Intravoxel Incoherent Motion Imaging exposes abnormal parenchyma and microvasculature in cerebral small vessel disease

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Target Audience: Neuroscientists interested in perfusion and diffusion imaging and cerebral small vessel disease

Purpose: Cerebral small vessel disease (cSVD) is an age and vascular risk factor related microvascular disease and may clinically manifest as lacunar stroke or vascular cognitive impairment. Moreover, it can lead to physical, psychiatric and cognitive disabilities. The pathophysiology of cSVD remains largely unknown. Early changes in cSVD include loss of microstructural integrity and a possible association with hypoperfusion, which were shown by previous studies using diffusion tensor imaging and perfusion imaging, respectively.[1-2] However these studies could not distinguish between contributions of parenchymal and vascular microstructures, leaving the more precise nature of the abnormalities undetermined. To examine the parenchymal microstructure and microvasculature, Intravoxel Incoherent Motion Imaging (IVIM) was performed.

Methods: *Subjects and data acquisition:* MR imaging was conducted on 64 cSVD patients (age 70±11y) and 36 healthy controls (age 68±12y) using a 3.0 Tesla MR scanner (Philips Achieva TX). IVIM was executed using a Stejskal-Tanner diffusion weighted (DW) spin echo single shot echo planar imaging (EPI) pulse sequence (TR/TE = 6800/84 ms, FOV: 221 x 269 mm^2, acquisition matrix: 110 x 112, 58 slices, 2.4 mm voxel size). To minimize the effect of cerebral spinal fluid (CSF), an inversion recovery prepulse (TI = 2230 ms) was implemented prior to the DW sequence.[3] Fifteen DW images were acquired using b-values (0, 5, 7, 10, 15, 20, 30, 40, 50, 60, 100, 200, 400, 700, 1000 s/mm^2, in the phase encoding direction). Images obtained with b-values 700 and 1000 s/mm^2 were repeated 2 and 3 times respectively. The total IVIM scan duration was 5:13 min. For anatomical segmentation a T1-weighted scan and a FLAIR scan were performed (fig.1 A,B).
Data analysis: IVIM employs a two-compartment diffusion model.[4] A model that accounts for effects of CSF and also differences in relaxation times of blood and tissue was used.[3] A bi-exponential signal decay can be obtained (fig.2) and the two-step method[5] was used for voxel wise fitting (fig. 1C-E). First *D* (parenchymal diffusivity) was estimated using b-values higher than 200 s/mm^2, and subsequently *f* (perfusion fraction) and *D** (microvascular diffusivity) were estimated using all b-values and fixed *D*. For each participant the brain was segmented into four regions of interest (ROI): normal appearing white matter (NAWM), deep gray matter (DGM), cortex and white matter hyperintensities (WMH)[6]. Average *f*, *D**, and *D* were calculated for each ROI.
Statistical analysis: Multivariate linear regression analysis corrected for age, gender and cardiovascular risk factors hypertension, diabetes mellitus, hypercholesterolemia, smoking and atrophy was conducted. Baseline characteristics were compared using independent samples t-tests and Chi-square tests.

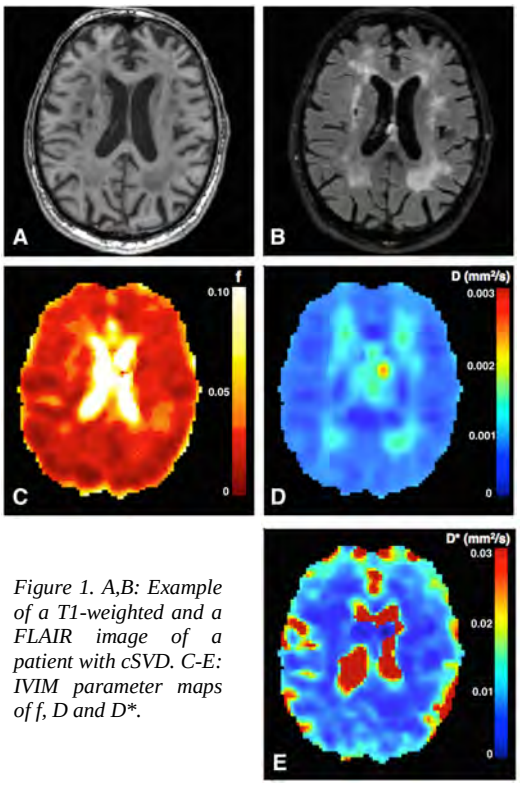

Figure 1. A,B: Example of a T1-weighted and a FLAIR image of a patient with cSVD. C-E: IVIM parameter maps of f, D and D.*

