DCE-MRI Permeability Analysis in Focused Ultrasound-induced Blood–Brain Barrier Opening: the Association with Mechanical Index

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Target Audience: The research involves MR-Guided Focus Ultrasound and kinetics of blood brain barrier permeability modulation and CNS drug delivery.

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. From previous studies, the mechanical index (MI, peak pressure amplitude divided by square root of frequency) has been reported to be able to serve as key index in evaluating the degree of FUS-induced BBB opening with dimensionless in frequency [1]. Since previously we have proposed that FUS-induced BBB opening kinetics can be evaluated via dynamic contrast-enhanced MRI (DCE-MRI) [2], the purpose of this study is therefore to evaluate the correlation between MI (dimensionless in frequency) with the kinetic change during FUS-BBB opening via DCE-MRI.

Material and method: Twenty-four Sprague-Dawley Rats of either age (300±25g) were used in this study; all rats were separated into four groups. Each Rat was under isoflurane anesthesia first. Two focused ultrasound transducers with different frequency (one is 0.4 MHz, diameter/curvature radius = 60/80 mm, another is 1 MHz, diameter/curvature radius = 25/20 mm) were used to transcranially sonicate one hemisphere of rat. Burst-tone mode ultrasound was delivered in four groups at 4 different acoustic pressures by 2 different mechanical indexes (1st group: FUS=0.4 MHz, peak pressure= 0.5 MPa, MI=0.8; 2nd group: FUS=0.4 MHz, peak pressure= 0.82 MPa, MI=1.3; 3rd group: FUS=1 MHz, peak pressure= 0.8 MPa, MI=0.8; 4th group: FUS=1 MHz, peak pressure= 1.3 MPa, MI=1.3; burst length = 10 ms, PRF = 1 Hz, duration = 90s) in the presence of ultrasound microbubbles (Sonovue, Bracco; 0.1 mL/kg IV injection). After sonication, rats were immediately moved to MR bore and conducted post-operational MRI scan (7T, ClinScan 70/30 USR, Bruker) for 10 mins with bolus injection of gadolinium-based MR contrast agent from tail vein (OMNISCAN™ (gadodiamide) , GE Healthcare, 0.3ml/kg). DCE T1-weighted imaging (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) was performed to evaluate the permeability of the opened BBB. Permeability information were obtained based on data post analysis using the Extended-Kety model [3] to generate permeability information including the K_{trans} (represents vessel permeability change) and V_e (represents extravascular-extracellular space change) map. ROIs of K_{trans} and V_e maps obtained from experimental and contralateral brains were selected for statistical analysis.

Result: A representative images of K_{trans} and V_e distributions after FUS-BBB opening was demonstrated (Fig.1). Both 0.4 and 1 MHz FUS exposures induced targeted BBB opening with local K_{trans} and V_e increase. It was noted that BBB-opened dimension was larger in 0.4 MHz exposure than 1 MHz both at low and high MI exposure. In Fig.2, K_{trans} at the exposure site at MI = 0.8 were 0.0089/ 0.0087 min^{-1} at frequency of 0.4/ 1 MHz exposure; in contrast, K_{trans} at MI=1.3 exposure were 0.0137/ 0.0131 min^{-1} at 0.4/ 1 MHz exposure. In Fig.3, it shows that the mean V_e in MI= 0.8 were 0.0687/ 0.0612 at 0.4/1 MHz exposure, and increased to 0.0982/ 0.0904 at MI = 1.3 at 0.4/ 1 MHz exposure. In summary, K_{trans} /V_e was increased 790% /760% in low and 1270%/1230% in high MI exposure when compare to unexposure site , but difference of K_{trans} /V_e between 0.4 and 1 MHz exposure was less than 5% and 13% at the same MI value (without statistical difference). Statistical analysis showed no significant difference between 0.4 and 1 MHz exposure ($p > 0.005$ in both K_{trans} and V_e measurement). This implies that there was MI when dimensionless of frequency provides good indication in FUS-BBB opening scale and kinetic change.

