Investigating the Use of Short Pulses in MRI-guided Focused Ultrasound Disruption of the Blood Brain Barrier

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Introduction

MRI-guided transcranial focused ultrasound disruption of the blood-brain barrier (BBB) is a promising technique for targeted drug delivery in the brain. Preclinical investigations into BBB disruption typically employ long ultrasound pulses which, combined with small animal models in which the distances between bone surfaces in the skull cavity are short, can give rise to standing waves creating high variability in results [1]. Investigations into the use of short pulses, of a few microseconds in length, have shown that they are effective at eliminating standing waves in rat models when repeated at a 50% duty cycle and can disrupt the BBB when repeated over therapeutic burst lengths, with more consistent disruption levels than continuous wave bursts [1]. This study examines the parameters surrounding the use of short pulses to disrupt the BBB.

Methods

Sonications were performed at eight locations (four control and four experimental) in each of 14 rats (Wistar, 225-433 g) with an estimated *in situ* pressure of 0.54 MPa. Rats were anesthetized using a mixture of ketamine (10 mg/kg) and xylazine (40-50 mg/kg) and their heads were depilated to remove the hair from the ultrasound path. Animals were placed on an MRI-compatible positioning system operationally similar to that described in [2] in a 1.5 T MRI (Signa 1.5 T, GE Healthcare, Milwaukee, WI, USA) with their heads coupled to the ultrasound transducer via a water bath. Sonication locations were selected from T2w images (FSE, TE =61.7 ms, TR =2000 ms, ETL = 4, FOV = 6 cm x 6 cm, slice thickness = 1 mm, 128 x 128). Definity Microbubble contrast agent (0.02 ml/kg, Lantheus Medical Imaging, MA, USA) was injected simultaneously with the start of all sonications and a minimum of five minutes was allowed between sonications for the contrast agent to clear. Ultrasound was generated using wideband-composite 8-sector spherically-focused array (10 cm aperture, FN=0.8, Imasonic, Inc., Voray-sur-L'Ognon, France) matched to 1.18 MHz using an external matching circuit. Ultrasound bursts consisted of single excitation cycles repeated with a short time delay for a total of 10 ms. The transducer rang for approximately 3 µs following a single excitation cycle. The control case consisted of 10 ms burst comprised of single cycles with a delay of 6 µs between cycles (50% duty cycle over the duration of the burst) at a 1 Hz burst PRF. Figure 1 shows the ultrasound timing diagram.

Eleven rats were used to examine the effects of delay between cycles over 2 minute sonications using bolus microbubble injections. Delays between cycles of 60 µs, 300 µs, 600 µs, and 1 s were examined. Bursts with 6 µs, 60 µs, 300 µs and 600 µs delays were 10 ms in length resulting in a reduced number of cycles per burst with increasing delay. In the case of the 1 s delay, a single cycle was repeated at a burst PRF of 1 Hz.

The remaining 3 rats were used to examine the effects of burst PRF over 5 minute sonications. A 6 µs delay between cycles was used for all burst PRFs, and 0.2 Hz, 1 Hz, and 2 Hz burst PRFs were examined over 5 minute sonications. All bursts were 10 ms in length for five minutes. Microbubbles were delivered in 4.5 min infusions using fringe-field compatible feedback controlled syringe pump (Chemyx NanoJetXF MRI Compatible Syringe Pump, Chemyx Inc., Stafford, TX, USA).

Contrast-enhanced (0.2 ml/kg Omniscan, GE Healthcare) T1w scans (FSE, TE = 10 ms, TR = 500 ms) were used to evaluate the level of BBB disruption and T2w images were examined for indicators of edema.

Results

The blood brain barrier was successfully disrupted using all investigated pulse parameters. Disruption occurred even in the case of a single excitation cycle per second. The relationship between mean enhancement measured on the T1w images and the number of cycles in a burst appeared logarithmic (fig.2), with enhancement mean not proportional to time averaged acoustic power. Statistically significant differences between the enhancement mean of control case and the 300µs, 600µs and 1s cases was found using a two-tailed paired t-test (p=0.033, p=0.016 and p=0.018 respectively), while no statistically significant difference was found between a 6 µs delay and a 60 µs delay (p=0.145). T2w enhancement indicating edema was observed for at least one sonication performed with each delay.

A reduction in burst PRF to 0.2 Hz produced a statistically significant decrease in enhancement mean over the control case (8 ± 1% vs. 22 ± 6%, p=0.04), while an increase in enhancement mean was observed at 2 Hz PRF, however without statistical significance (20 ± 6% vs. 14 ± 3%, p=0.4). Figure 3 shows a contrast enhanced T1w image showing enhancement at six of eight sonication locations.

Discussion

Results of this study show that the BBB can be disrupted using long delays between pulses and a range of repetition frequencies. The level of BBB disruption is not directly proportional to the time averaged acoustic power. The presence of edema in at least one sonication with each parameter suggests no improvement in safety with longer delays, however using sonications as short as 3 µs in length could improve throughput by allowing more targets to be sonicated within the 1 s repetition time. No statistical improvement in enhancement was seen with increasing burst PRF, however statistical significance may potentially be reached if a greater number of animals are used.

Acknolwedgments

This work was supported by the National Institutes of Health under Grants No. R01EB003268 and R01EB009032

References

[1] O'Reilly et al, *Phys.Med.Biol.,* 2010;21:5251-5267 [2] Chopra et al, *Med. Phys,* 2009; 36:1867-1874, 2006;340:1085-1090

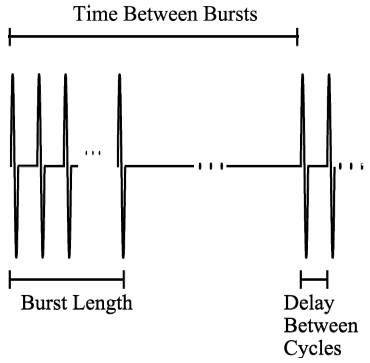

Fig.1 – Ultrasound timing diagram (function generator output)

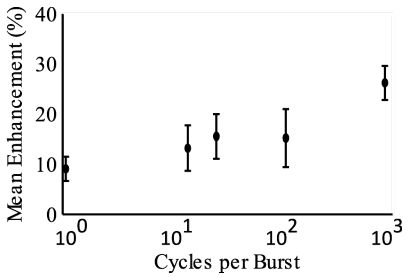

Fig.2 – Mean enhancement versus number of cycles per burst

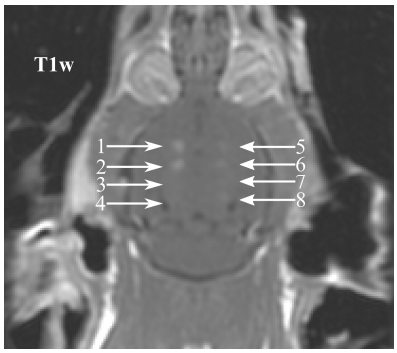

Fig.3– Contrast enhanced T1w image with enhancement at 6 of 8 sonication locations. (1-2) 2Hz PRF, (3-4) 0.2Hz PRF, (5-8) 1Hz PRF