Dual temporal resolution DCE-MRI reveals increased blood-brain barrier leakage in cerebral small vessel disease

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Target audience: Neuroscientists interested in perfusion imaging and cerebral small vessel disease.

Purpose: Cerebral small vessel disease (cSVD) has a major impact on society since it is responsible for a quarter of all ischemic strokes and 45% of all dementias. It is considered the underlying cause of lacunar stroke (LS) and vascular cognitive impairment. Furthermore, it can lead to physical, psychiatric and cognitive disabilities. The pathophysiology of cSVD still remains to be elucidated. Blood-brain barrier (BBB) dysfunction with increased permeability is expected to play a crucial role.[1,2] Methods to measure the permeability of the BBB were proposed by several groups[3,4] using dynamic contrast enhanced MRI (DCE-MRI) which yields pharmacokinetic parameters: the transfer constant (K_i) and fractional plasma volume (v_p). However, thus far the temporal resolution was relatively low (~30 s), which complicates the interpretation of permeability and intravascular enhancement. The aim of this study is to investigate quantitative differences in BBB permeability between patients with cSVD and healthy controls by assessing K_i and v_p using dual temporal resolution DCE-MRI. It is hypothesized that the permeability (K_i) will be higher for cSVD patients compared with healthy controls.

Methods: *Subjects and data acquisition:* MR imaging was performed on 53 cSVD patients (age 69±11y) and 32 age-matched healthy controls (age 69±11y) on a 3.0 Tesla MR scanner (Philips Achieva TX). For dynamic imaging dual temporal resolution DCE-MRI was conducted, which enables the assessment of the contrast agent in the microvascular blood space and an accurate quantification of the extravasation through the BBB. Dual temporal resolution DCE-MRI consists of two dynamic sequences with different dynamic scan times (DST), the fast and slow sequence (fig.1). Both sequences are saturation recovery gradient recalled sequences with flip angle of 10° and have a 90° non-selective saturation prepulse with a time delay (TD) of 120 ms. First, the fast sequence was applied during bolus injection (DST 3.2 s, TR/TE = 5.6/2.5 ms, FOV: 256 x 200 mm^2, acquisition matrix: 128 x 100, 10 slices, pixel size of 2 mm and slice thickness 5 mm). This was followed by the slow sequence (DST 30.5 s, TR/TE = 5.6/2.5 ms, FOV: 256 x 256 mm^2, acquisition matrix: 256 x 256, 50 slices, pixel size of 1 mm and slice thickness 2 mm). This resulted in 29 dynamic scans of the fast sequence including 4 pre-contrast scans and 45 dynamic scans of the slow sequence including 3 pre-contrast scans. The sequences overlap in the periventricular region. Gadobutrol was used as contrast agent (dose 0.1 mmol/kg) and injected in the antecubital vein at a rate of 3 ml/s. For conversion of contrast enhanced signal intensity to concentration, T1-mapping was conducted using consecutive scans with increasing TD (120, 300, 600, 1000 and 4000 ms)[3]. A T1-weighted scan and a T2-weighted FLAIR scan were performed for anatomical segmentation.

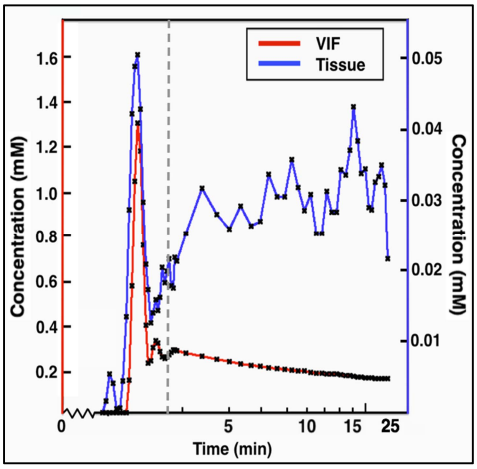

Figure 1. Concentration over time in the inferior sagittal sinus (red) and white matter tissue (blue) in a patient with cSVD. The grey dashed line indicates the transition from the first to the second sequence. The first sequence enables the time-resolved measurement of the contrast agent in the microvascular blood space and the second sequence the extravasation through the BBB. It can be observed that the tissue concentration increases while the blood concentration decreases over time.

