion coefficient, and water-diffusion coefficient values in the spinal cord and white and gray matter of healthy individuals and MS patients. Significance threshold was set at $P < .05$.

Results

Between the healthy and MS groups, no significant differences were found in the spinal cord or the white or gray matter ROIs for any of the IVIM indices (ie, perfusion fraction, pseudo-diffusion coefficient, and water-diffusion coefficient) (see **Figure 4**). The white matter ROI perfusion fraction and pseudo-diffusion measurements had lower P values of .082 and .055, respectively (see **Table**). The white matter ROI had the lowest P values for all 3 IVIM metrics analyzed, whereas the gray matter ROI had the highest P values. Among the ROIs, the gray matter showed the highest perfusion fraction with the white matter ROI being the lowest. This relationship was also seen for the pseudo-diffusion coefficient with white matter showing the lowest value followed by the spinal cord and gray matter exhibiting the highest value.

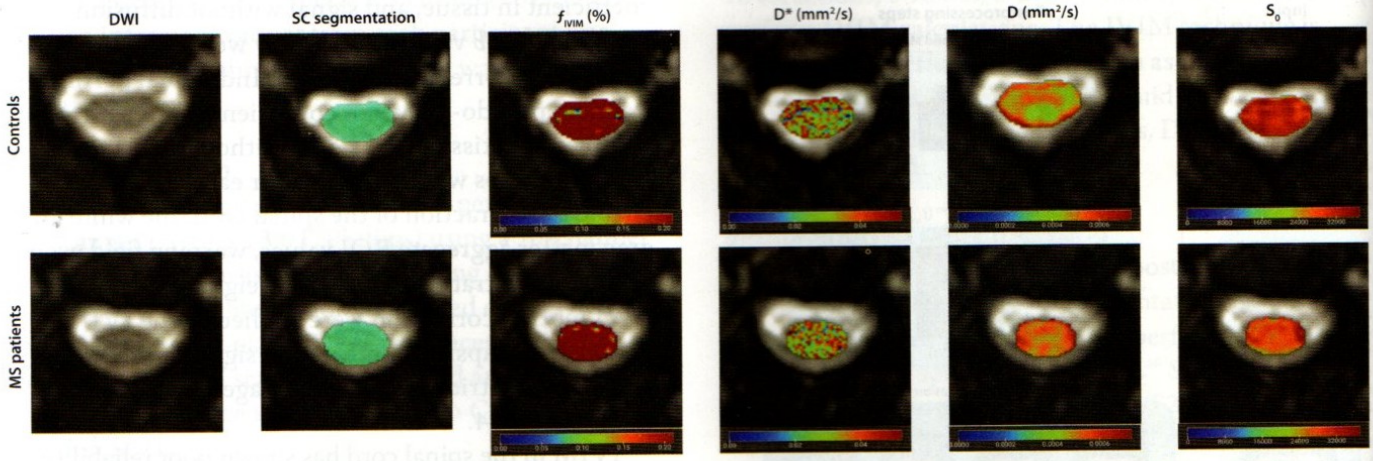

Figure 3. *Example of DWI for control participants (top row) and MS patients (bottom row) with SC segmentation and calculation of IVIM metrics (f_{IVIM}, D*, D, and S_0 [magnetic resonance signal intensity relative to baseline]). Images courtesy of the authors.*

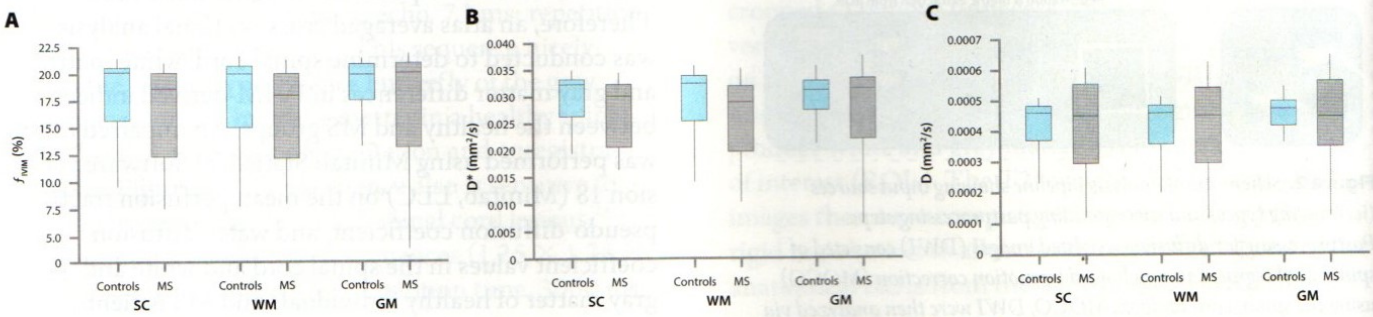

Figure 4. *Whisker boxplots of IVIM metrics in control participants and MS patients for SC, WM, and GM. A. IVIM perfusion fraction. B. Pseudo-diffusion coefficient. C. Water-diffusion coefficient. Figures courtesy of the authors.*

