MRI assessment of the blood-to-brain transfer constant estimates for Gd-DTPA in ischemic brain tissue: validation of MRI methods by comparison to quantitative autoradiograpic estimates

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INTRODUCTION: Pathological changes in brain tissue during and after stroke can often involve injury to the blood-brain barrier (BBB). In this study, changes in BBB permeability in ischemic tissue were monitored and quantitatively assessed in a rat model of transient focal ischemia that produces BBB injury acutely and hemorrhagic transformation at 24 hours. Changes in the blood-to-brain transfer constant (K_i) were measured by both magnetic resonance imaging (MRI) and quantitative autoradiographic (QAR) methods using identical non-labeled and radiolabeled versions of gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) preparations, respectively. Post-reperfusion BBB changes between MRI and QAR methods were highly correlated in areas with BBB disruption.

METHODS: Transient ischemia was induced in male Wistar rats (n=5) by intraluminal suture occlusion of the middle cerebral artery and withdrawal of the occluding filament after 3 hrs. All MRI studies were performed at 7 Tesla. Quantitative MRI assessment of the ischemia induced BBB permeability changes was performed approximately 2 hrs after reperfusion using a Look-Locker based T_1–weighted imaging sequence to generate estimates of K_i via the Patlak plot methodology[1]. MRI localization of areas with BBB opening was performed by tracking contrast enhancement changes produced by Gd-DTPA administration using a Look-Locker T_1 sequence. The Gd-DTPA injection was delivered using a stepped down continuous i.v. infusion protocol that maintained a relatively constant plasma Gd-DTPA concentration for approximately 20 minutes. After completion of MRI studies, the rats were infused with ^{14}C-labeled Gd-DTPA using the same continuous infusion procedure, and then sacrificed for QAR estimates of K_i. Both versions of the Gd-DTPA preparation were homemade and identically prepared. Tissue sections were prepared for QAR to provide quantitative estimates of the blood-to-brain transfer constant (K_i-QAR) and for confirmation of BBB disruption. The ischemic area regions of interest (ROIs) with BBB opening were segmented from normal tissue using the iterative self organizing data analysis (ISODATA) segmentation algorithm[2] in conjunction with the serially acquired Look-Locker T_1 maps. The MRI defined ROIs were superimposed onto the ^{14}C-labeled Gd-DTPA autoradiograms for validation of leakage areas and measurements of BBB permeability. A scatterplot of the MRI versus QAR estimates of K_i for the non-labeled and radiolabeled Gd-DTPA preparations is shown in the Figure.

RESULTS: Acute BBB disruption was detected in the preoptic area (PO) and/or striatumin all rats (6 areas in 5 rats) by Gd-DTPA enhanced MRI and corresponded closely with areas identified by ^{14}C-Gd-DTPA QAR. Estimates of K_i by both MRI and QAR methods were significantly elevated after reperfusion as compared to brain regions with intact BBB function and showed relatively good agreement between methods. The MRI based K_i estimates for ROIs with an injured BBB are shown plotted as a function of Ki-QAR values (see Figure). The results indicate a high degree of correlation between MRI and QAR methods with a R^2 value of 0.926 and a p-value of 0.002.

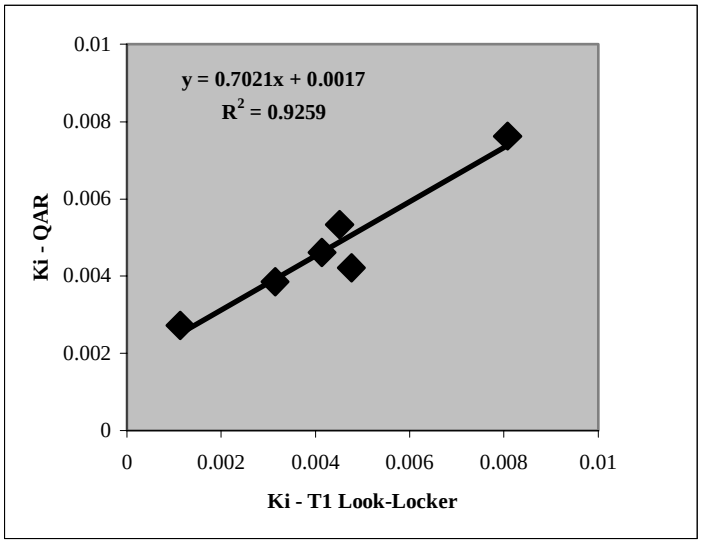

Figure: Scatterplot plot of K_i estimates as measured by MRI using T_1 estimates plotted as a function of K_i estimates as measured by QAR.

CONCLUSION: Estimates of the blood-to-brain transfer constants for identical non-labeled and radiolabeled versions of the Gd-DTPA tracer compounds using a stepped down continuous infusion schedule for both MRI and QAR methods during reperfusion provides a one-to-one validation of the Patlak methodology for estimating BBB permeability in reperfused ischemic infarct. With further substantiation, this approach may have potential application in the clinical setting for assessing acute BBB injury that may precede later hemorrhagic transformation.

References:

1. Ewing et al. Magn Reson Med (2003);50: 283-292.
2. Bezdek, J. IEEE (1980);2:1-8.