

Increased Blood-Brain Barrier Leakage in Alzheimer's Disease Detected with Dual Time-Resolution Dynamic Contrast Enhanced MRI

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Target audience. Neuroscientists, neuroradiologists, physicists

Purpose. Blood-brain barrier (BBB) disruption is a potential underlying mechanism for dementia¹. Dynamic Contrast Enhanced (DCE)-MRI in combination with pharmacokinetic modeling can be used to detect BBB defects by measuring the leakage rate of contrast media². To investigate the distribution of contrast medium in the brain, a dual-temporal resolution DCE-MRI protocol was applied. Our aim was to detect differences in terms of leakage (K_l) and fractional plasma volume (v_p) in brains of patients suffering from dementia due to Alzheimer's Disease (AD) compared to healthy controls.

Methods. *Acquisition:* The dual-temporal resolution protocol consisted of two integrated DCE-MRI sequences (3T Achieva TX, Philips). A saturation recovery gradient recalled sequence (TR/TE 5.2/2.5 ms, 25.6x20x5 cm³ FOV, 128x100x10 voxels, Dynamic Scan Time (DST) 3.2 s) with a 90° nonselective saturation prepulse given at a delay time (TD, 120 ms) was used during bolus injection for 1.5 minutes. This resulted in 29 volumes including 4 precontrast scans. Immediately afterwards a different saturation recovery gradient recalled sequence (TR/TE 5.6/2.5 ms, 25.6x25.6x10 cm³ FOV, 256x256x50 voxels, DST 30.5 s) with the same saturation prepulse was used for 25 minutes, resulting in 45 volumes with 3 precontrast scans. The two scans spatially overlapped at the periventricular region. The contrast agent, gadobutrol, was injected intravenously (dose 0.1 mmol/kg, injection rate 3 ml/s) using a power injector. T2w-FLAIR scans were used to detect abnormal appearing white matter (AAWM). T1 weighted structural scans served for segmentation the brain into white matter, Gray Matter (GM) and CSF³. For the translation of contrast-enhanced signal changes to concentration curves, a scan series with different TD settings (120-4000 ms) was used to determine pre-contrast T1 maps².

Subjects: 13 patients with mild cognitive impairment (n = 9) and AD (n = 4) were included; mean age 74.9±8.3 Y (mean±sd), Mini Mental Status Examination (MMSE) score 26.7±1.6, Fazekas 2.0±0.9, AAWM volume 14.3±15.1 cm³. 14 healthy controls were included; mean age 75.8±6.6 Y, MMSE 29.7±0.5, Fazekas 1.2±0.9, AAWM volume 4.3±6.0 cm³.

Analysis: White matter was segmented into AAWM and NAWM using the FLAIR scans⁴. A vascular input function (VIF) was obtained from the sagittal sinus. The Patlak plot analysis was used to calculate K_l and v_p in each voxel⁵. Histogram analysis of K_l and v_p at bin level was applied to compare patients with controls. Significance was inferred from Student's t-tests when p<0.05.

Results. Example time curves are given in fig. 1. In the K_l range 0.8 - 1.3 x 10⁻³ min⁻¹ patients exhibited significantly stronger leakage than controls in NAWM (fig. 2) but not in GM. Similar analysis showed no difference in v_p distribution throughout the NAWM or GM. The mean K_l or v_p did not differ between the groups in NAWM or GM and was not correlated with AAWM volume. This was also evident in the K_l maps, which revealed rather spatially diffuse patterns of higher leakage which did not systematically colocalize with AAWM.

Conclusion/Discussion. The results suggest significantly stronger leakage in NAWM in the patients compared to the healthy controls, which confirms our hypothesis that BBB leakage is increased in patients with (preclinical) Alzheimer's dementia. Longitudinal research is necessary to reveal the exact relationship with Alzheimer pathology and small vessel disease.

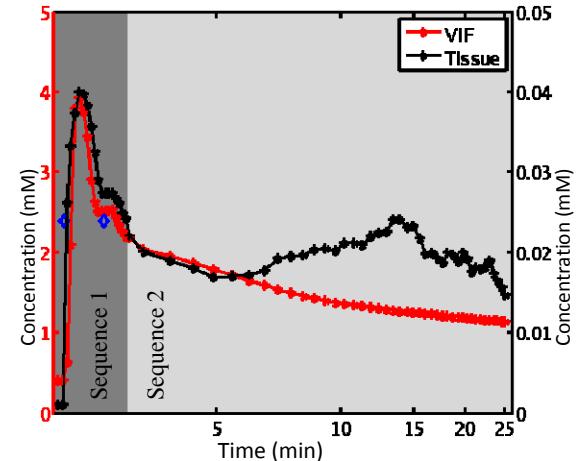


Figure 1: An example of the concentration over time in blood (red) and tissue (black) in one patient. DCE-MRI sequence 1, which has a higher temporal resolution, is used during bolus arrival (dark gray), while sequence 2, which has a higher spatial resolution, is used during contrast agent dispersal throughout the brain and body (light gray). While the v_p in tissue is most accurately determined from the first bolus arrival, leakage (K_l) is more accurately calculated from the longer period when contrast agent concentration accumulates into the tissue. The blue data points show the VIF which would have been measured when only sequence 2 was used, which illustrates the need for a dual-temporal resolution DCE-MRI sequence.

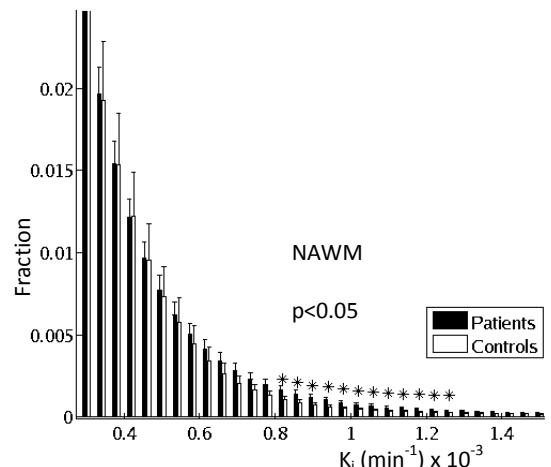


Figure 2: Normalized distribution of K_l in NAWM in patients versus controls. The error bars represent the standard error of the mean.

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