Assessment of BBB damage in patients with VCI using MRI

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Introduction

Accurate quantification of Blood Brain Barrier (BBB) permeability is of importance in order to assess the degree of BBB damage in neurological disorders. *In vivo* quantification of BBB defects is important in predicting and measuring the response of BBB to therapy, especially in inflammatory disorders such as stroke. In the past decade, research has been conducted to quantify the disruption of BBB and to extract *in vivo* information about the BBB response to therapy in animal models by non-invasive measurement techniques, such as PET and MRI. Existing *in vivo* methods rely on the evaluation of Time Activity (TA) of a marker in both tissue and plasma compartments assuming that BBB controls the passage of marker to the tissue compartment. Recently, an MRI technique was proposed to quantify BBB permeability by multiple time graphical analysis method based on unidirectional tracer kinetics in one compartment [1]. This technique was successfully adapted in our MRI laboratory for investigating and evaluating the efficacy of BBB blocking drugs in a rat stroke model. In this study, the MRI based graphical technique has been used to quantify BBB damage in human subjects with VCI. Patients with VCI typically have a history of hypertension (HTN) and/or diabetes mellitus (DM) characterized by microangiopathy due to occlusive disease of small penetrating cerebral arteries and arterioles [1]. Additionally, the disease process involving the medullary vessels of the WM caused by HTN or DM has been proposed to damage the blood brain barrier (BBB), leading to VCI.Thus, aim of this study was to translate a MRI based BBB quantification technique that was developed and tested on animal models to human subjects for quantification of BBB disruption in patients with VCI.

Material and Method

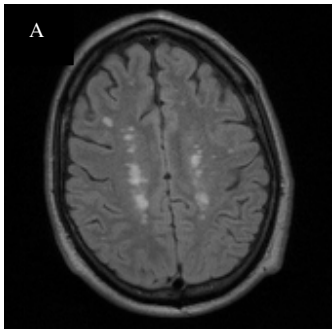
The study was approved by the local Human Research Review Committee and Institutional Review Board. In this study, 5 patients with VaD (age range 69-85, 5 males) were imaged on a 1.5T Siemens whole body scanner retrofitted with Sonata gradients (Malvern, PA, USA). After acquiring the localizer and structural scans consisting of FLAIR, T1 and T2w images, permeability study protocol was implemented as part of the MRI protocol using the following parameters, T1 acquisition with Partial Inversion Recovery (TAPIR) [2] sequence-a fast T1 mapping technique, axial plane, TR/TE 13.0/2.0ms, flip angle 25º, matrix size 128 x 128, Slice thickness 5 mm, # slices 6, FOV 220mm x 220mm, acquisition time 3m 14s. All the slices were prescribed superior to the ventricles since the goal of the study was to study BBB damage in WM lesions. In this acquisition, a reference baseline aquistion using the fast T1 mapping protocol was obtained before injecting the contrast agent. 0.025 mM/kg of Gd-DTPA was injected intravenously via the indwelling catheter at the rate of 5ml/second using a power injector about 10 seconds after the start of the imaging protocol (to allow acquisition of the baseline dataset). This was followed by imaging with the fast T1 mapping protocol for a total time of ~ 23 minutes resulting in a total of 7 times points. Due to technical reasons and MR protocol restrictions, a non-conventional lower dose of Gd-DTPA was elected for this study. The acquired data set was transferred to a dedicated computer workstation for further processing. Postprocessing of the raw data involved applying kalman filter to the raw data, generation of T1-maps and recontruction of slice per slice permeability maps. All the data processing was performed using in-house software written in 64-bit MATLAB (Mathworks, Natick, MA). Additional post processign steps included motion correction of raw MR images, thresholding of permeability maps to remove background noise and creating mask of white matter lesion areas from anatomical images and overlaying on the permeability maps to accurately identify location of lesions. Permeability coefficient estimates were obtained from color permeability coeffcient maps by drawing ROI with guidance from structural scans. Data was read into spreadsheet for further analysis.

Results and Discussion

On the structural FLAIR images, white matter lesions are seen as hyperintense regions in the white matter. The corresponding color coded permeability map shows some of the matching white matter areas as regions with high permeability. It is interesting to note that not all white matter lesions were identified as areas with high permeability. The regions with high permeability (> 1 x 10^{-3} ml/g-min) correspond to regions with BBB breakdown in patients with VCI. The mean permeability coefficient in the white matter lesions was 2.1 ± 0.06 x 10^{-3} ml/g-min (mean ± SD). The mean permeability coeffcient for normal white matter was 0-1 x 10^{-3} ml/g-min. An observation made from the permeability maps was that the regions of high permeability in the lesions were localised to the center of the lesion rather than the edges suggesting that lesion center is the most likely site for active BBB damage. The significance of this finding is that it could serve as a differentiaing feature between white matter lesions seen in other neurological disoders such as multiple sclerosis.

References

[1] Ewing, et al, MRM 2003. 50:283. [2] Steinhoff S, et al. MRM 2001. 46:131-140.



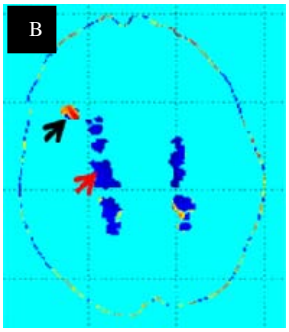


Figure A is a FLAIR image showing regions of high signal intensty in white matter. These hyperintense regions are the lesions seen in patients with VCI. It is proposed that chronic hypoperfusion induced hypoxia due to reduced blood flow to regions of white matter, is the underlying mechanism for the lesions. Additionally, it is postulated that there is increased BBB permeability in these white matter lesions, probably resulting from hypoxic damage. Fig. B shows a color-coded permability coefficient map for the slice matching the FLAIR image. In the permeability coefficient maps reconstructed using MRI data, pixel signal intensity values are proportional to permeability coefficient values. Pixels with high and low signal intensity correspond to pixels with high (black arrow-top) and low (blue arrow-bottom) permeability coefficient values respectively.