

Blood-Brain Barrier Disruption in Pigs by Transcranial Focused Ultrasound: Correlation of Cavitation Signals and MR Imaging for Treatment Monitoring

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Introduction

Magnetic resonance guided focused ultrasound (MRgFUS) has been demonstrated to reversibly disrupt the blood-brain barrier (BBB) for targeted drug delivery (1). While successful studies have been performed transcranially on small animal models, limited research has been reported on large animals (2). For large animals, a precise control of the location and pressure of the ultrasound focus is difficult due to the deflection and absorption of the ultrasound beam by the relatively thicker skull. In this study, a low frequency (230kHz) MRgFUS brain system was used to demonstrate the feasibility of localized BBB disruption in pigs without craniotomies. Cavitation signals from sonicated microbubbles were detected by hydrophones as a mean to monitor the treatment in real-time. The levels of cavitation signals at various acoustic powers were correlated to the levels of BBB disruption and tissue damage measured by T1-weighted and T2-weighted MR images.

Methods

A modified clinical MRgFUS brain system (ExAblate 4000, Insightec, Tirat Carmel, Israel) was used with a 3T MR scanner (Signa MR750, GE Healthcare, Milwaukee, WI, USA). The FUS system consists of a 1000-element hemispherical phased-array with a diameter of 30 cm and a central frequency of 230 kHz. The array was filled with degassed water and covered by a latex membrane (0.15 mm thick), on which the pig's head rested against (Fig.1). Experiments were performed on 12 pigs (~20 kg) under general anesthesia. Isoflurane was turned off 15 minutes before sonication and switched to ketamin/xylazine drip. Multiple locations in the brain were sonicated by electronically steering the ultrasound beam. Two-to-five minute sonifications (10 ms pulses at 1 Hz) at 5-15 W acoustic power were applied simultaneously with the intravenous injection of microbubbles (Definity, 0.02ml/kg, Lantheus Medical Imaging, N. Billerica, MA, USA). Proton resonance frequency (PRF)-based MR thermometry was applied to monitor any temperature change. MR contrast agent (Omniscan, GE Healthcare, Milwaukee, WI, USA) was injected to verify the BBB disruption with T1-weighted FSE imaging. Potential tissue damage or edema after the treatment was verified by T2-weighted FSE sequence. The animals were sacrificed after experiments and the brains were harvested for histology evaluation. In the last 5 pigs, a hydrophone was attached to the pigs' head skin to detect cavitation signals from the brain (Fig.2). The hydrophone was made in house with PZT-5H, 3mm diameter, 520kHz central frequency, 40% bandwidth. Cavitation signals were acquired in real-time and analyzed offline. Subharmonic signals indicating microbubble activities were correlated to MRI findings and histology.

Results

Localized BBB disruptions were observed after most sonifications at or adjacent to the targeted positions. Fig.3 shows an example of four BBB openings in one pig brain. The average diameter of Gd-enhanced openings in T1w images was 5 mm. No temperature elevation was observed in any sonication. Subharmonic cavitation signals were detected at various acoustic powers (Fig.4). Narrow-band, low-level stable cavitations were correlated with localized BBB openings with little edema or hemorrhage, while wide-band, high-level inertial cavitations associated with higher powers correlated to edema in extended volume in T2w images and hemorrhage in histology.

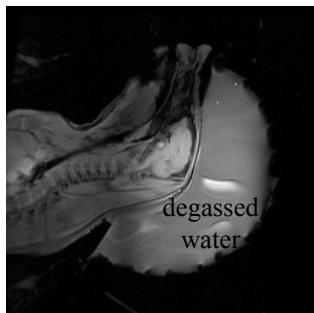


Fig.1 A sagittal MR image showing the experimental setup. The hemispherical FUS array (filled with degassed water) was sealed by a thin latex membrane, on which the pig's head rested against.

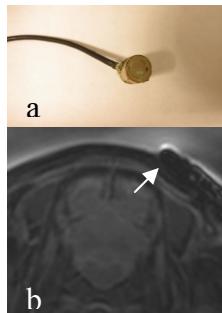


Fig.2 a. A PZT hydrophone (3mm in diameter); b. An axial MR image shows the location of the hydrophone (arrow) relative to the brain.

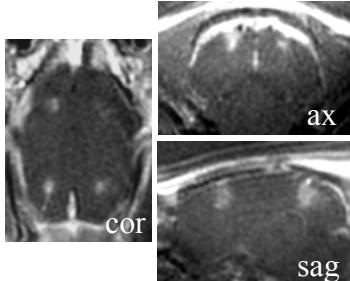


Fig.3 Gd-enhanced T1 images of four BBB openings at coronal, axial and sagittal planes. The average diameter of the openings was 5mm.

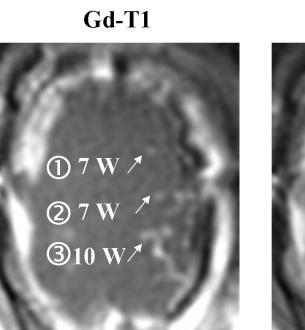


Fig.4 Three BBB openings (arrows) at 7 and 10W. Cavitation signals on the right show different characteristics at the 3 locations. For the first two locations at 7W, narrow-band cavitation at 115 kHz indicated stable cavitation, while 10W at the 3rd location induced wide-band, inertial cavitation signals, which correlate to the extended BBB opening in Gd-T1 and edema in the T2 image.

Discussion

Targeted BBB disruption was achieved noninvasively (without craniotomies) by a modified clinical FUS device in a large animal model. The average thickness of pig skulls was 5mm. Using the low frequency helped to reduce ultrasound deflection. However, variability of focal pressure remained. Therefore, monitoring microbubble activities is crucial as a real-time control of the focal pressure to avoid bleeding. Our study shows that cavitation signals detected by the hydrophone attached to the skin correlated to the extent of BBB openings and tissue damage revealed in MR images. The next step is to use the cavitation signals in the real-time control of the ultrasound power to minimize inertial cavitation. This opens up the possibility of a feedback-controlled procedure of BBB disruption for drug delivery to patients.

Acknowledgements

The authors thank Eyal Zadicario from Insightec for the technical support of the ExAblate system.

References

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