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Session 1pBAb: Ultrasound Contrast Agents and Passive Cavitation Mapping of High Intensity Focused Ultrasound Lesion Formation  

1pBAb7. Transcranial spatial and temporal assessment of microbubble dynamics for brain therapies  
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Harnessing ultrasound/microbubble interactions in the brain may make possible a number of therapeutic ultrasound applications, such as targeted drug delivery, sonothrombolysis, and cavitation-enhanced ablation. However, methods to guide these emerging therapies are presently lacking. Here, we integrated a linear US imaging transducer with a clinical transcranial MRI-guided focused ultrasound (MRgFUS) system and evaluated passive cavitation imaging to monitor microbubble-enhanced sonifications. A nonhuman primate skull filled with brain-mimicking phantom was used for the experiments. First, we sonicated the phantom over a range of powers (20-60 W) to induce cavitation-enhanced heating. Using transcranial passive cavitation mapping and MR thermometry, we assessed the ability of the integrated system to simultaneously visualize temperature changes and microbubble activity. In another experiment, we traversed the phantom with a 2 mm channel through which microbubbles could flow and applied burst sonications (5 W) to generate stable and inertial cavitation. In the first experiment, cavitation activity and heating were colocalized. In the second, the location of the cavitation activity was coincident with the targeted location in the channel within the expected resolution of the passive imaging. We conclude that combined MR/ultrasound imaging can provide comprehensive guidance to simultaneously localize and quantify both acoustic cavitation activity and heating.

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Introduction

Therapeutic ultrasound harnesses viscous heating, acoustic cavitation or both for noninvasive treatments for cancer and other disorders. To selectively promote and sustain the desired effect and interaction, one typically selects an appropriate set of acoustic parameters (i.e. frequency, burst length, pulse repetition frequency) and then tunes the amplitude to achieve the desired temperature rise or level of cavitation activity and bioeffect. While one can generally know the acoustic pressure amplitude or intensity in vitro with high accuracy, it can be extremely challenging in vivo due to uncertainties in the acoustic, thermal, and vascular properties of the tissues along the ultrasound beam path. One also needs to ensure that the FUS beam is correctly localized and that unwanted effects do not occur at non-targeted regions. Therefore, to obtain safe and efficacious focused ultrasound (FUS) treatments and, more importantly, to enable their widespread clinical translation, precise spatiotemporal assessment of FUS-induced heating and/or cavitation during the treatment is critical.

Acoustic cavitation can be detected and monitored by recording the waves emitted by oscillating microbubbles (i.e. acoustic emissions) using piezoelectric transducers operated in passive mode (passive cavitation detector-PCD). The frequency content of the emissions recorded by the PCD is used to identify the onset of cavitation and characterize the type of oscillation. Strong harmonics, sub-harmonics and ultra-harmonics are generally associated with stable cavitation; broadband emissions signify the onset of inertial cavitation and micro-bubble collapse. Passive imaging methods that can map cavitation activity synchronously to the treatment have also been developed [References]. They have great potential for monitoring cavitation-based FUS therapies, as they do not interfere with the treatment [Gyongy and Coussios, 2010], they can be used to isolate the specific type of oscillation [Haworth et al., 2012], and they can potentially be more accurate than active imaging approaches when sonicating behind highly aberrating media such as the skull [O’Reilly et al., 2010], since the pressure wave only passes once through the aberrating media. Real-time mapping of cavitation activity holds great promise for translating acoustic cavitation induced therapeutic effects to clinical practice.

On the other hand, monitoring of FUS-induced heating has been achieved by the development of MR temperature imaging (MRTI) [Ishihara et al., 1995]. MRTI exploits the temperature sensitivity of the proton resonance frequency shift (about -0.01 ppm/°C) [Ishihara et al., 1995], allowing for accurate measurement of temperature rise. While MRTI has limitations (low spatiotemporal resolution, insensitivity in fat, for example), it has enabled the development of clinical MRI-guided FUS (MRgFUS) systems that are currently either approved or are being investigated for thermal ablation in numerous targets [Hynynen et al., 2001b, Martin et al., 2009, McDannold et al., 2010]. These systems also exploit MRJ’s superior tissue contrast and ability to image in any orientation, which is useful for treatment planning and post-FUS evaluation of the treatment outcome. The information provided by US and MR imaging is complementary and combining the two modalities can enhance our ability to plan, monitor, and validate the outcome of FUS based therapies. The combined capabilities of such a system may also lead to the development and validation of new procedures and therapeutic strategies.

