Cerebral blood flow dependency on systemic arterial circulation in progressive multiple sclerosis

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Disclosures:

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Slide 1

Background:

- Using *in-vivo* MRI methods such as DSC-PWI, studies have demonstrated changes in cerebral perfusion that occur as early as appearance of first MS symptoms and become more prominent in the progressive phase.[1,2]

- After hypercapnic stimuli, GM CVR is reduced in MS patients when compared to healthy controls, with reductions having been associated with MS lesion volume and GM atrophy.[3]

Objectives and hypothesis:

- Under normal conditions and proper functioning of the neurovascular unit, we would not expect direct associations between the cerebral arterial blood flow and SABF.

- When compared to their RRMS counterparts, we hypothesized that the cerebral perfusion in PMS patients would be directly associated and dependent on the SABF.

- To test this association, we measured and compared the *in-vivo* rate of cerebral and systemic arterial blood flow in a heterogeneous group of CIS/RRMS and PMS patients.

PERFUSION WEIGHTED IMAGE

CBF

DSC-PWI - dynamic susceptibility contrast perfusion-weighted imaging, MRI – magnetic resonance image, MS – multiple sclerosis, GM – gray matter, CVR – cerebrovascular reactivity, SABF – systemic arterial blood flow, CIS – clinically isolated syndrome, RRMS – relapsing remitting multiple sclerosis, PMS – progressive multiple sclerosis

[1]Lagana MM, Neural Regen Res, 2020, 15:646-652, [2]Lapointe E et al. AJNR AM J Neuroradiol 2018, 10.3174/ajnr.A5504, [3]Marshall O et al JAMA Neurol, 2014, 71:1275-1281, Pelizzari L et al. Brain Imaging Behav, 2020, 14(5):1889-1898.

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Methods:

Study population:

The MS patients included in this analysis were part of a larger, prospective study that investigated the cardiovascular, environmental and genetic risk factors in MS (CEG-MS).[1]

Inclusion criteria: 1) age of 18-75 years old. 2) diagnosed with MS based on the 2010-revised McDonald criteria[2] or CIS patients. 3) clinical visit, echo-color Doppler, and MRI examination within 30 days of each other.

Exclusion criteria: 1) pregnant or nursing mothers 2) presence of known congenital morphological vascular pathology (such as Klippel–Trenaunay–Weber, Parkes Weber, Servelle–Martorell, or Budd–Chiari syndromes), 3) contraindications prohibitive to performing a MRI exam and 4) clinically-defined relapse or use of intravenous corticosteroids within 30 days of the study visit.

Ultrasound Doppler acquisition and analysis:

The total SABF was determined using an echo-color Doppler (Biosound MyLab 25 Gold; Esaote, Genoa, Italy) 7.5-10MHz transducer.[3]
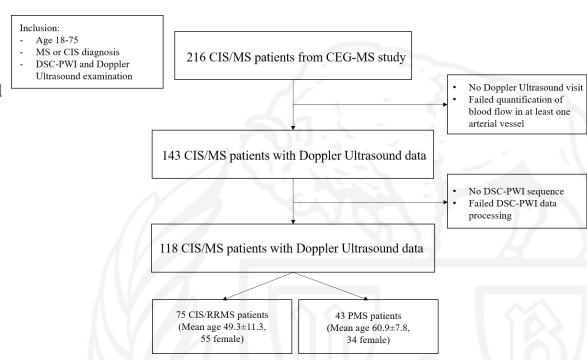
- The blood flow of the bilateral CCA was measured at approximately 1.5cm below the bifurcation of the external and internal carotid artery.
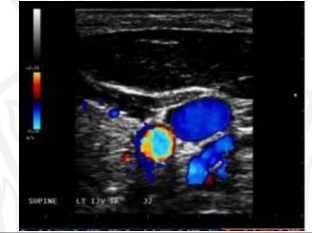- The blood flow of the bilateral VA was obtained at the C5-C6 level.

The total SABF was derived as a sum of all four vessels and quantified in milliliters per minute (mL/min).

