Passive cavitation detection-based feedback control for ultrasound-mediated blood-brain barrier opening in non-human primates

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Background, Motivation and Objective

Noninvasive focused ultrasound (FUS) combined with microbubbles has been proven capable of locally and reversibly increasing the blood-brain barrier (BBB) permeability allowing the extravasation of several clinical relevant substances (Hynynen et al. 2001). Despite its progress, neuro-inflammatory responses (Kovacs et al. 2016) and the high variability of the FUS transmission in the brain due to skull heterogeneity make the control of the acoustic parameters challenging. Based on that, real time microbubble activity monitoring has been employed to ensure efficacy and safety. However, further pre-clinical investigations using large animals are necessary for obtaining reliable acoustic parameters control to avoid harmful bio-effects. In this study, we developed a high-field magnetic resonance (MR) guided FUS system with passive cavitation detection (PCD) feedback control for exploring BBB opening in non-human primates (NHP).

Statement of Contribution/Methods

The animals (n= 4; 7 sessions) had the head shaved and were positioned in a 2D stereotaxic frame in sphinx position inside a 7-T Agilent MR imaging system. The FUS transducer was fixed in the stereotaxic frame and coupled to the animal's head with an expandable balloon filled with degassed water. A 14-element annular array transducer was driven at 500 kHz during 2 min with pulse length of 10 ms and pulse repetition frequency of 5 Hz. The PCD was performed by a planar mono-element 1.5 MHz transducer positioned at the center of the FUS transducer. A bolus of gadolinium (Gd) (MRI contrast agent) and microbubbles was injected intravenously before sonications. PCD baseline acquisitions were performed before injections.

Results/Discussion

The targeting and acoustic coupling quality (optimal with no bubbles trapped in the gel/balloon) were confirmed using T_2-w (weighted) MR images. Contrast enhanced T_1-w dynamic MR images after contrast agent injection confirmed the BBB opening and measured its uptake kinetics. T_2- and T_2*-w MR images acquired after sonication revealed potential hemorrhages. Safe pressure range from 228±27 to 328±4 kPa was found during sessions with no feedback-controlled sonications. The amount of Gd in the sonicated area was maximum around 15-20 min post injection. PCD harmonic emissions correlated with safe BBB opening, whereas broadband and sub-harmonic emissions were present in 1 sonication that resulted in permanent lesion (400 kPa estimated in the brain). Safe sonications were achieved in 3 sessions using real-time PCD-based feedback control of the acoustic pressure. The high resolution anatomical images and the high temporal/spatial resolution of contrast agent diffusion provide a unique tool for studying the mechanisms of BBB disruption and drug delivery in NHP. Furthermore, the PCD-based feedback control allows repeatable safe sonication regardless variation of skull attenuation.

Hynynen et al. Radiology 220, 640–646, 2001
Kovacs et al. PNAS 201614777, 2016

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