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Simultaneous investigation of microvasculature and parenchyma in cerebral small vessel disease using intravoxel incoherent motion imaging

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ABSTRACT

Introduction: Cerebral small vessel disease (cSVD) is associated with microvascular and parenchymal alterations. Intravoxel incoherent motion (IVIM) MRI has been proposed to simultaneously measure both the microvascular perfusion and parenchymal diffusivity. This study aimed to evaluate the application of IVIM in cSVD to assess the microvasculature and parenchymal microstructure.

Methods: Seventy-three patients with cSVD (age 70 ± 11 y) and thirty-nine controls (age 69 ± 12 y) underwent IVIM imaging (3T). Group differences of the perfusion volume fraction f and the parenchymal diffusivity D were investigated using multivariable linear regression accounted for age, sex and cardiovascular factors. To examine the relation between the IVIM measures and the disease severity on structural MRI, white matter hyperintensity (WMH) load served as surrogate measure of the disease severity.

Results: Patients had a larger f ($p < 0.024$) in the normal appearing white matter (NAWM) than controls. Higher D ($p < 0.031$) was also observed for patients compared with controls in the NAWM and grey matter. Both f ($p < 0.024$) and D ($p < 0.001$) in the NAWM and grey matter increased with WMH load.

Conclusions: The increased diffusivity reflects the predicted microstructural tissue impairment in cSVD. Unexpectedly, an increased perfusion volume fraction was observed in patients. Future studies are needed to reveal the precise nature of the increased perfusion volume fraction. IVIM imaging showed that the increases of f and D in cSVD were both related to disease severity, which suggests the potential of IVIM imaging to provide a surrogate marker for the progression of cSVD.

1. Introduction

Age and vascular risk factor related cerebral small vessel disease (cSVD) is a common microvascular pathology underlying burdensome diseases like lacunar stroke and vascular cognitive impairment (Pantoni, 2010; Makin et al., 2013; Pantoni & Gorelick, 2011). Alterations in the parenchyma have been described in cSVD as structural MRI abnormalities like lacunes, white matter hyperintensities, microbleeds and enlarged perivascular spaces (PVS) (Wardlaw & Smith, 2013). However, little is known about the precursors of these alterations, although MRI has provided some insight in this. Using perfusion MRI, hypoperfusion was found for the white matter in patients with cSVD (Markus et al., 2000; O'Sullivan et al., 2002). Diffusion weighted imaging studies have provided indications that the loss of microstructural integrity in the white matter may be associated with cSVD (Jones et al., 1999; Chabriat et al., 1999; O'Sullivan et al., 2001). Parallel data of the microvasculature and the parenchyma in the same patient group are lacking. More pathophysiological insights may be obtained by evaluating both structures concurrently and by linking them together.

Intravoxel incoherent motion (IVIM) imaging is a non-invasive MRI technique that proposes to simultaneously measure such microvascular and parenchymal microstructural tissue properties (Le Bihan et al., 1988). In contrast to conventional diffusion weighted techniques, where the microvascular signal confounds the parenchymal signal, it is assumed that IVIM can separate the MRI effects of the

Abbreviations: BMI, body mass index; cSVD, cerebral small vessel disease; DGM, deep grey matter; DW, diffusion weighted; FOV, field of view; FLAIR, fluid attenuated inversion recovery; IVIM, intravoxel incoherent motion imaging; LS, lacunar stroke; mVCI, mild vascular cognitive impairment; NAWM, normal appearing white matter; PVS, perivascular spaces; ROI, region of interest; SNR, signal-to-noise ratio; WMH, white matter hyperintensity.

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microvasculature and parenchyma. Promising results of IVIM in various clinical applications (e.g. oncology (tumor staging) and neuroimaging (management of cerebral infarction)) have been shown (Iima & Le Bihan, 2016). The purpose of the present study was to investigate the applicability of IVIM in cSVD by assessing the microvasculature and parenchymal microstructure.

2. Methods

2.1. Standard protocol approvals, registrations and patient consents

This is a retrospective study and has been approved by the Medical Ethics Committee of Maastricht University Medical Centre. All participants were included after written informed consent was obtained.

2.2. Study population

Between April 2013 and December 2014, 83 patients with clinically manifest cSVD and 40 healthy controls were included. Participants were included from the Maastricht University Medical Centre and Zuyderland Medical Centre, The Netherlands. Clinically manifest cSVD was defined as the occurrence of a recent lacunar stroke or the diagnosis of mild vascular cognitive impairment (mVCI) due to cSVD.

Patients with lacunar stroke (n = 44) had a first-ever acute lacunar syndrome with a compatible recent small subcortical infarct on brain MRI (Wardlaw et al., 2013a). If no such lesion was visible on imaging, established clinical criteria for lacunar syndrome were used (Appendix 1.1) (Bamford et al., 1987). Exclusion criteria for these patients include a potential cardiac embolic source (e.g. atrial fibrillation), or stenosis of ≥50% of one or both internal carotid arteries. Patients were included 3 months after the acute stroke to avoid acute stroke phase changes.

