Magnetic-Resonance Analysis of Dynamic Permeability Change in Focused-Ultrasound Induced Blood-Brain Barrier Disruption in Small Animals

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Introduction

Microbubble-enhanced burst-mode focused ultrasound (FUS) has been reported to be able to transiently and locally disrupt the blood-brain barrier (BBB), which opens a wide spectrum of opportunity for delivering therapeutic agent into the brain [1]. Magnetic resonance imaging has been recognized to serve as a post-operational evaluation tools for evaluate BBB disruption, such as the use of dynamic contrast-enhanced MRI (DCE-MRI) to identify BBB-disrupted region. Besides of DCE-MRI, MR perfusion/permeability analysis may also provide valuable information to explore the pharmacokinetics/pharmacodynamics (PK/PD) of the delivered drugs of this approach. This may be particularly essential when FUS-induced BBB disruption only sustained for a limited duration (usually a few hours) and the permeability during this period is highly dynamic. The purpose of this study is to evaluate perfusion/permeability change in the FUS-induced BBB disruption process.

Material and method

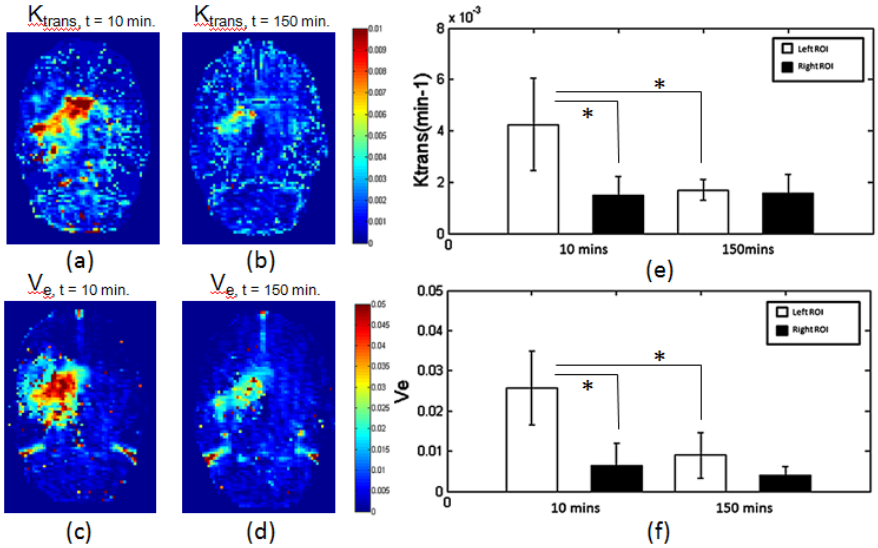
Six Sprague-Dawley Rats of either age (300±25g) were used in this study. Each Rat was under isoflurane anesthesia first. A spherically focused ultrasound transducer (400 kHz, diameter/curvature radius = 60/80 mm) was used to transcranially sonicate one hemisphere of rat (peak pressure = 0.4MPa, burst length = 10 ms, PRF = 1 Hz, duration = 90s) in the presence of microbubbles (Sonovue, Bracco; 0.025 mL/kg IV injection). After sonication, animals were immediately moved to MR bore and conducted post-operational MRI scan (7T, ClinScan 70/30 USR, Bruker) for 10 mins. immediately with bolus injection of gadolinium-based MR contrast agent from tail vein (Agnevist, Bayer Healthcare, 0.5ml/kg). Two Dynamic susceptibility-contrast (DSC)-MRI were acquired at 10/150 mins. after BBB-disruption (3D FLASH T1-weighted sequence, TE/TR = 0.76 ms/ 2.31 ms; slice thickness = 0.8 mm; flip angles = 5°/20°; matrix size:192×132). Perfusion/permeability information were obtained based on data post analysis using the Extended-Kety model [2] 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 statistic analysis.

Result/ Discussion

A representative images sets showing the K_{trans}/ V_e distribution was demonstrated (Fig. 1a-1d).The dynamic change of K_{trans}/ V_e can be demonstrated when comparing K_{trans}/ V_e maps acquired at 10 and 150 min. Both K_{trans} and V_e presents a local enhancement at the BBB-disrupted site when compared to the right hemisphere, implies that both vessel permeability and extravascular-extracellular space were altered. Distribution of local K_{trans}/ V_e differed, also implies that the local vessel permeability and extravascular-extracellular space change were heterogeneous and independent, and may depend on the vessel/ extravascular space volume fraction difference. When observing at 150 min. after FUS sonicaiton, both K_{trans}/ V_e change at the BBB-disrupted region dropped apparently. The mean K_{trans} values at the target ROI at 10/150 mins. were 4.2×10^{-3} /1.7×10^{-3} , showing a decrease about 60%; the mean V_e value of at the target ROI were 2.58×10^{-2} /0.9×10^{-2} and was also decrease 64%. This implies the local permeability change induced from FUS-induced BBB-disruption were highly dynamic.

Conclusion

Our results provide evidence that FUS-induced BBB disruption induce dynamic perfusion/ permeability increase within a limited time period (> 60% within 150 min). This information also provides useful insights that an optimal drug-delivering procedure should be design to meet the limited high-permeability change window in the focused-ultrasound induced brain drug delivery.



Reference:[1] H-L Liu et al. Radiology, Vol. 255, No. 2, pp. 415-425, 2010. [2]Toft PS et al. J Magn Reson Ima 1999.

Fig. 1. (a-d) K_{trans}/ V_e maps obtained at 10/ 150 mins. after FUS-BBB disruption; (e, f) Comparison of the K_{trans}/ V_e value obtained from experimental (white) and contralateral control (black) brain . Two time points at 10/ 150 mins. were shown; "*" represents $p < 0.05$ in students *t*-test.