Discussion

In this study, use of the PWI technique IVIM was investigated to assess microvascular perfusion and diffusion in the spinal cord of MS patients. IVIM has been used to assess the microcirculation of various organs,[29-32] including the brain.[28] However, a single study was located that evaluated IVIM of the spinal cord. This is the first known study using IVIM in the spinal cord in a patient population.[26] No significant difference between healthy individuals and patients with MS was found; however, the spinal cord, white matter, and gray matter in the MS group showed a reduced perfusion fraction and pseudo-diffusion coefficient compared with the healthy group. These findings suggest that IVIM has potential as a tool for assessing the microcirculation of the human spinal cord in patients with MS.

These findings are consistent with the current PWI literature focused on MS in the brain. MS PWI findings have shown decreased cerebral blood flow and cerebral blood volume in chronic MS lesions when compared with NAWM and controls.[15-17,44,45] The gray matter of patients in the MS group in this study also showed reduced perfusion when compared with the healthy group.[8,10,46] Although this hypoperfusion has not been reported for active MS lesions.[9,10] Results showed that the gray matter perfusion fraction was higher than that of the white matter, which also is consistent with the current literature.[26] However, using IVIM, Yin et al observed a significantly elevated perfusion fraction for nonenhancing lesions compared with NAWM in regions proximal and distal to the chronic lesions.[47]

Table

Perfusion Fraction and Diffusion Coefficients of Regions of Interest from the Healthy and MS Groups

Region of interest	Healthy group, Mean (SD)	MS group, Mean (SD)	95% CI	*t*	*P*[a]
IVIM perfusion fraction (f_{IVIM}), %					
Spinal Cord	17.81 (4.43)	16.67 (4.18)	−0.367-3.241	1.58	.117
White matter	17.68 (4.69)	16.00 (4.37)	−0.217-3.582	1.76	.082
Gray matter	18.26 (4.30)	17.62 (4.38)	−1.182-2.457	0.7	.488
Pseudo-diffusion coefficient (D*), mm^2/s					
Spinal Cord	2.895E-02 (7.060E-03)	2.698E-02 (6.210E-03)	−0.00081-0.00476	1.41	.163
White matter	2.897E-02 (7.480E-03)	2.604E-02 (6.820E-03)	−0.00007-0.00593	1.94	.055
Gray matter	2.896E-02 (7.000E-03)	2.849E-02 (7.120E-03)	−0.00248-0.00343	0.32	.751
Water-diffusion coefficient (D), mm^2/s					
Spinal Cord	4.175E-04 (9.570E-05)	4.060E-04 (1.540E-04)	−0.000042-0.000066	0.44	.662
White matter	4.140E-04 (1.000E-04)	4.000E-04 (1.610E-04)	−0.000042-0.000071	0.51	.614
Gray matter	4.320E-04 (1.040E-04)	4.270E-04 (1.450E-04)	−0.000048-0.000058	0.18	.858

Abbreviations: CI, confidence interval; IVIM, intravoxel incoherent motion; MS, multiple sclerosis.
[a] *Significant at* $P < .05$.

Acquiring and processing the IVIM data in the spinal cord is a major obstacle[26] and a reason there are limited studies using PWI techniques for the assessment of MS lesions in the spinal cord compared with the brain.[24] One of the main challenges is the technical difficulty in obtaining and processing the IVIM data, which requires the use of high-resolution imaging, multiple *b* values, and complex mathematical modeling. The IVIM biexponential model is a signal representation highly sensitive to biases from patient and physiological motion.[48] In addition, the interpretation of the IVIM parameters in the spinal cord can be challenging because of the limited understanding of the underlying microstructural changes and the potential confounding factors such as the partial volume effect, B0, and B1 inhomogeneities.[26]

Limitations

Several factors restrict the conclusions drawn from this study. First, the number of individuals in this study was small, and all patients in the MS group were women. The large slice thickness employed in this study might have further convoluted the various effects within each voxel, increasing the errors. The IVIM literature also reports a large variation in perfusion fraction and pseudo-diffusion coefficient for white and gray matter in healthy individuals.[49]

Conclusion

IVIM is a promising imaging technique for the evaluation of the spinal cord in patients with MS. It has the potential to provide valuable information on the microvascular perfusion and diffusion in the spinal cord, which might be related to disease progression and response to treatment. However, further research is needed to improve the technical and methodological aspects of IVIM and to better understand the underlying microstructural changes and the potential confounding factors. In addition, more studies comparing IVIM with other imaging techniques, such as conventional MR imaging and histopathology, are needed to establish the clinical utility of IVIM in the spinal cord of MS patients.

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