Transient Permeability/ Perfusion Change during Microbubble-Facilitated Focused Ultrasound Blood-Brain Barrier Opening: A Small-Animal Observation

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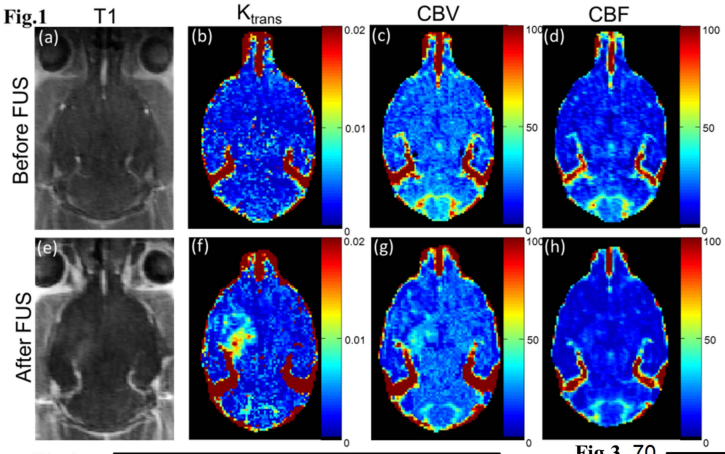
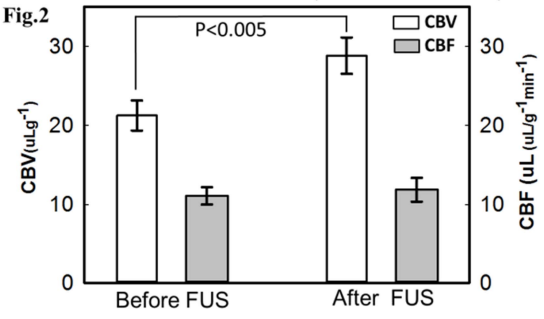
Target Audience: The research involves MR-Guided Focus Ultrasound and perfusion in brain.

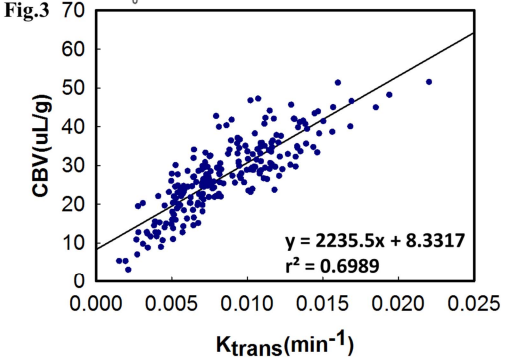
Introduction: Focused ultrasound (FUS) with the presence of microbubbles can temporarily open the blood-brain barrier (BBB) and open up new windows for noninvasive and targeted CNS drug delivery. During BBB disruption, vessels can be characterized to have distinct permeability change types [1]. Dynamic contrast-enhanced MRI (DCE-MRI) has been employed to provide evaluation to identify BBB-opened region, and blood-brain permeability can be estimated. However, no reports so far elicit whether FUS-BBB opening would cause corresponding cerebral blood flow or volume change. The purpose of this study is to evaluate perfusion change caused by FUS-BBB opening, and evaluate the correlation with the permeability change.

