In-vivo Temporal Characterization of Focal Openings of the Blood-Brain Barrier Using MR guided Focused Ultrasound

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Introduction:

The use of contrast agents and therapeutic agents in the brain is limited by the blood-brain barrier (BBB), which restricts their entry into the brain. Focal or regional opening of the BBB in a non-invasive and controlled way may provide the administration of specifically targeted therapeutic agents to a localized area.

Magnetic resonance guided focused ultrasound (MRgFUS) is a promising non-invasive modality currently approved for the treatment of uterine fibroids and bone metastases; possible applications to brain and other organs are being investigated. Traditional MRgFUS uses MR images to guide the delivery of high amounts of energy, in a focal location deep inside tissue, while depositing minimal amounts of energy elsewhere. Another more experimental use of MRgFUS, uses low amounts of energy to produce acoustic pressure at a desired frequency without heating up the tissue. This effect does not cause significant tissue damage but is sufficient to dislodge thrombus from blood vessels (thrombolysis) or break microbubbles and open the BBB in a very focal area.

The purpose of this work was to characterize the opening of the BBB temporally, during the 60 minutes immediately post-sonication with microbubbles; this is important to determine the optimal time window to administer intra-venous brain therapeutic agents.

Methods:

Three Sprague-Dawley rats (~250g) underwent MRgFUS using a dedicated small animal focused ultrasound system (FUS, Toronto, Canada). The FUS system is composed of a single transducer, which operates at 1.06 MHz and can be moved mechanically under computer control with sub-millimeter accuracy. Each animal received one or two sonications immediately after the injection of 2cc of microbubbles, with no more than one sonication per brain hemisphere. Each sonication had a duration of 120sec.; acoustic pressure, 1MPa; burst time, 10ms; period, 5sec. Animals were anesthetized with a mixture of Ketamine/Xylazine (50/5mg/Kg) and kept under anesthesia with a single bolus of the same mixture every 90 minutes. Animals breathed spontaneously during the entire study. All scans were done in a 3 Tesla clinical system (Trio, Siemens Medical Solutions) using a TX/RX surface RF loop coil. MR imaging was performed after multiple injections of 0.2cc of Gadodiamide (Omniscan, GE Healthcare, Canada), using a contrast-enhanced protocol (CE-T1w), at baseline, 15min., 30min. , 45min. and 60 min. post-sonication; FOV, 60x60mm^2; in-plane resolution, 0.3x0.3mm^2; slice thickness, 2.0mm; TR/TE,110/3.2ms. Protocol was approved by our Institutional Animal Care & Use Committee.

Results:

Focal opening of the BBB was observed in all cases at 30min. post-sonication (Fig. 1B & 2). While at 30-45min. post-sonication the SNR of the focal point was highest with a 2.1 increase (Fig. 1 & 2). The area of contrast extravasation kept increasing up to the last time point at 60 min. post-sonication (Fig. 2), to a mean value around 2.3 times the initial value immediately after sonication. After 30 min. the borders of the area of extravasation were less defined and appeared more diffuse (Fig. 1C).

Discussion:

From this preliminary animal study, we found that for highly localized delivery of intravenous therapeutic agents to the brain, we have to wait 30 min. after sonication using the parameters above and microbubbles. For therapeutic delivery in larger areas of the brain, for example areas surrounding a glioma, we may have to wait at least 60 min. before injecting an agent via I.V. Since the area of open BBB was still increasing for all animals after 60 min. post-sonication, future longitudinal studies should probe this at longer time periods.

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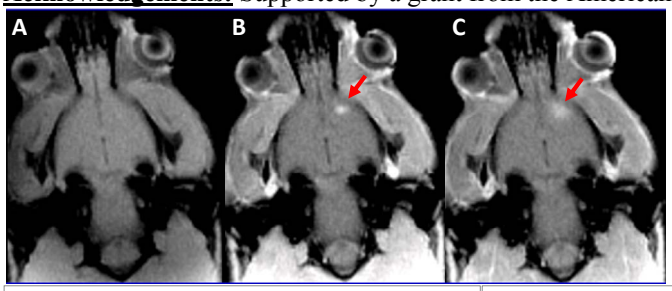

Figure 1A: Baseline CE-MRI of in-vivo rat brain model. **B:** 30 minutes post-sonication with microbubbles. Note the very well defined borders of the focal BBB opening (red arrow), very suitable for precise delivery of therapeutic agents to the brain. **C:** 60 minutes post-sonication. Note the diffuse and wider area of BBB opening (red arrow), more suitable for larger extended deliveries of therapeutic agents, for example to the areas around a brain tumor. All images are from the same animal.

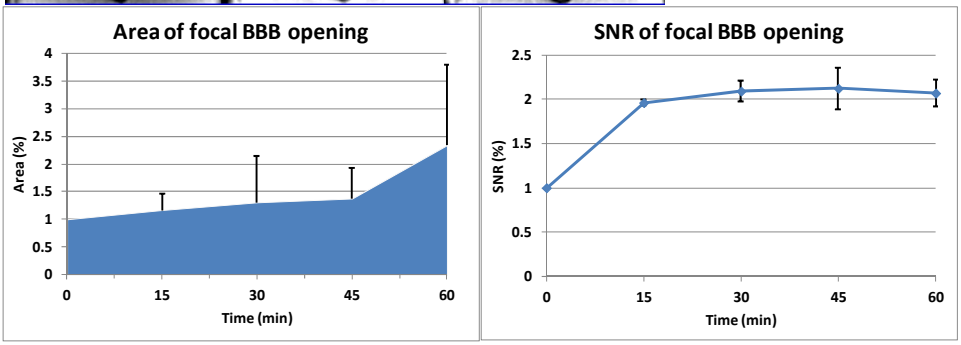

Figure 2: Temporal quantification and characterization of focal openings of the BBB, induced by MRgFUS with microbubbles. **Left:** Percentage area opened over time, post-sonication. Note the steady increase all the way to 60 minutes. **Right:** Increase of SNR over time up to 30 minutes post-sonication, followed by a slight decrease until 60 minutes. Error bars represent STD.