MR-Guided Blood-Brain Barrier Disruption by Transcranial Focused Ultrasound: Preclinical Testing on a Trans-Human Skull Pig Model

Yuexi Huang[1], Ryan Alkins[1], Michael L. Schwartz[2], and Kullervo Hynynen[1,3]

[1]*Sunnybrook Research Institute, Toronto, ON, Canada,* [2]*Division of Neurosurgery, Sunnybrook Health Sciences Centre, Toronto, ON, Canada,* [3]*Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada*

Introduction

Magnetic resonance-guided focused ultrasound (MRgFUS) has been demonstrated to reversibly disrupt the blood-brain barrier (BBB) for targeted drug delivery (1). Many small and large animal models have been developed to investigate the effectiveness and characteristics of BBB disruptions. However, in translation for a clinical trial, the treatment protocol needs to be optimized according to properties of human skulls and capabilities of the current clinical prototype device. In addition, a cavitation-based safety mechanism needs to be tested in vivo for minimizing risks of hemorrhage. In this study, a BBB disruption protocol was developed in a trans-human skull pig model with human applications in mind. The capability using MRI for confirming BBB disruption and detecting potential hemorrhage was verified.

Methods

A modified clinical MRgFUS brain system (ExAblate 4000, 230 kHz, Insightec, Tirat Carmel, Israel) was used with a 3T MR scanner (Signa MR750, GE Healthcare, Milwaukee, WI, USA). Wide craniotomies were applied on 11 pigs (~15kg). The skin was closed and the surgical site was filled with degassed saline. A partial human skull was positioned over the pig's brain (Figure 1). The FUS array was positioned horizontally (facing up). The pig was positioned supine, with the head coupled directly with degassed water. Anesthesia was applied by isoflurane with medical air.

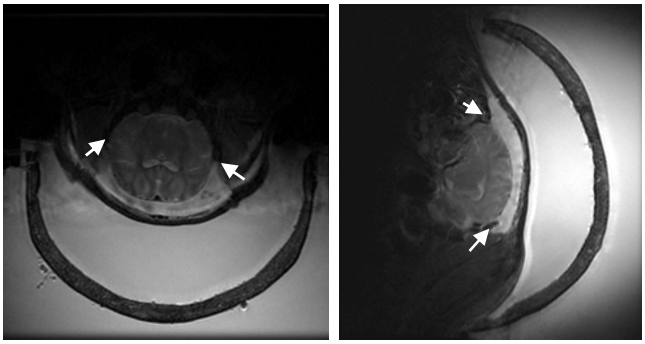
The ultrasound beam was steered during sonications over a 3x3 grid of 9 spots at 3 mm spacing. For each spot, 2 ms on, 28 ms off pulses were repeated for 300ms before steering to the next spot. The overall PRF for each spot was 2ms/30ms/9 = 0.74%. Total sonication time was 50 s. Acoustic power levels from 3 to 20 W were tested. The maximum dosage of the Definity microbubble (Lantheus Medical Imaging, N. Billerica, MA, USA) is 20ul/kg on the label. As multiple sonications with stepwise increases in power are anticipated in human treatments, one-fifth (4ul/kg) of the maximum dose was tested for each sonication. Bolus injection was simultaneous with the start of the sonication.

Cavitation signals were recorded and averaged by two receivers. Cavitation signal was sampled at 2 MHz for each 2 ms pulse, synchronized to the pulses. Spectrum integration from 75 kHz to 155 kHz was calculated and two threshold levels (3-sample average and 10-sample average) of the spectrum integration were defined in the safety algorithm to terminate the sonication. During the study, these cavitation levels were lowered twice based on hemorrhage levels in sonicated volumes in histology.

Post sonications, Gd (Gadovist, Bayer)-enhanced FSE T1-weighted images were acquired to verify the BBB disruption, and T2*-weighted GRE images (TE=15ms) to detect hemorrhage, both with the body coil. After treatments, pigs were repositioned and same sequences were repeated with the head coil. Evans blue (2%, 2 ml/kg) was injected before transcardial perfusion and brains were dissected for histology.

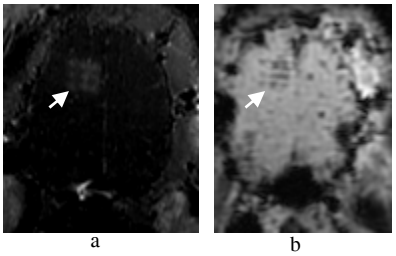
Results

BBB disruptions were achieved repeatedly at 4 to 5 W acoustic powers. However, before cavitation thresholds were lowered to the final levels, BBB disruptions (Gd enhancement in Fig.2a) could be accompanied by excessive hemorrhage in the treated volume (dark signals in T2*w images in Fig.2b). With lowered thresholds, BBB disruptions (Fig.3a,b) were successfully accomplished without hemorrhage (Fig.3c). Brain cuts confirmed Evans blue (albumin) extravasation (Fig.3d), and H&E staining detected only scattered extravasation of red blood cells in the volume. In cases the cavitation signals were above thresholds, sonications were terminated. Despite much shortened sonication time in these cases, BBB disruptions were still visualized without hemorrhage.



a b

Fig.1 Axial (a) and sagittal (b) T2w MR images (body coil) showing the human skull cap over a pig brain with a wide craniotomy. Arrows indicating the end of the pig skull after the craniotomy.



a b

Fig.2 a) Gd-enhanced T1 image shows BBB disruption at the 3x3 grid. b) T2*w image shows hemorrhage (head coil). Cavitation thresholds were lowered after.

Discussion

The trans-human skull pig model demonstrated the feasibility and safety of the ExAblate system for BBB disruptions in preparation for human applications. Gd-enhancement showed small gaps in the 3x3 grid with 3mm spacing. A 2 mm spacing was used in a previous monkey study (2) with more uniform BBB distruption in the volume. A 3mm spacing was chosen to increase the volume to be around 1cm^3 preferred for human applications. It remains to be seen if the delivered drug can diffuse across the gaps. We do not expect an impact on other parameters if the spacing needs to be reduced to 2 mm. Enhancement with a grid pattern, on the other hand, might help detect the treated volume as natural leakage and enhancement around brain tumors might be complicated, especially with noisy T1 images by the body coil. A dedicated coil which can be combined with the system is preferred for this application.

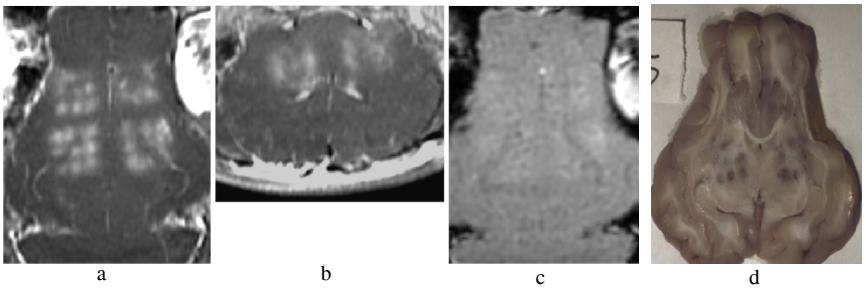
Acknowledgements

The authors thank Omer Brokman from Insightec for the technical support of the ExAblate system.

References

1.Hynynen K et al. Radiology 2001;220:640-6.

2.McDannold N et al. Cancer Research 2012;72:3652-63.



a b c d

Fig.3 Coronal (a) and axial (b) Gd-enhanced images showing four BBB disruption volumes. No hemorrhage was detected in T2*w image (c). Evans blue extravasation (d) confirmed BBB disruption for macromolecules.