The aim of the present study was to integrate passive cavitation mapping with a clinical MRgFUS system designed for transcranial thermal ablation. We tested it during sonications with parameters utilized for two cavitation-based approaches that have been investigated for use in the brain: cavitation-enhanced thermal ablation [Holt and Roy, 2001, Sokka et al., 2003, Arvanitis and McDannold, 2011] and microbubble-enhanced drug delivery [Hynynen et al., 2001a]. First, the ability of the system to simultaneously map heating and cavitation activity was explored in an ex vivo nonhuman primate skull filled with a tissue-mimicking gel. Next, we assessed the ability of the system to map microbubble activity during low-power, burst sonications with a microbubble agent flowing through a vessel-mimicking channel that traversed the phantom that filled the skull. The hybrid system (US&MRgFUS) was used to plan, monitor, and assess the sonications. The research US imaging engine was programmed to operate in passive mode, collect the ultrasound RF data from the US array elements synchronously, determine and display their power spectrum in real time, and perform cavitation mapping offline. Prior to the sonications, images of MR fiducial markers that were also clearly visible in B-mode US imaging were collected and used to determine the transformation matrix in order to register the images from the two modalities [Arvanitis and McDannold, 2011].

Materials and Methods

Apparatus for Multi-Parametric US and MR Imaging

The experimental apparatus was comprised of a clinical prototype transcranial MRgFUS system (ExAblate 4000, InSightec, Haifa, Israel), a linear US array that was connected to a research US imaging engine (Versasonics Inc, Redmond, WA, USA) through the MR penetration panel, and an ex vivo nonhuman primate skull filled with brain tissue-mimicking gel that was placed at the geometrical focus of the FUS (Fig.1).
C. Arvanitis and N. McDannold

**Experimental procedures**

Sonications were performed in an *ex vivo* macaque skull filled with brain tissue-mimicking gel. The recipe for the gel was proprietary and was provided by the vendor of the MRgFUS system (see McDannold 2010 IEEE UFFC for more details). The skull was suspended so that the center of the skull cavity was within the FUS focal region (Fig. 1). The focal point was steered to different locations electronically using software written in Matlab (Mathworks, Natick, MA, USA). Passive cavitation maps were reconstructed using an algorithm described previously [Gyongy and Coussios, 2010].

Data collection was synchronized in two different ways. For cavitation-enhanced heating, continuous wave sonications were employed, and acquisition of the US images was triggered by the MR system during its RF excitations. For these experiments, 40 180 μs RF waveforms were captured by the US imaging engine at a 5 Hz frame rate during each sonication. The data were filtered with a 0.9 MHz high-pass Butterworth filter (Mathworks, Natick, MA, USA) in order to reduce signals at the fundamental frequency (220 kHz) and from nonlinear propagation of the transmitted FUS beam. To avoid interference between MRI and US imaging, a 5 ms delay was added to the trigger so the acoustic emissions were recorded when the MR gradients were inactive. When the MRgFUS system operated in burst mode (2nd set of experiments), an arbitrary waveform generator (33220A, Agilent Technologies, USA) was used to trigger the passive cavitation mapping acquisition [Arvanitis et al., 2012] and to gate the MRgFUS system. A 180 μs RF waveform was captured at the beginning of every 10 ms burst with pulse repetition frequency of 1 Hz; no MR imaging was performed during sonication in these experiments.

For tests with low-power burst sonications and an ultrasound contrast agent, the phantom was traversed by a vessel-mimicking channel (Fig. 1) through which we could inject the microbubble agent. The sonications consisted of 10 ms bursts applied at a pulse repetition frequency of 1 Hz for 40 sec, similar to what is generally used for FUS-induced blood-brain barrier disruption [1]. Targets that included this channel were selected in the frequency encoding direction that were evident in the experiments. These distortions are caused by magnetic field inhomogeneities and occur regularly with the MRTI parameters used here with this MRgFUS system; they were not due to the introduction of the passive imaging system.
the axial MRI plane that was aligned with the ultrasound imaging plane. Each sonication was performed after the ultrasound contrast agent Definity (Lantheus Medical Imaging) was injected into the channel. The acoustic power level ranged from 3-5 W, which yielded an estimated pressure amplitude in the brain 380-500 kPa (Table 2) [Arvanitis et al., 2012]. Cavitation maps were normalized to maps obtained during sonication with identical parameters with the channel filled with saline. In this range, stable and inertial cavitation could be instigated. After the experiments, we investigated if the location of the maximum activity within the cavitation maps was colocalized with the position of vessel mimicking channel in MRI.

