MR-guided unfocused ultrasound disruption of the rat blood-brain barrier

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Introduction: The blood-brain barrier (BBB) presents a problem for drug delivery to brain tissues. While there are several invasive ways to disrupt or bypass the barrier with numerous side effects, therapeutic ultrasound with microbubble contrast agent presents a non-invasive method of temporarily disrupting the BBB to allow for drug delivery. It can be localized and measured using contrast-enhanced MRI (CE-MRI), where gadolinium entry into the brain is indicative of the degree and location of BBB opening. Previous studies used focused ultrasound treatment, which is appropriate for the targeted delivery of drugs such as chemotherapeutic agents. [1, 2] The purpose of this study was to investigate the effects of unfocused ultrasound on BBB opening across the whole brain using CE-MRI.

Methods: In 5 Sprague-Dawley rats under isoflurane anesthesia, gadolinium-based MR contrast agent (Gd; Bayer Healthcare, Magnevist, 0.5ml/kg)) was administered concurrent with ultrasound microbubble contrast agent (GE Healthcare, Optison, 0.5ml/kg) and allowed to circulate for 10 seconds before sonication. A 753 kHz planar PZT transducer, 70% efficiency, diameter 1.8cm, was used to sonicate each rat at 300, 400, or 500mV$_{pp}$ for 10 seconds in continuous wave mode, or at 500 or 600mV$_{pp}$ in 20ms pulses at 10Hz for 30 seconds total. After sonication, coronal T1-weighted (TE/TR- 10/500 ms, FOV 6cm, 4 NEX, 2mm slice thickness, 4 ETL, 256x128) FSE images were acquired with a 3 inch surface coil (GE, Milwaukee, WI). The imaging protocol was repeated three times 1 to 12 minutes after treatment. A control animal was given Gd and microbubbles, but not sonicated. Signal change in ROIs over the muscle, mesencephalon/ventricles, and the cortex/striatum were measured at 3 time points: 10 seconds, 3±1.7 minutes, and 8.8±2.9minutes after sonication. Signal intensity was converted to % signal change compared to the initial image. Mesencephalon signal was measured in a slice approximately 5mm rostral to the interaural line, and cortex/striatum combination measurements were measured approximately 10mm rostral to the interaural line.

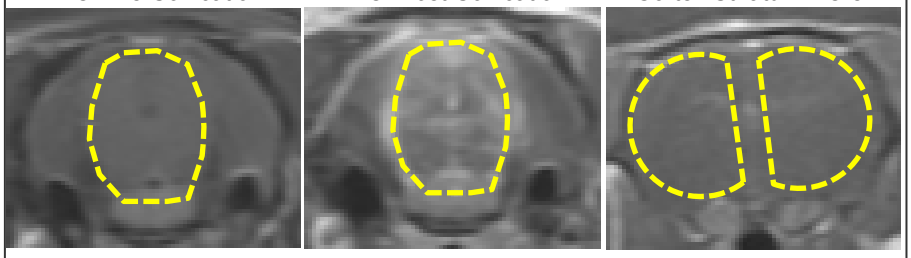

Figure 1: Sample Images and the measured ROIs. Mesencephalon increase in signal was larger, and more localized, while signal increase in cortex was more evenly distributed. Measurements in left and right ROIs were averaged together.

Results and Discussion: In the control experiment, CE-MRI showed brightening of surrounding structures, but not of the brain itself. In the experimental datasets, the signal intensity was raised across the whole brain. Data from two representative slices from each subject are given here. All showed initial similar patterns of large increase in signal around the mesencephalon and ventricles compared to that in the cortex/striatum (Figure 1). The numerical results for change after sonication are shown in Figure 2. On average, the Gd in the muscle washed out at the later timepoint. All subjects saw an increase in signal in both the cortex/striatum and mesencephalon, increasing for the second time point. The continued increase was more substantial in the cortex/striatum. In the mesencephalon, white and grey matter meet, causing a mixture of mechanical tissue properties which may lead to shear stress [3] that may increase the ability of ultrasound to open the BBB. Ventricles are also known to be susceptible to BBB opening. [2]

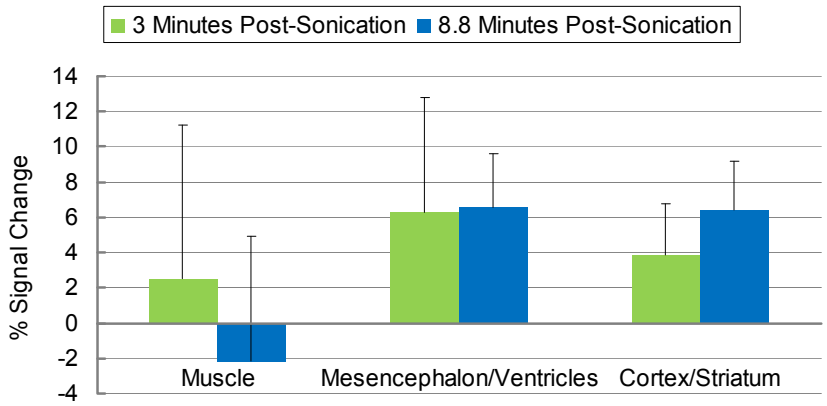

Figure 2: Percent signal change in series acquired after sonication averaged across all subjects. Error bars indicate 1 SD.

Conclusion: After unfocused ultrasound sonication, the BBB is disrupted across the whole brain, including cortex and deep grey matter nuclei. As time passes, the continued passage of Gd into the brain can be visualized using CE-MRI.

References: [1]Treat et al. Int J Cancer. 2007;121;901-907., [2] Bing et al. Ultrasound in Med Biol. 2009; 35; 1298-1308. [3] Schmidt and Grady. J Neurotrauma, 1993; 10; 415-430.

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