Material and method: Six Sprague-Dawley Rats of either age (300±25g) were used in this study. Before FUS exposure, DCE MRI was performed first for baseline of perfusion and permeability values. Each Rat underwent anesthesia (isoflurane) and moved to MR bore and perform scanning (7T, ClinScan 70/30 USR, Bruker), with an immediate bolus administration of gadolinium-DTPA (Agnevist, Bayer Healthcare, 0.5 ml/kg). After the first DCE MRI (3D FLASH T1-weighted sequence, TE/TR = 0.76 ms/ 2.31 ms; slice thickness = 0.8 mm; flip angles = $5^0/20^0$; matrix size:192×132) scan finished, animal underwent microbubble administration (Sonovue, Bracco; 0.025 mL/kg IV injection) with the following burst-tone FUS exposure (400 kHz, diameter /curvature radius = 60/80 mm; peak pressure = 0.4MPa, burst length = 10 ms, PRF = 1 Hz, duration = 90s). After FUS exposure, a second DCE MRI was acquired. Permeability information was obtained based on data post analysis using the Extended-Kety model [2] to generate K_{trans} (represents vessel permeability change) and V_e (represents extravascular-extracellular space change). For perfusion calculation, first pass analysis was considered in concentration curve before contrast recirculation. CBV was calculated by finding the area under the measured concentration curve Ct(t) and normalizing it to the integrated Ca(t) (Arterial Input Function) and density of the brain tissue. [3] Due to FUS-BBB opening, there is an overestimation of CBV in the regions where contrast leaks into EES. CBV was corrected to eliminate fractional leakage space volume (V_e) term. [4] In CBF calculation, tissue concentration Ct(t) is represented in term of the convolution of Ca (t) and R(t) using the equation: $Ct(t) = \rho \cdot H \cdot CBF(Ca(t) \otimes R(t))$, [3] where $\otimes$ representing the convolution, R(t) is the residue function, H is hematocrit, ρ is brain tissue density. De-convolution of Ct(t) with Ca(t) results in CBF (R(0)=1). ROIs of permeability / perfusion map obtained from before and after experimental brains were selected for statistical analysis.

Result: A typical image of T1/K_{trans}/CBV/CBF distribution before and after FUS-BBB opening was demonstrated (Fig. 1a-1h). FUS-BBB opening induces a local K_{trans} increase. The BBB-opening both induce apparent K_{trans} change and CBV change, which implies that both vessel permeability and volume were altered simultaneously. The mean K_{trans} and V_e values at the target ROI after sonication were 8.9×10^{-3}/9.2×10^{-2}. In Fig.2, the mean CBV value of at the target ROI at before / after sonication were 21.65/ 29.36 (uL/g^{-1}), showing an increase about 36%. On the other hand, no apparent change of CBF was found. The mean CBF value of at the target ROI were 10.34/ 11.98/(uL /g^{-1} min^{-1}) and increase less than 1.5%. Correlation between K_{trans} and CBV change after FUS exposure was performed, and pixel by pixel comparison in BBB-opening site was showed in Fig.3.







Discussion: The BBB-opening both induce apparent K_{trans} change and CBV change, which implies that both vessel permeability and volume were altered simultaneously. Furthermore, CBV increase ratio is much higher than CBF that implies the CBV change is more significant than CBF change when BBB-opening was induced by FUS. A good correlation (r^2=0.7) was observed between K_{trans} and CBV, which implies vessel permeability and volume increase after sonication are highly dependence.

Conclusion: FUS exposure to open the BBB can be observed from MRI permeability and perfusion analysis. The permeability increase after BBB opening highly correlates with the cerebral blood volume increase, and independent of the cerebral blood flow. This information provides useful insights in understanding the pharmacodynamic behavior when intending to apply this approach to deliver drugs into the brain.

Reference: **1.**Eunice E Cho et al. Two-photon fluorescence microscopy study of cerebrovascular dynamics in ultrasound-induced blood–brain barrier opening. J Cerebral Blood Flow & Metabolism 2011;31: p1852-1862. **2.** Toft PS et al. Estimating Kinetic Parameters From Dynamic Contrast-Enhanced T1-Weighted MRI of a Diffusible Tracer: Standardized Quantities and Symbols. J MRI 1999, 10:223–232. **3**. Ostergaard L et al. High resolution measurement of cerebral blood flow using intravascular tracer bolus pass- ages. PartI: Mathematical approach and statistical analysis. MRM.1996; 36: 715-725. **4.** Anup Singh et al. Quantification of Physio-logical and Hemodynamic Indices Using T1 Dynamic Contrast-Enhanced MRI in Intracranial Mass Lesions. J MRI 2007;26:871–880.

Fig.1. (a-d) T1/K_{trans}/CBV/CBF maps before FUS (e-h) after FUS.
Fig.2. Mean value of CBV/CBF before and after FUS at BBB disruption site
Fig.3. Correlation between K_{trans} and CBV