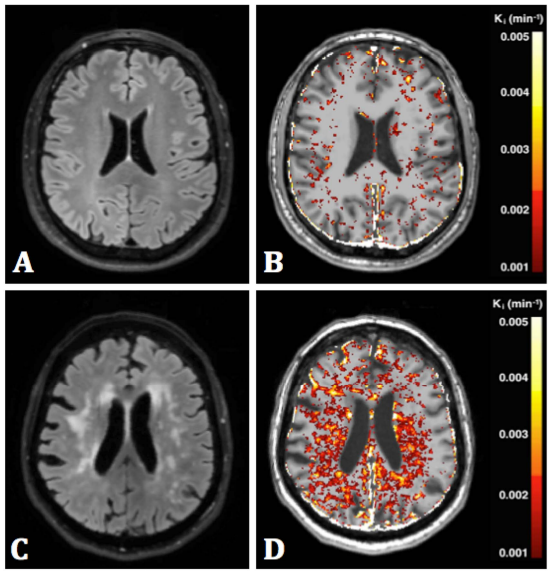

Figure 2. Example of a T2-weighted (FLAIR) image and K_i map superimposed on a T1-weighted image of a healthy control (A,B respectively) and a patient with cSVD (C,D respectively). Here only $K_i > 0.001$ min^{-1} is shown. It can be appreciated that the patient with cSVD shows stronger leakage than the control.

Data analysis: Voxel wise calculation of K_i and v_p was performed by the Patlak plot analysis.[5] The periventricular region was segmented into four regions of interest (ROI): normal appearing white matter (NAWM), deep grey matter (DGM), cortex and white matter hyperintensities (WMH).[6] For each region the 75th percentile of K_i and v_p, denoted as $K_{i,75th}$ and $v_{p,75th}$, was calculated. 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.

Results: Significantly higher $K_{i,75th}$ was found for patients with cSVD ($1.1\pm0.4\times10^{-3}$ min^{-1}, n=53) (mean±SE, n) compared with healthy controls ($1.0\pm0.4\times10^{-3}$ min^{-1}, n=32) in the NAWM (p = 0.049). In DGM a trend can be seen towards higher $K_{i,75th}$ for patients with cSVD ($1.5\pm0.8\times10^{-3}$ min^{-1}, n=53) compared with healthy controls ($1.2\pm0.8\times10^{-3}$ min^{-1}, n=32) (p = 0.065). No significant differences were found for $v_{p,75th}$ or other regions. Patients suffered significantly more from hypercholesterolemia (p = 0.003) compared with controls.

Discussion & Conclusion: Higher $K_{i,75th}$ and a trend towards higher $K_{i,75th}$ were found in patients with cSVD compared with healthy controls in the NAWM and DGM, respectively. Higher $K_{i,75th}$ for the patient group suggests BBB impairment in cSVD (fig.2). Previously, a more qualitative increase of the BBB permeability was shown in the NAWM of patients with LS.[1,2] Our results confirm these findings. Patients with cSVD may therefore be at increased risk for occurrence of lacunar infarcts and white matter hyperintensities. Longitudinal studies can now be initiated to investigate the role of increased BBB permeability in the course of cSVD.

References: **1.** Wardlaw JM *et al.*, Annals of Neurology; 2009;65:194-202 **2.** Wardlaw JM *et al.*, Stroke; 2008;39:1327-32 **3.** Larsson HBW *et al.*, MRM, 2009;62:1270–81. **4.** Taheri S *et al.*, MRM, 2011;65:1036–42 **5.** Patlak CS *et al.*, J Cereb Blood Flow Metab, 1985;5:58 4–590. **6.** De Boer R *et al.*, Neuroimage, 2009;45(4):1151–61