ACOUSTIC CAVITATION ASSESSMENT OF THE REVERSIBILITY AND PERMEABILITY OF THE ULTRASOUND-INDUCED BLOOD-BRAIN BARRIER OPENING

Tao Sun¹, Gesthimani Samiotaki¹, Shutaow Wang¹, Cherry Chen¹, Camilo Acosta¹ and Elisa E. Konofagou¹,²
¹Department of Biomedical Engineering, Columbia University, New York, NY; ²Department of Radiology, Columbia University, New York, NY.

Introduction:
Focused ultrasound (FUS) in combination with microbubbles is a technique for noninvasive, transient, localized and reversible blood-brain barrier (BBB) opening in order to aid the drug delivery to the brain. Various molecules have been shown to cross the BBB under this technique and exhibit therapeutic effects. However, safety, and real-time monitoring thereof, remains one of the key elements before clinical translation of this technique. The objective of this study is to investigate if acoustic cavitation can be potentially used to assess the reversibility and permeability of the induced BBB opening.

Method:
This study links the microbubble dynamics, represented by the cavitation dose, as monitored during BBB opening to the reversibility of BBB opening. The dependence of acoustic emissions on the reversibility, including the closing timelines of the BBB opening volume and its permeability, was investigated under three different clinically relevant acoustic pressures (0.30, 0.45 and 0.60 MPa) and microbubble sizes (of diameters of 1 - 2, 4 - 5, or 6 - 8 μm). A 10-MHz, single-element, pulse-echo ultrasound transducer served as a passive cavitation detector was used to acquire the cavitation signals generated during sonication that targeted the mouse right hippocampus (n=49). The stable cavitation dose (SCD) and inertial cavitation dose (ICD) were monitored during sonication. Contrast-enhanced dynamic and T1-weighted MR scans were performed immediately after sonication on Day 0 and every 24h up to 6 days thereafter. Volumes and diffusion rates of the contrast agent (Gd-DTPA-BMA) were quantified as indicators for the induced amount of BBB opening.

Results:
Cavitation response was found to be well correlated with (1) the duration for the induced BBB to close ($r^2 = 0.80$ for SCD and $r^2 = 0.27$ for ICD); (2) the permeability of the induced BBB opening ($r^2 = 0.82$ for SCD and $r^2 = 0.72$ for ICD) and (3) the likelihood of safe opening ($p < 0.05$: compared the SCD of safe opening cases to the cases with mild damage). Stable cavitation was found to be more reliable at predicting the BBB opening than inertial cavitation.

Conclusion:
In summary, we have shown that monitoring of cavitation behavior during FUS has
the potential to reliably predict the duration of opening, the permeability of the induced BBB opening and the likelihood of safe opening. The stable cavitation dose may therefore provide a real-time predictor of the properties of the induced reversible disruption. Finally, the dependence of the BBB reversibility on the bubble diameter and FUS pressure allows us to control the safety profile of this technique.