Real-time prediction of the reversibility of the ultrasound-induced blood-brain barrier opening using passive cavitation detection with MRI validation

Tao Sun¹, Gesthimani Samiotaki¹ and Elisa E. Konofagou¹²

¹Department of Biomedical Engineering, Columbia University, New York, NY; ²Department of Radiology, Columbia University, New York, NY.

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 the technique.

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 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=45). Contrast-enhanced dynamic and T1-weighted MR scans were performed immediately after sonication on Day 0 and 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.

The stable cavitation dose (SCD), which represents harmonic oscillations of the bubbles as a result of the FUS wave, increased with the number of days required for closing while it reached a plateau after Day 4. However, the inertial cavitation dose (ICD), representing the collapse of the bubbles, exhibited an exponential increase with the duration of the opening. A linear correlation between the cavitation dose (defined as the sum of normalized SCD and ICD) and the number of days of BBB opening was found. Moreover, the volume and permeability indicator $K_{\text{trans}}$ were found to be both pressure- and bubble size-dependent (i.e., smaller bubble-size and lower pressure resulted in shorter duration of opening).

In summary, we have shown that monitoring of cavitation behavior during FUS can predict the closing timeline of the induced BBB opening. The total cavitation dose may therefore provide a real-time predictor of the properties of the induced disruption. Finally, the dependence of the BBB reversibility on the bubble-diameter and FUS pressure allows us to predict and control the safety profile of this technique.