Flow diagram:

Inclusion:
- Age 18-75
- MS or CIS diagnosis
- DSC-PWI and Doppler Ultrasound examination

216 CIS/MS patients from CEG-MS study

- No Doppler Ultrasound visit
- Failed quantification of blood flow in at least one arterial vessel

143 CIS/MS patients with Doppler Ultrasound data

- No DSC-PWI sequence
- Failed DSC-PWI data processing

118 CIS/MS patients with Doppler Ultrasound data

75 CIS/RRMS patients (Mean age 49.3±11.3, 55 female)

43 PMS patients (Mean age 60.9±7.8, 34 female)

DSC-PWI - dynamic susceptibility contrast perfusion-weighted imaging, CIS – clinically isolated syndrome, MRI – magnetic resonance imaging, SABF – systemic arterial blood flow, CCA – common carotid artery, VA – vertebral artery, CIS – clinically isolated syndrome, RRMS – relapsing remitting multiple sclerosis, PMS – progressive multiple sclerosis

1. Jakimovski D et al. Mult Scler 2020;26:322-332. 2. Polman CH et al. Ann Neurol 2011;69:292-302. 3. Marr K et al. Ultrasound Med Biol 2018;44:1762-1769.

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Methods – continued:

MRI acquisition and analysis:

- Patients underwent an MRI examination on a 3.0T GE Signa Excite scanner (Milwaukee, WI, USA) with eight-channel head and neck coil.

- The MRI protocol included an axial 3D spoiled gradient recalled (SPGR) T1-weighted image (WI), an axial 2D T2-WI Fluid Attenuated Inversion Recovery (FLAIR) and dynamic susceptibility contrast perfusion-weighted imaging (DSC-PWI) sequence.

- T2 and T1-LV were derived using semi-automated, threshold and contour segmentation, while WBV was obtained with the cross-sectional package from Structural Image Evaluation, using Normalisation, of Atrophy (SIENAX; version 2.6, Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, Oxford, UK).[1]

- JIM Perfusion Toolkit was used to produce the PWI-derived measures of mean transit time (MTT) and time-to-peak (TTP) time. The structural and perfusion segmentations were co-registered and aligned in the same MRI space. Mean values for NAWB and GM MTT and TTP were calculated.

Statistical analyses:

- All statistical analyses were performed on SPSS version 26.0 (IBM, Armonk, NY, USA). Data distributions were evaluated using the Kolmogorov-Smirnov test and visual inspection of the Q-Q plots.

- The comparison of demographic and clinical characteristics parametric and non-parametric tests as appropriate.

- Moreover, age, sex, BMI and WBV-adjusted linear regression models determined whether SABF explains additional variance of the perfusion-based measures.

- Patients were further divided into SABF quartiles and the DSC-MRI measures were compared with age, sex, BMI and WBV-adjusted analysis of covariance (ANCOVA). The pair-wise comparisons from the ANCOVA analysis were Bonferroni adjusted.

SABF – systemic arterial blood flow, BMI – body mass index, WBV – whole brain volume, NAWB – normal-appearing whole brain, GM – gray matter, MTT – mean transit time, TTP – time-to-peak.

1. Smith SM et al. Neuroimage 2002;17:479-489.

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Results:

	MS (n=118)	CIS/RRMS (n=75)	PMS (n=43)	CIS/RRMS vs. PMS p-value
Female, n (%)	89 (75.4)	55 (73.3)	34 (79.1)	0.715
Age, mean (SD)	53.52 (11.6)	49.25 (11.3)	60.97 (7.8)	**<0.001**
BMI, mean (SD)	27.6 (5.9)	27.6 (6.1)	27.6 (5.8)	0.945
Disease duration, mean (SD)	20.1 (10.3)	16.5 (9.1)	26.2 (9.5)	**<0.001**
EDSS, median (IQR)	3.0 (1.5-6.0)	2.0 (1.5-3.0)	6.0 (3.75-6.5)	**<0.001**
MSSS, median (IQR)	2.3 (1.1-5.0)	1.5 (09-3.1)	5.6 (2.7-6.3)	**<0.001**
T25FWT, median (IQR)	5.26 (4.5-7.3)	4.8 (4.4-5.7)	7.4 (6.1-11.8)	**<0.001**
9HPT, median (IQR)	23.1 (19.7-28.3)	21.1 (18.8-23.8)	26.2 (24.3-34.5)	**<0.001**
Hypertension diagnosis, n (%)	21 (17.8)	8 (10.7)	13 (30.2)	**0.012**
SBP, mean (SD)	124.7 (13.7)	125.1 (12.7)	123.9 (15.4)	0.68
SABF, mean (SD)	947.7 (262.2)	954.4 (260.3)	928.2 (279.0)	0.610
WBV, mean (SD)	1451.2 (94.4)	1485.4 (81.1)	1393.5 (87.5)	**0.006***
NAWB MTT	3.29 (0.7)	3.22 (0.7)	3.44 (0.8)	0.139
GM MTT	3.26 (0.8)	3.17 (0.7)	3.42 (0.9)	0.106
NAWB TTP	7.08 (1.3)	7.01 (1.3)	7.19 (1.1)	0.469
GM TTP	7.08 (1.3)	6.99 (1.4)	7.22 (1.2)	0.357
DMT, n (%)				
Interferon-β	40 (33.9)	28 (37.3)	12 (27.9)	
Glatiramer acetate	30 (25.4)	18 (24.0)	12 (27.9)	
Natalizumab	4 (3.4)	3 (4.0)	1 (2.3)	0.655
Oral medications	12 (11.9)	8 (13.3)	4 (9.4)	
Off-label medications	4 (3.4)	2 (2.7)	2 (4.7)	
No DMT use	26 (22.0)	14 (18.7)	12 (27.9)	

- Higher systolic blood pressure was significantly associated with lower SABF (r==0.265, age and BMI-adjusted p=0.006). These findings were driven only by the PMS subgroup.

Legend: MS – multiple sclerosis, CIS – clinically isolated syndrome, RRMS – relapsing-remitting multiple sclerosis, PMS – progressive multiple sclerosis, BMI – body mass index, EDSS – Expanded Disability Status Scale, SBP – systolic blood pressure, SABF – systemic arterial blood flow, WBV – whole brain volume, DMT – disease modifying therapy, SD – standard deviation, IQR – interquartile range, NAWB – normal-appearing whole brain, GM – gray matter, MTT – mean transit time, TTP – time-to-peak.

Data regarding DMT status was missing for 2 CIS/RRMS patients.

The groups were compared with χ^2 and Student's t-test as appropriate. P-value lower than 0.05 was considered statistically significant and shown in bold. * - age-adjusted analysis of covariance (ANCOVA)

Age and disease duration are shown in years, SABF is shown as milliliters per minute (mL/min) and WBV is shown as mL. Both MTT and TTP measures are absolute data in seconds and shorter MTT and TTP times represent greater blood flow at the capillary level.

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Results - continued:

Table. Adjusted relationship between cerebral and systemic blood flow in PMS patients.

NAWB TTP	R^2	SE of estimate	t-statistics	standardized β	p-value
Block 1	0.137	1.096			
Age			1.678	0.26	0.103
Sex			0.374	0.057	0.711
BMI			-0.84	-0.141	0.407
WBV			0.87	0.149	0.391
Block 2	0.269	1.024			
SABF			-2.405	-0.384	**0.022**
GM TTP	R^2	SE of estimate	t-statistics	standardized β	p-value
Block 1	0.144	1.133			
Age			1.648	0.257	0.109
Sex			0.397	0.061	0.694
BMI			-1.021	-0.173	0.315
WBV			0.86	0.149	0.396
Block 2	0.254	1.074			
SABF			-2.174	-0.351	**0.037**

Legend: PMS – progressive multiple sclerosis, BMI – body mass index, WBV – whole brain volume, SABF – systemic arterial blood flow, NAWB – normal-appearing whole brain, GM – gray matter, TTP – time-to-peak, SE – standard error.

The linear regression models are built with first block which force-enters and corrects for the effect of age, sex, BMI and WBV. The second step-wise block is built only if SABF provides additional and significant explanatory power.