Patients with mVCI (n = 39) had subjective cognitive complaints, failure in one or more cognitive domains determined by neuropsychological assessment, and extensive MRI abnormalities associated with cSVD, i.e. white matter hyperintensities (WMHs) Fazekas score 3 or Fazekas score 2 or 3, and/or with microbleeds, and/or lacunes and no other apparent cause for the cognitive deficits (Gorelick et al., 2011). Furthermore, participants in whom a neurodegenerative disease other than vascular cognitive impairment was suspected (e.g. Alzheimer's disease), with another neurological or psychiatric disease interfering with cognitive testing or with severe cognitive impairment defined as Mini Mental State Examination <20 and/or Clinical Dementia Rating >1, were excluded.

Controls (n = 40) were stroke-free and had back pain or peripheral neuropathies without (subjective) cognitive failures. Controls were matched on age and sex.

All participants with a history of cerebrovascular disease, or other diseases of the central nervous system or with MRI contraindications were excluded. Baseline characteristics were recorded, including age, sex, education (Verhage, 1964), and cardiovascular factors such as hypertension (history of hypertension/antihypertensive medicine (including calcium antagonists)), hypercholesterolemia (history of hypercholesterolemia/statin), diabetes (history of diabetes/diabetes medication), current smoking and body mass index (BMI).

2.3. MRI acquisition

Patients underwent brain imaging on a 3.0 Tesla MR scanner (Achieva TX, Philips Healthcare, Best, the Netherlands) using a 32-element head coil suitable for parallel imaging. For anatomical segmentation a T1-weighted sequence (TR/TI/TE = 8.3/800/3.8 ms; FOV 256 × 256 × 160 mm^3; 1.0 mm^3 isotropic voxel) and a T2-weighted FLAIR sequence (TR/TI/TE = 4800/1650/299 ms; FOV 256 × 256 × 180 mm^3; 1.0 mm isotropic voxel) were performed respectively.

IVIM imaging was conducted as described before (van Bussel et al., 2015). In brief, a Stejskal-Tanner diffusion weighted (DW) spin echo single shot echo planar imaging pulse sequence (TR/TE = 6800/84 ms; FOV 221 × 269 × 139 mm^3; 2.4 mm isotropic voxel; acquisition time 5:13 min) was used. To minimize the signal contamination of CSF, an inversion recovery pulse (TI = 2230 ms) was given prior to the DW sequence (Hales & Clark, 2012). Fifteen DW images were acquired in the anterior-posterior direction using multiple diffusion sensitive *b*-values (0, 5, 7, 10, 15, 20, 30, 40, 50, 60, 100, 200, 400, 700, and 1000 s/mm^2). To increase the signal-to-noise ratio (SNR) (Appendix 1.2) at high *b*-values the number of signal averages for the highest two *b*-values were two and three, instead of one, respectively.

2.4. Image analysis

2.4.1. Brain segmentation

The regions of interest (ROIs) were: the normal appearing white matter (NAWM), WMHs, deep grey matter (DGM) and the cortex. All ROIs were automatically segmented on T1-weighted images (Freesurfer software (Fischl et al., 2002) and FSL (v5.0) (Jenkinson et al., 2002)). The WMHs were automatically segmented (de Boer et al., 2009) on FLAIR images and visually checked under supervision of vascular neurologists, who also identified and excluded infarcts and scored PVS (Appendix 1.3). The WMH load was calculated by normalizing the WMH volume to the intracranial volume.

2.4.2. IVIM analysis

Preprocessing of the IVIM images has been described previously (van Bussel et al., 2015) and consisted of distortion corrections (EPI and eddy current distortions) and head displacements (ExploreDTI v.4.8.3) (Leemans et al., 2009). Hereafter, the images were registered to the corresponding T1-weighted image and spatially smoothed with a 3 mm full-width-at-half-maximum Gaussian kernel. The SNR at b = 1000 s/mm^2 was 45 (Association NEM, 2008) (Appendix 1.2), which is larger than the minimum value (i.e. 30) recommended for accurate IVIM estimation (Wu et al., 2015).

The diffusion-attenuation curve is approximated with a two-compartment diffusion model (Le Bihan et al., 1988):

$$\frac{S(b)}{S_0} = (1-f)e^{-bD} + fe^{-b(D^*+D)} \quad (1)$$

where S_0 is the signal intensity S at *b*-value 0 s/mm^2, $S(b)$ the signal intensity at *b*-value *b*, f the perfusion volume fraction, D the parenchymal diffusivity and D^* the pseudodiffusion coefficient. The IVIM model considers the presence of a vascular and non-vascular compartment. The vascular part embodies the fast water motion in blood flowing into a network of small vessels, which has an architecture with many microvessel orientations. This gives rise to the pseudodiffusion coefficient, hereafter called intravascular diffusivity D^*, and the perfusion volume fraction f. The perfusion related measure $f{\cdot}D^*$ was obtained by taking the product $f{\cdot}D^*$. The non-vascular compartment is described by the water diffusion in the parenchymal microstructure represented by the slower parenchymal diffusivity D. To account for the CSF suppression and differences in relaxation time of blood and tissue, a modified IVIM model (Hales & Clark, 2012) was employed (Appendix 1.4).

Model fitting was performed on a voxel-by-voxel basis using a two-step method (Federau et al., 2014) (Appendix 1.5). This yields the IVIM measures (f, D^*, $f{\cdot}D^*$ and D), which were averaged over each ROI. The analysis accounted for the goodness of fit of the model (Appendix 1.5).

2.5. Statistical analysis

To examine differences between cSVD patients and controls, independent Student's *t*-test and χ^2 test were used where appropriate. The differences in IVIM measures between cSVD patients and controls