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Transcranial Blood-Brain Barrier Opening and Power Cavitation Imaging Using a Diagnostic Imaging Array

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***Abstract*— Typically, focused ultrasound (FUS)-mediated blood-brain barrier (BBB) opening requires multiple components that include the therapeutic transducer itself and a separate monitoring technique. Combining the therapeutic transducer and monitoring technique into a single transducer has yet to be shown. In this study, we investigated the use a single diagnostic array for both FUS-mediated BBB opening and cavitation monitoring. Our phantom experiments confirm that using a standard diagnostic transducer, power cavitation images were able to be acquired during focus transmits. These power cavitation images were able to estimate the size of the focus in the imaging plane, which match well with the measurements taken with a hydrophone. Furthermore, in vivo experiments in mice and non-human primates were performed, with successful transcranial BBB opening and cavitation monitoring in both animal models. BBB opening were confirmed using contrast-enhanced magnetic resonance imaging, which correlated well with the corresponding power cavitation maps showing high cavitation activity.**

Keywords*— blood-brain barrier opening, cavitation mapping, theranostic

I. Introduction

Focused-ultrasound (FUS) mediated blood-brain barrier (BBB) opening is an efficacious method to noninvasively deliver drugs to the central nervous system (CNS) [1]. However, many ongoing clinical trials require magnetic resonance imaging (MRI) guidance for proper targeting and monitoring [2]. Additionally, typical focused ultrasound systems consist of either a custom built geometrically focused transducer with a fixed focal point or a large, multi-element array that are complex. On the other hand, diagnostic ultrasound systems are readily available in the clinic and more accessible to clinicians and researchers. Few studies have investigated the feasibility of using a diagnostic transducer for BBB opening [3]. The advantage of using a diagnostic array is its simplicity, electronic beam focusing, and ability to image acoustic cavitation simultaneously. The aim of this study is to investigate the feasibility of using a linear array as a tool for BBB opening and monitoring in both mice and non-human primates.

II. Materials and Methods

A. Theranostic Transducer

A Philips P4-1 phased array (Bandwidth: 1.5 MHz – 3.5 MHz, Number of elements: 96) was connected to a Verasonics Vantage Ultrasound System. The P4-1 was programmed to transmit ~3 cycle pulses at a 1.5 MHz (Figure 1A). Time delays were calculated for each element to generate a focused transmit at the desired focal spot (Figure 1B). These focused pulses were transmitted at a pulse repetition frequency (PRF) of 1,000 Hz. Between each focused transmit, power cavitation images were acquired.

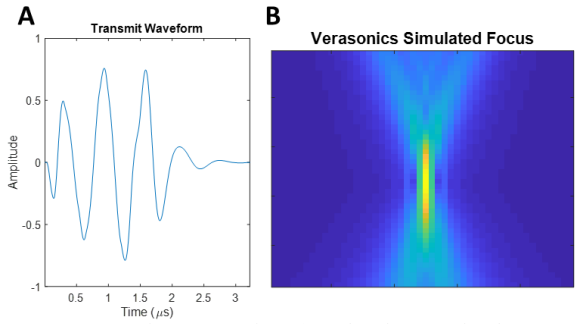

Figure 1. P4-1 waveform properties. (A) The elements for the P4-1 were driven by a 3 cycle, 1.5MHz pulse. (B) Time delays applied to each element were used to generate a focal spot within the imaging field-of-view. This focus was simulated in the Verasonics using the show TXPD() function.

B. Power Cavitation Imaging (PCI)

Channel data was acquired between each focused transmits and beamformed using a delay-and-sum (DAS) beamforming algorithm [4]. Additionally, the delays used in the DAS algorithm also took into account the appropriate time delays based on the focused transmits. An ensemble of *n* PCI images were accumulated over time and then spatiotemporally filtered using a singular value decomposition (SVD) filter. The SVD filter was crucial in order to remove stationary reflections (e.g. reflections from the skull) and slow-moving flow (e.g. tissue movement from breathing). Afterwards, the power of the SVD filtered images were taken to generate a power cavitation image.

C. *Phantom Experiments*

Phantom experiments were carried out in a water bath filled with in-house made polydispersed microbubbles (MB) [5]. The P4-1 was submerged in the MB bath, transmitting focused pulses at 1,000Hz. After an ensemble of 1,000 PCI images were acquired (~1 second), SVD filtering was applied to the ensemble. A final cumulative PCI image was generated after the spatiotemporal filtering, representing the MB cavitation.