- After correction for demographic covariates and WBV, the SABF in PMS patients remained significantly associated with the TTP of NAWB and GM.

- Addition of SABF resulted with significant R^2 increase from 0.137 to 0.269, additionally explaining 13.2% of the remaining NAWB TTP variance.

- After adjusting for age, sex, BMI and WBV effects, higher SABF remained significantly associated with shorter GM TTP as well.

PMS – progressive multiple sclerosis, SABF – systemic arterial blood flow, BMI – body mass index, WBV – whole brain volume, NAWB – normal-appearing whole brain, GM – gray matter, TTP – time-to-peak.
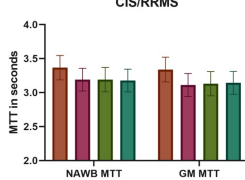
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Results - continued:

- After adjusting for sex, age, BMI and WBV effects, there were significant differences between the PMS-based SABF quartiles in NAWB MTT (p=0.023), GM MTT (p=0.014), NAWB TTP (p=0.012) and GM TTP (p=0.025).
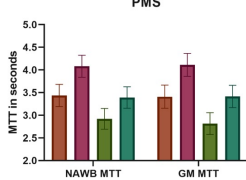
- These differences remained significant after further correction for the presence of hypertension and EDSS scores.
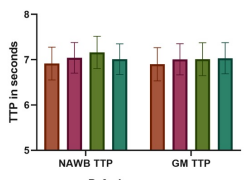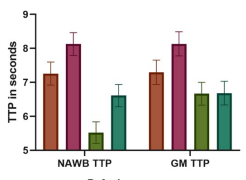
Legend: PWI – perfusion-based imaging, CIS – clinically isolated syndrome, RRMS – relapsing-remitting multiple sclerosis, PMS – progressive multiple sclerosis, MTT – mean transit time, TTP – time-to-peak, NAWB – normal-appearing whole brain, GM -gray matter, SABF – systemic arterial blood flow.
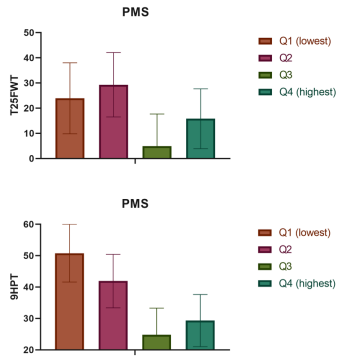
The MS patients were divided based on the SABF quartiles. Age, sex, BMI and WBV-adjusted differences of MTT and TTP measures are shown. MTT and TTP are shown as estimated means in seconds and the bars represent the standard error.

PMS – progressive multiple sclerosis, SABF – systemic arterial blood flow, BMI – body mass index, WBV – whole brain volume, NAWB – normal-appearing whole brain, GM – gray matter, MTT – mean transit time, TTP – time-to-peak, EDSS – Expanded Disability Status Scale

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PMS (T25FWT chart)

Legend: Q1 (lowest), Q2, Q3, Q4 (highest)

PMS (9HPT chart)

Legend: Q1 (lowest), Q2, Q3, Q4 (highest)

- Hypertension-induced decreases in SABF would particularly affect MS patients with CVR impairment and potentially worsen the disability progression.

PMS – progressive multiple sclerosis, SABF – systemic arterial blood flow, CIS – clinically isolated syndrome, RRMS – relapsing remitting multiple sclerosis, BMI – body mass index, WBV – whole brain volume, CVR – cerebrovascular reactivity,

Summary:

- Cerebral perfusion in PMS patients is directly associated and potentially dependent on the SABF, but not in the CIS/RRMS patients.

- These associations remained significant after correcting for effects of aging and BMI as well as total WBV.

- The discrepancies between the MS subtypes may be attributed to failure in the CVR, where PMS patients would not be able to appropriately redistribute the insufficient inflowing arterial blood flow.

Conclusions:

- The direct relationship between systemic and cerebral blood flow seen in PMS patients may suggest failure in cerebrovascular reactivity mechanisms and insufficient perfusion control.

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