Relative recirculation (rR): a potential tool for monitoring blood-brain barrier disruption in secondary progressive multiple sclerosis

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Introduction:
Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that results in demyelination, destruction of oligodendricytes, and, eventually, long-term functional impairment. MS is a dynamic process with approximately 30-40% of relapsing-remitting MS patients deteriorating to secondary progressive disease—a phase marked by a continuous clinical worsening of the disease over a minimum of 6 months [1]. While the inflammation and resultant focal blood-brain barrier (BBB) disruption associated with relapsing-remitting MS is readily identified using gadolinium-enhanced T1-weighted MRI, the value of these conventional MRI markers in the monitoring of secondary progressive MS is far less clear [2,3]. Increasingly, quantitative and semi-quantitative hemodynamic parameters are being explored for the characterization of MS lesions with contrast-enhanced MRI [4-6]. It has been previously shown that relative recirculation (rR), a parameter extracted from dynamic susceptibility contrast (DSC) data, can successfully identify regions of BBB disruption in patients with acute ischemic stroke [7]. The purpose of this study was to determine the rR of secondary progressive MS lesions and its relationship with a standard clinical measure of disability and MS severity.

Materials and Methods:
Nineteen patients aged 46-82 years (average age ± SD 58.7 ± 9.8 years; 8 men and 11 women) with secondary progressive MS participated in the study. Patients were not on any disease modifying drugs >3 months prior to the study. All MR imaging was performed on a 3.0T Philips Achieva MRI system (Philips Healthcare, Markham, Canada). Proton density (PD)/T2-weighted images, as well as volumetric T1-weighted FSPGR images were acquired in order to identify MS lesions. Relative recirculation (rR) measurements were obtained from a 2D T2*-weighted field echo EPI scan with the following parameters: TR 1611 ms, TE 30 ms, FOV 220 mm, matrix 95 x 95, flip angle 90º, slice thickness 4 mm. The total acquisition time for 80 dynamics was 129 seconds. Gadolinium contrast (0.1 mmol/kg, Gadovist, Bayer Healthcare) was injected as a bolus following acquisition of the 10th dynamic. Contrast injection was immediately followed by a 20-mL saline flush; both contrast and saline were injected at a rate of 5 mL/s via power-injector. All data were analyzed offline, beginning with the PD/T2- and T1-weighted images: gray matter, white matter, and cerebrospinal fluid regions were segmented using a validated parcelation method (SABRE; Semi-Automated Brain Region Extraction) [8]. These regions were then imported into Analyze 8.0 (Analyze AVW, Rochester, MN, USA) [9] on which additional regions of interest (ROIs) corresponding to white matter lesions (areas of PD hyperintensity) were superimposed. An example WM lesion mask obtained from a representative patient is provided in FIG. 1a. Note that ROIs were also selected from within normal-appearing white matter (NAWM), usually from within the homologous location in the contralateral hemisphere. All lesion and NAWM ROIs were subsequently copied to the equivalent DSC MRI data sets (FIG. 1b-d). The rR corresponding to each ROI was calculated using in-house software (MR analyst v. 4.0) developed in MATLAB (The Mathworks, Natick, MA) as previously described [7,10] (FIG. 1e-g). Patient level mean values of rR were determined by calculating the weighted average rR over all lesion or contralateral ROIs for each patient. Two-tailed paired t-tests were used to detect differences between mean rR values in lesion and contralateral ROIs. Mean rR values were adjusted for age using an Analysis of Covariance (ANCOVA) procedure. The correlation between rR and disability (the expanded disability status score, EDSS) was assessed using Spearman's rank correlation.

Results:
All 19 patients successfully completed the study. The median EDSS was 6.5 (range 2.0-8.0). The weighted average rR over all lesion ROIs was significantly higher than in NAWM (0.15 ± 0.02 vs. 0.07 ± 0.02, $P < 0.0001$; FIG. 2). We did not detect any gender differences in lesion rR (0.14 ± 0.02 vs. 0.15 ± 0.02, male vs. female patients; $P = 0.67$). The ANCOVA revealed that age was not a significant covariate of rR (P=0.47). Finally, the correlation between lesion rR and EDSS was not found to be statistically significant (Spearman's rank correlation = -0.210, $P = 0.39$).

Discussion:
The results demonstrate persistent BBB disruption in the absence of clinical markers of increased disease severity. BBB disruption has been recognized as a necessary step in MS plaque pathogenesis and may precede new lesion development. Whether rR can also serve as a marker of subtle, widespread disease remains to be investigated.

Fig. 1:

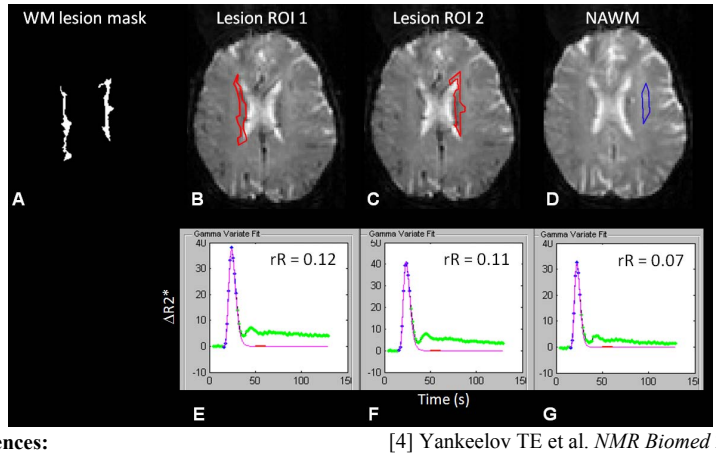
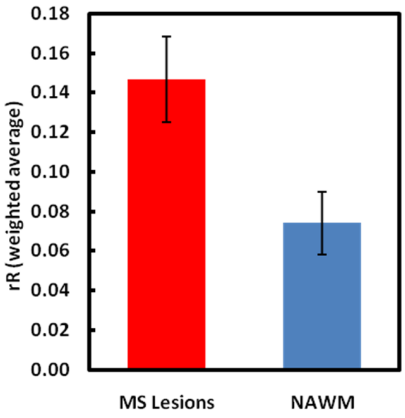


Fig. 2:



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