Discussion: The permeability of BBB opening region was higher in large MI value than in low MI value, but there was no significant difference at both exposure frequencies at the same MI value. This implied that BBB-opened degree was directly dependent with MI rather than exposure frequency. In addition, increased K_{trans} and V_e distribution dimension was larger in low frequency exposure than in high frequency one, which implied the BBB opening dimension under the given MI would be altered by exposure frequency.

Conclusion: This study demonstrated that FUS-BBB opening with different frequency can be observed via DCE-MRI analysis. The degree of BBB permeability and kinetic change directly correlates with MI and can be dimensionless of exposure frequency, whereas the BBB opened dimension directly correlates with the focal dimension predetermined by exposure frequency. This information provides useful insights toward the selection of exposure level and frequency when intending to apply this approach to deliver drugs into the CNS.

Reference: **1**. N. McDannold, et al. Blood brain barrier disruption induced by focused ultrasound and circulating preformed microbubbles appears to be characterized by the mechanical index. Ultrasound Med. Biol. 2008, 34; 834–840. **2**. W.Y. Chai et al. Magnetic resonance image for kinetic analysis ofpermeability changes during focused ultrasound induced blood brain barrier opening and brain drugdelivery. JCR, 2014, 192; 1-9. **3**. 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.

Fig.1

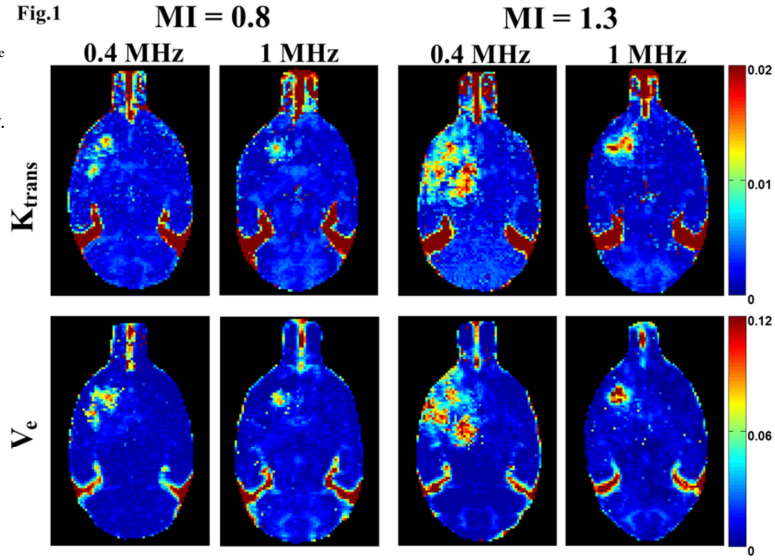

Fig.1 K_{trans}, V_e maps with different MI and frequency.

Fig.2

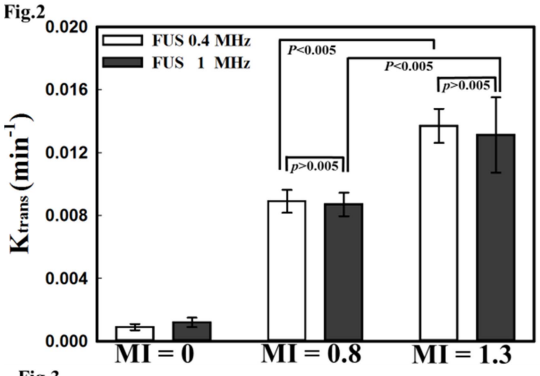

Fig.2 Mean value of K_{trans} with different MI and frequency.

Fig.3

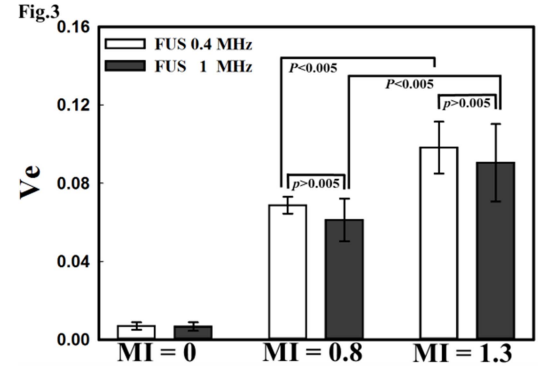

Fig.3 Mean value of V_e with different MI and frequency.