Monitoring and Control of Ultrasound Induced Blood-Brain Barrier: Implementation on A Confocal Dual-Frequency Transducer

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Abstract
Burst-mode focused ultrasound (FUS) exposure combined with micro-bubbles (MBs) has been proved to induce temporal and local blood-brain barrier (BBB) opening. Traditional contrast-enhanced imaging confirmation after focused ultrasound exposure serves as a postoperative indicator of the effectiveness of FUS-BBB opening, however, an indicator that can concurrently report the BBB status and BBB-opening effectiveness is required to provide effective feedback to implement this treatment clinically. In this study, we demonstrate the use of subharmonic acoustic emission detection with implementation on a confocal piezoelectric ceramic structure to perform real-time monitoring of FUS-BBB opening.

Materials and Method

FUS transducer
A confocal dual-frequency focused ultrasound transducer was designed (figure 1). The inner ring (1.1 MHz) was employed to deliver FUS exposure to induce BBB-opening, and the outer ceramic (0.55 MHz) was employed to receive the subharmonic emissions from the focus point.

In-vivo experiment
In stage-1 experiment (n = 52), we employed energy spectrum density (ESD) to analyze and optimized 0.55 MHz ESD level change which was shown to effectively discriminate the occurrence of BBB-opening (figure 2). Wideband acoustic emissions received from outer ceramic were also analyzed to evaluate its correlations with erythrocyte extravasations. In stage-2 real-time monitoring experiments (n = 38), we applied the predetermined ESD change as a detection threshold in PC-controlled algorithm to predict the FUS exposure intra-operatively.

Acoustic emission analysis
Figure 3. An illustration of energy spectrum density (ESD) : Green part means the subharmonic which was employed to predict the occurrence of BBB-opening. Blue part means the inertial cavitation (IC) which was used to predict extractions.

Result

In stage-1 experiment
Figure 4. Comparison of acoustic emissions received via PCD transducer and confocal FUS transducer. Microbubbles were injected at 120 second (dashed line).

In stage-2 experiment: Real-time feedback control
Figure 5. Distribution of ESD with respect to FUS exposure level received by confocal FUS transducer. Dashed line = ESD change level of 5.5dB. The markers in “O” and “X” represent successful and failed BBB opening.

In stage-2 experiment, we employed the inner-ring transducer (1.1MHz) to induce BBB-opened and received acoustic emissions via the confocal outer-ring transducer (550KHz). The sensitivity that defined as the percentage of successfully predict BBB-opening and the specificity defined as the proportion of successfully predict BBB failed both reached over 92%.

Conclusion
The proposed system configuration and corresponding analysis based on subharmonic acoustic emissions has the potential to be implemented as a real-time feedback control structure for reliable induction of intact FUS-BBB opening for CNS brain drug delivery.

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