Imaging of the permeability dependence of focused ultrasound-induced blood-brain barrier opening at distinct pressures and microbubble diameters

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Introduction

Focused ultrasound (FUS) in the presence of circulating microbubbles in the bloodstream can locally, non-invasively and transiently open the blood-brain barrier (BBB) (1). The spatial extent and the intensity of the opening have been shown to depend on various sonication parameters, which affect the permeability properties of the sonicated capillaries. In this study, the permeability of BBB opening in the murine hippocampus is assessed using dynamic contrast-enhanced MRI (DCE-MRI) *in vivo* (2). Different acoustic pressure amplitudes and microbubble diameters have been used to correlate the kinetic-modeling-derived transfer rate constants with the FUS parameters used and detect the lowest and highest permeability values that can be reached in the BBB-opened region.

Methods

Forty (n=40) wild-type male mice were injected intravenously with customized, lipid-shelled, monodispersed microbubbles at a concentration of 10^7 #/mL. Each mouse was sonicated transcranially at the right hippocampal region using FUS (1.5 MHz frequency; 100 cycle pulse length; 10 Hz pulse repetition frequency; 1 min sonication duration) immediately after IV microbubble administration (Fig. 1). The entire mouse cohort was divided into nine groups. Each group was sonicated at a distinct rarefactional acoustic pressure amplitude (0.30, 0.45 or 0.60 MPa) using a specific bubble diameter (1-2, 4-5 or 6-8 μm). Upon completion of the FUS procedure, DCE-MR images were acquired before and after intraperitoneal injection of gadodiamide (Gd-DTPA, 6.25 mM/kg) over a period of 60 min. The dynamic acquisitions were fitted to the generalized Tofts-Kermode kinetic model (3) using a population-averaged arterial input function (AIF), derived from the internal carotid artery. The extracted K_{trans} maps provided both volumetric and quantitative permeability measurements of the BBB opening (Fig 1). Histological examination was performed seven days after sonication for the macroscopic assessment of damage.

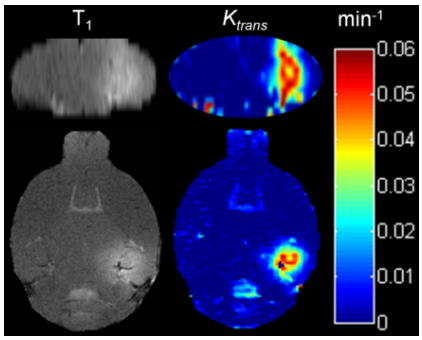

FIG. 1. Coronal (top) and transverse (bottom) T_1 images (left) and their corresponding K_{trans} maps (right) (0.60 MPa, 4-5 μm bubbles).

Results

The K_{trans} maps showed the spatial Gd-DTPA uptake in the right hippocampal region and its proximity. The volumetric measurements revealed a linear increase of the BBB-opened region volume with both the microbubble diameter (R^2=0.9999) and the acoustic pressure (R^2=0.949), varying between 1.5 to 37.7 mm^3 (Fig. 2a). On the other hand, the quantitative measurements revealed the presence of a K_{trans} plateau of approximately 0.048 ± 0.008 min^{-1} at higher pressures (0.45 and 0.60 MPa) for the larger bubbles (4-5 and 6-8 μm) (Fig. 2b). The plateau reached was found to be equal to the mean K_{trans} of the epicranial muscle (0.047 ± 0.007 min^{-1}) (Fig. 2b), implying that the permeability properties of the sonicated hippocampal vessels are similar to the properties of the vessels that do not possess such a barrier. Histological examination revealed some structural damage in a small subset of mice (7.5%) and only at higher pressures (≥0.45 MPa) and for larger bubbles (≥4-5 μm).

Discussion and Conclusion

In this study, the relationship between permeability, the microbubble diameter and the acoustic pressure was investigated using DCE-MRI. Our findings indicated that the BBB-opened region volume and permeability increase with both the pressure and the bubble diameter. Thus, the permeability maps may be used as an *in vivo* diagnostic marker for the quantification of the efficacy of drug delivery of the FUS-induced BBB opening.

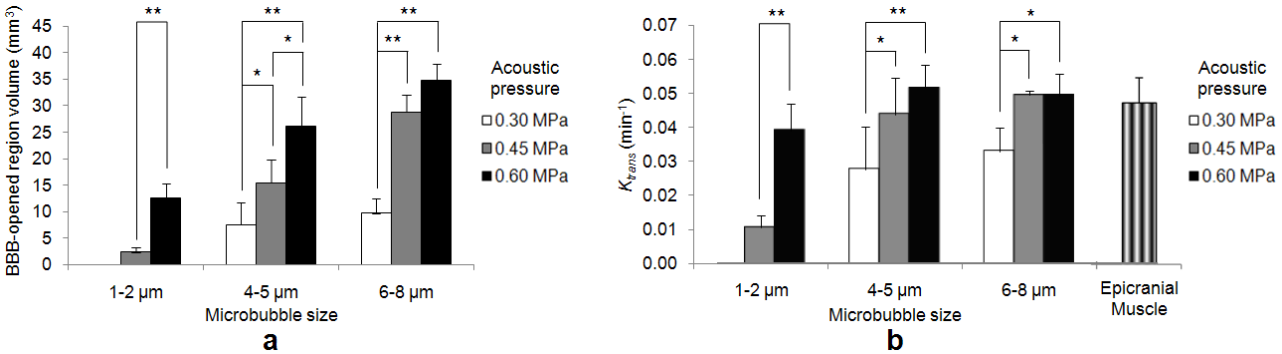

FIG. 2. Mean (a) volumetric and (b) quantitative K_{trans} measurements at different microbubble diameters and acoustic pressures. The K_{trans} of the epicranial muscle is also shown for comparison. One asterisk (*) denotes p<0.05 and two asterisks (**) denote p<0.01.

References

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