D. *In vivo animal experiments*

In vivo animal experiments were carried out in both wild-type C57BL/6 mice (N = 4) and in rhesus macaque monkey (N = 1). In both animals, a burst of 100 transmits at a PRF of 1,000 Hz was used for focus transmits, equating to 100 PCI images acquired every burst. The burst repetition frequency was set to 0.5 Hz, in order to allow bubble reperfusion in the brain between bursts. For mice, the estimated free field transmit peak negative pressure (PNP) was about 1.5 MPa, while in the NHP, the estimated free field transmit PNP was about 3.5 MPa.

III. Results

A. *Power cavitation maps in bubble bath align well with hydrophone measurements*

A cumulative power cavitation image of 1,000 frames was acquired in a water bath of MBs (Figure 2A). The P4-1 was electronically focused to 35 mm, which matches well with the focus location seen in the power cavitation image. When compared to hydrophone measurements, axial and lateral cross sections of the focus overlap well. The hydrophone measurement estimated the focus to be 12.4 mm axially and 1.2 mm laterally. The power cavitation image estimates the focus to be 7.9 mm axially and 1.7 mm.

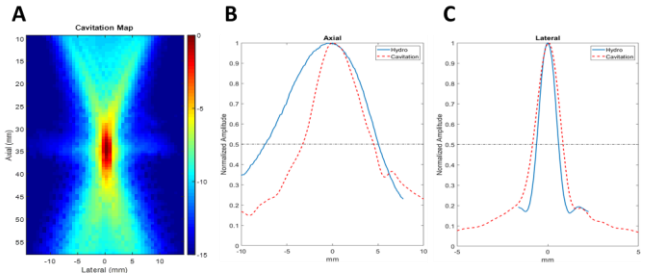

Figure 2. (A) Cumulative power cavitation image in a water bath of MBs. Cross sectional plots (B) axially and (C) laterally of the power cavitation image were compared to measurements taken from a hydrophone.

B. *In vivo animal experiments*

Transcranial BBB opening using the P4-1 linear array was confirmed in both mice and NHP. For the mice (Figure 3A), the power cavitation images revealed greater amounts of cavitation signal in the left hemisphere compared to the right hemisphere. Moreover, contrast-enhanced MRI images reveal contrast enhancement in the similar region of the brain. For the NHP (Figure 3B), power cavitation images revealed detectable cavitation signals throughout the beam path, which correlated well with the contrast enhancement observed on in the MRI. Within the beam focus, there is a 25.3 dB increase in signal intensity through the monkey skull after microbubbles are injected.

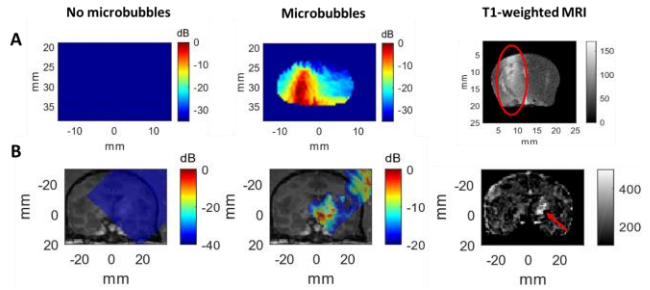

Figure 3. Spatiotemporally filtered power cavitation images and contrast enhanced MRI imaging confirming BBB opening using a linear array in (A) mice and (B) NHP. First column shows spatiotemporally filtered power cavitation images with no microbubbles, while the second column show filtered power cavitation images with microbubbles. Last column shows contrast enhanced T1-weighted MRI images, confirming BBB opening in the indicated areas.

IV. Discussion & Conclusions

In this study, initial feasibility of using a single transducer for both FUS-mediated BBB opening and cavitation monitoring has been demonstrated. Power cavitation images generated using focused transmits in a water bath of MBs agree well with hydrophone measurements, demonstrating the feasibility of using a single theranostic transducer to excite microbubbles and to localize their cavitation using power cavitation imaging. Next, we investigated the feasibility of using this theranostic transducer in vivo. In both mice and NHP, transcranial power cavitation maps were able to be acquired during FUS-mediated BBB opening. In both animal models, contrast enhanced T1-weighted MR images confirmed successful BBB opening using the theranostic transducer. Furthermore, initial comparison between the transcranial power cavitation maps and the contrast enhanced in the MR images align well, suggesting the cavitation maps can be used to localize BBB opening, in vivo.

In summary, this study demonstrated the feasibility of using a traditional diagnostic transducer for FUS-mediated BBB opening and cavitation monitoring. In the future, this technique may be used to further facilitate the transition of FUS-mediated BBB opening into the clinic.

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