Quantitative Magnetic-Resonance Pharmacodynamic Analysis of Transcranial Focused-Ultrasound Induced Blood-Brain Barrier Disruption in Small Animal

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Purpose/Introduction: Focused ultrasound under a suitable frequency selection has been confirmed to be able to transcranially induce blood-brain barrier (BBB) disruption and deliver therapeutic agents into the brain. The induced BBB-disrupted duration has reported to be limited, however dynamic change of the permeated small molecules into brain parenchyma through has not yet been fully disclosed. The purpose of this study is to use magnetic-resonance relaxivity technology to perform quantitative PK/PD analysis of small molecule.

Subjects and Methods: Six Sprague-Dawley rats under isofluorane anesthesia were sonicated with left hemispheres by using a 400-kHz focused ultrasound (peak pressure = 0.4MPa, burst length = 10 ms, PRF = 1 Hz, duration = 90s) in the presence of microbubbles (Sonovue, Bracco; 0.025 mL/kg IV injection). Animals were post-operationally monitored by using a 7.0-T MR imager (ClinScan 70/30 USR, Bruker). Two T1-weighted with different flip angles were acquired to calculate spin-lattice relaxivity maps by transferring two images with different flip angles (gradient-recall-echo sequence, TR/ TE = 2.3 ms/0.76 ms, slide thickness = 0.8 mm; matrix = 132×192, flip angle = 5°/20°).Animals were injected Evans blue dye immediately after sonication and Gd-DTPA before MR scanning and were sacrificed about 6 hr after sonication, the concentration of dye extracted from each brain sections were determined by spectrophotometry, and the correlation between permeated Evans blue dye and the Gd-DTPA were analyzed. Area-under-receiver operative characteristic curve (AUC) map were then transferred from a series of time-dependent R1 maps (up to 60 min.) to perform PD characteristic of Gd-DTPA in order to reflect Evans blue permeate dynamics.

Results/Discussion: A series of R1 maps obtained at different time point after FUS-BBB disruption shows dynamical change of the Gd-DTPA accumulation in the brain, and particularly have high leakage at the sonication site (Fig. 1). The accumulated distribution of the Gd-DTPA (i.e., AUC) highly matches with the distribution of the Evans blue observed when animal was sacrificed. The analyzed accumulated R1 relaxivity provide high correlation with the Evans blue (r^2 = 0.8042), implies that the R1-based pharmacodynamic analysis provide reasonable mapping to the permeability of the Evans blue into the BBB-disrupted region (Fig. 2). The accumulated Gd-DTPA in the experimental and control sites were quantified to be 385.9 and 172.3 μM (about 224% increase) (Fig. 3), implies that a total 1.83 μM of Evans blue were gained into the BBB-disrupted region.

Conclusion: This study provides an improved quantitative MR protocol for analyze pharmacodynamic behavior of the therapeutic molecule leakage when using focused ultrasound to induce BBB disruption for future brain drug delivery.

Reference:

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Keywords: Focused ultrasound, blood-brain barrier, pharmacodynamic analysis

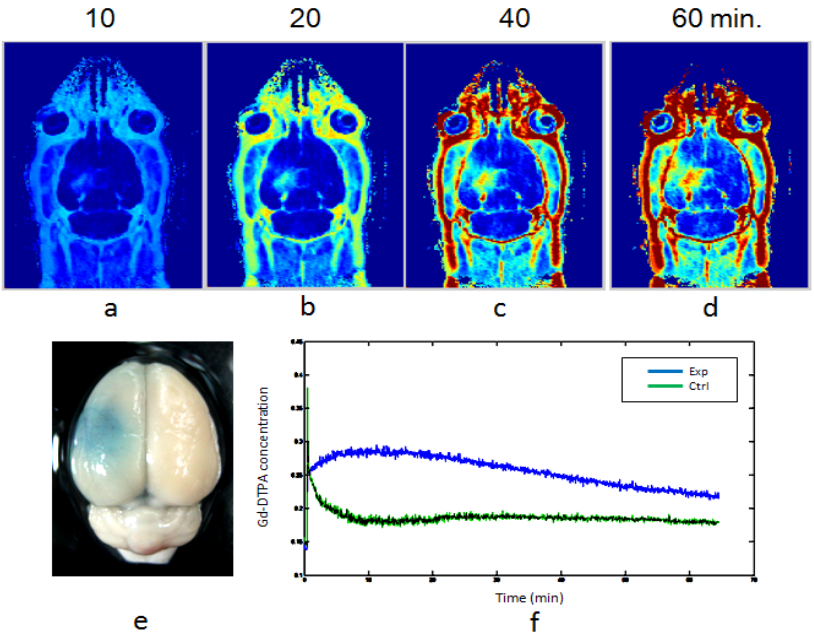

Fig.1 Series of AUC maps & GD curve
(a) AUC map (10min) (b) AUC map (20min) (c) AUC map(40min);
(d) AUC map (60min) (e) Brain tissue (f) Gd-DTPA concentration curve

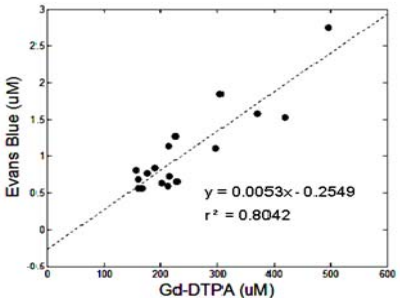

Fig. 2 Correlation between GD & EB

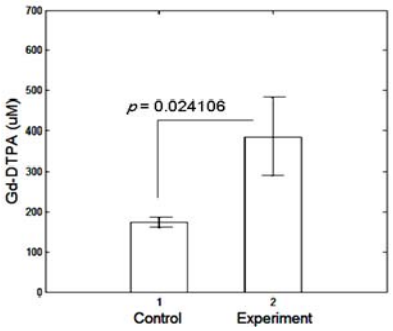

Fig. 3 GD concentration (uM)