**TABLE 1.** The experimental conditions used in the two experiments

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Phantom</th>
<th>Power (W)</th>
<th>Pressure (kPa-PNP)</th>
<th>USCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1</td>
<td>Skull/brain-mimicking gel</td>
<td>20-60</td>
<td>990 - 1700</td>
<td>No</td>
</tr>
<tr>
<td>Experiment 2</td>
<td>Skull/brain-mimicking gel/vessel- mimicking channel</td>
<td>3-5</td>
<td>380 - 500</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Results**

**Cavitation Enhanced Ablation**

The introduction of the ultrasound imaging probe for passive cavitation mapping into the MRgFUS system, along with a brass reflector to direct the imaging plane into the head, did not significantly affect the ability of the MRgFUS device to sonicate a given target. Despite the fact that this reflector blocked a small portion of the FUS beam, the size and shape of the heating profile in MRTI was not appreciably different with it in place. We sonicated the brain-mimicking gel inside the *ex vivo* monkey skull at 3 locations at increasing power levels until broadband emission was detected, an indication that the cavitation threshold was reached. During the sonications we simultaneously collected data from the two modalities and successfully formed cavitation and temperature maps (Fig. 2A). Good colocalization of cavitation activity and temperature rise was observed, suggesting that skull-induced aberration of the diverging pressure wave emitted by the microbubbles was minor through the monkey skull. Due to differences in resolution in axial and transverse directions of the array the region with the apparent cavitation activity appeared elongated in the axial direction. The signal strength in the cavitation maps in these experiments was 40 dB or higher compared to signal in the absence of cavitation activity. When inertial cavitation activity was not detected, the temperature rise at the focus was less than about 10°C; a significant temperature increase was observed when broadband emissions were present (Fig 2B). Similar results were observed at the other targets. However, in addition to cavitation activity at the focus, we also observed activity originating from the previous target, probably due microbubbles that had not been resolved and the hemispherical geometry of the FUS. However, heating was observed only at the targeted location.

**FIGURE 2.** Simultaneous cavitation and temperature mapping acquired during transcranial sonication in a phantom-filled macaque skull. (A) A temperature map, a cavitation map, and fusion of the two for a sonication in an *ex-vivo* non-human primate skull. (B) The temperature rise at the target and the respective averaged noise power spectrum (NPS).

**Microbubbles in a vessel-mimicking channel**

We found that it was possible to map cavitation activity through the macaque skull during low-power burst sonications with an ultrasound contrast agent. At the power levels used (3-5W), sonication in the phantom material without the microbubble agent produced little or no cavitation activity. When the microbubble agent was introduced, pronounced cavitation activity was observed. Pronounced signals at multiple harmonics and ultraharmonics of the FUS device were observed, along with broadband emissions. Overall, 40 passive cavitation maps were obtained during each sonication. In every case, localized activity was evident. Fusion of the cavitation maps with pre-sonication MRI (Fig. 3) showed good colocalization of the microbubble activity (white circle) to the targeted area (black circle). The peak cavitation activity overlapped in the axial direction with the location of the vessel mimicking channel. There was a slight mismatch in the transverse direction. The average spectral content of the emissions are also shown in Fig. 3. The spectrum from each US RF data obtained by the US imaging probe (180µs long) was displayed in real-time on the computer that was used to control the US research engine.
FIGURE 3. Evaluation of the colocalization of the cavitation activity and the resulting BBB disruption. (A) Fusion of cavitation activity with a treatment planning image showing the channel that was filled with ultrasound contrast agent. The region where the average signal in the cavitation maps was within 5% of the maximum activity is shown in red. The location of this activity overlapped with the position of the channel. The corresponding power spectrum for this sonications is shown on the right.

Discussion and Conclusions

The ability to localize and characterize cavitation activity is promising for advancing microbubble-enhanced procedures such as blood-brain barrier disruption, microbubble-enhanced ablation, and sonothrombolysis. If they are to reach clinical use, methods need to be established to monitor and control the sonications. Such control is critical in the brain, where mistargeting or overexposure could result in serious side effects. Here we showed that it is possible to perform passive cavitation activity within the MRI environment. Furthermore, we were able to integrate the imaging array into a clinical prototype MRgFUS system developed for brain applications, a challenging environment due to the geometry of the transducer and the need to image transcranially. We demonstrated that localization of cavitation activity can be achieved transcranially using an ex vivo nonhuman primate skull. Further work is needed to assess different therapeutic protocols, to test the method in vivo, to optimize the imaging system, and to investigate whether transcranial imaging can be achieved through the thicker human skull. By combining MR and US imaging, a comprehensive method to guide the broad range of thermal and cavitation-based therapies that are possible with FUS is enabled.

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References


