

Altered cerebrovascular reactivity and its restoration with Interferon beta treatment in multiple sclerosis

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Purpose: Cerebrovascular reactivity (CVR) is the capacity of blood vessels to increase blood flow to brain tissue, a process essential for preserved neurovascular coupling¹. Evidence suggests that CVR may be altered in Multiple Sclerosis (MS) as a result of inflammatory processes². This alteration may affect functional brain responses and may contribute to the development of damage in MS³. Modulating inflammation may restore CVR in MS, thus contributing to the preservation of tissue physiology and integrity. Here we hypothesise that CVR is reduced in MS patients compared to healthy volunteers, but immunomodulatory treatment aimed at reducing inflammation can restore CVR in patients. As carbon dioxide (CO₂) is a potent vasodilator, we used rises in arterial CO₂ with breath-holding to induce cerebral blood flow increases and thus increases in BOLD functional MRI (fMRI) signal. These fMRI changes provided an indirect measure of CVR.

Methods: MS patients⁴ underwent 3 MRI scans, 2 before and 1 following the commencement of IFN beta 1a given 3 times/week subcutaneously (Rebif 44 mcg). Age and sex matched healthy volunteers formed the control group and underwent 1 scan only. MR measurements were acquired using a Siemens Magnetom Verio 3T. In patients only, post-Gadolinium (Gd) T1-weighted images were acquired to detect inflammatory activity. T1-weighted 3D structural scans were acquired in patients and in controls to map grey matter (GM) density. BOLD fMRI signal changes (GE EPI, TR/TE = 3000/30ms, 64x64; 50 slices 3mm thick, 92 vols) were acquired in response to breath-hold (BH) induced hypercapnia. Five 16 s breath-holds were alternated with 34 s recovery periods. End tidal CO₂ was recorded via nasal cannula. Behavioural data were analysed using Matlab. Imaging data were analysed using software from the FSL toolbox. A first level linear regression analysis was used to extract GM voxel-wise measures of CVR (%BOLD signal change/mmHg CO₂) using the recordings of changes in end tidal CO₂ induced by the task. Second-level regression analysis incorporating GM density as a covariate was performed to compare patients with controls and changes in CVR over time in patients. Results are reported as mean±SE unless otherwise stated.

Results: 25/26 patients (age 34±1 years, F/M 20/5, disease duration 22±6 months, median EDSS 1.5, range 0-3.0) and 19/22 controls (age 34±2 years, F/M 14/5) had readable breath-hold traces and entered the analysis. Mean±SE intervals were 45±2 days between Scan 1 and Scan2 and 85±4 days between Scan 2 and Scan3. At baseline, 14/25 patients showed Gd-enhancing scans (Fig.1). Compared to controls, patients had distributed GM density reduction. Prior to treatment, global GM CVR was significantly lower in patients than in controls (-17±8%, p<0.05) (Fig.2). No significant difference was seen between Scans 1

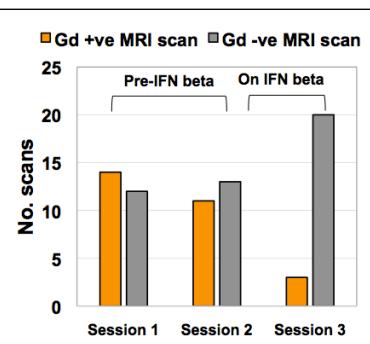


Fig.1. Number of Gd-positive (yellow) and Gd-negative scans (grey) before and during IFN beta. There is a reduction in the number of Gd-enhancing scans on IFN beta treatment (Scan 3).

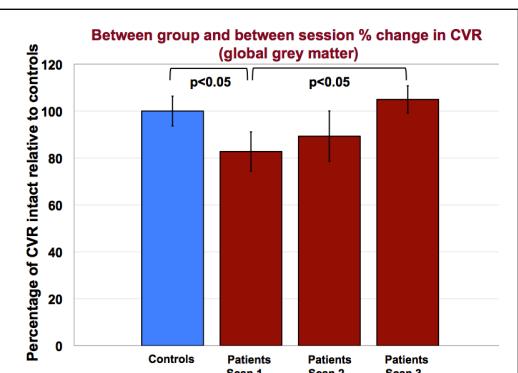


Fig.2. CVR in patients (red) before and during IFN-beta and in controls (blue). CVR is reduced in patients before treatment, but exhibits an increase during IFN beta.

and 2. In Scan 3, global GM CVR increased compared to Scan 1 (+27±5%, p<0.05) (Fig.2). The greatest mean local increases in CVR were in the frontal lobe (31±6%, p<0.01), where significant differences with controls were observed at baseline (Fig.3), but also in the temporal (27±6%, p=0.01), parietal (25±7%, p=0.01) and occipital (24±7%, p=0.02) lobes. Mean changes in CVR were observed independent of GM density alterations. In parallel, on IFN-beta treatment, a sharp reduction in the number of Gd-enhancing scans was noted (Fig.1).

Discussion: CVR was significantly lower in patients compared to controls at baseline and this difference was over and above changes in grey matter volume. Abnormally low CVR in patients appeared to be restored with IFN-beta treatment. The effect of immunomodulation on CVR in patients suggests that altered CVR is related to MS inflammatory activity and supports further investigations on the use of regional CVR as a potential early marker of therapeutic effect.

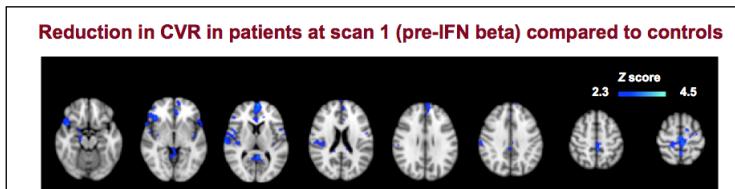


Fig.3. Reduced baseline CVR in patients compared to controls. Between group differences are noted in the frontal lobe.

References: [1] Schwertfeger N, Neu P, Schlattmann P et al. J Neurol Sci 2006. [2] Settakits G, Molnár C, Kerényi L, et al. Eur J Neurol 2003. [3] Trapp B, Stys P. Lancet 2009. [4] Polman CH, Reingold SC, Edan G et al. Ann Neurol 2005.

Acknowledgements: The study was supported by a grant from Merck Serono Switzerland and by the Du Pre' Grant from the MS International Federation (Dr V. Tomassini). Data was collected from the Department of Neurology and Psychiatry, Sapienza University of Rome, Italy.