Results: Patients suffered significantly more from hypercholesterolemia (p=0.01) and significantly more smokers were present in the patient group (p=0.03). Significantly higher *f* was observed for the patient group (2.32±0.03x10^{-2}, n=64) (mean±SE, n) compared with controls (2.20±0.03x10^{-2}, n=36) in the NAWM (p=0.03). A trend towards higher *f* was found for patients (3.26±0.05x10^{-2}, n=64) in comparison with controls (2.94±0.03x10^{-2}, n=36) in the DGM (p=0.06). Significantly higher *D* was found for patients (7.32±0.04x10^{-4} mm^2/s, n=64) compared with healthy controls (7.09±0.04x10^{-4} mm^2/s, n=36) in the NAWM (p=0.02). In DGM significantly higher *D* was found for patients (7.78±0.05x10^{-4} mm^2/s, n=64) compared with controls (7.51±0.05x10^{-4} mm^2/s, n=36) (p=0.02). No differences were found for *D** or other regions.

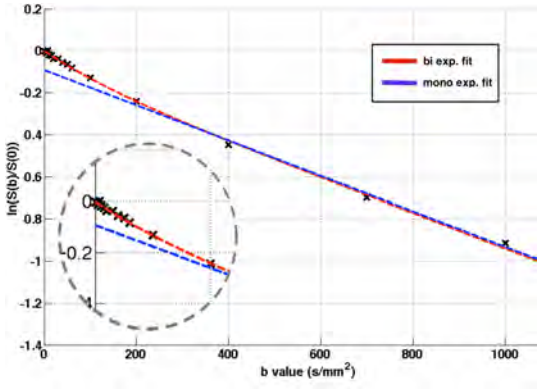

Figure 2. A two-step method was used to fit the bi-exponential decay. First a mono exponential curve is fitted for b-values larger than 200 s/mm^2 (blue line). Subsequently a bi-exponential curve was fitted for all b-values (red line) with fixed D. The inserted circle shows the bi-exponential behavior, visible for b-values <200 s/mm^2.

Discussion & Conclusion: Larger microvascular perfusion fraction *f* and higher parenchymal diffusivity *D* were found in the NAWM and DGM for patients with cSVD. The larger *f* might be related to more tortuous vessels[7] (fig. 3) that lead to a stronger dephasing of spins contributing to the fast decaying component. Furthermore the higher *D* may imply loss of parenchymal microstructural integrity. This suggests early parenchymal changes in cSVD that precede the formation of WMH. Longitudinal studies are needed to verify this. In this study, we demonstrate the potential of IVIM in providing novel pathophysiological information of the normal appearing brain tissue in cSVD.

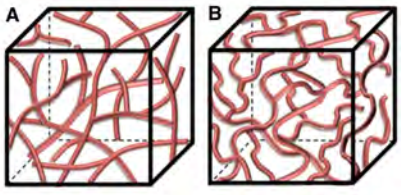

Figure 3. Illustration of voxels containing straight vessels (A) and tortuous vessels(B).

References: **1.** O'Sullivan M *et al.*, Neurology 2001;57:2307-2310. **2**. Markus HS *et al.*, J Neurol Neurosurg Psychiatry 2000;69:48-53. **3.** Hales PS *et al.*, J Cereb Blood Flow Metab 2013;33, 67-75 **4.** Bihan D *et al.*, Radiology 1986; 161: 401-7 **5.** Federau *et al.*, JMRI 2014; 39: 624-632 **6.** De Boer R *et al.*, Neuroimage, 2009;45(4):1151–61 **7.** Brown WR *et al.* Neuropath Appl Neuro, 2011; 37-56-74