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Session 2aBA: Bubbles Bubbles Everywhere I

2aBA7. The use of twinkling artifact of Doppler imaging to monitor cavitation in tissue during high intensity focused ultrasound therapy

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In high intensity focused ultrasound (HIFU) therapy, it is important to monitor the presence and activity of microbubbles in tissue during treatment. The current methods, - passive cavitation detection (PCD) and B-mode imaging - have limited sensitivity, especially to small-size, non-violently-collapsing microbubbles. Here, a new method for microbubble detection is proposed, based on "twinkling" artifact (TA) of Doppler imaging. TA occurs when Color Doppler ultrasound is used to image hard objects in tissue (e.g., kidney stones), and is displayed as brightly colored spots. As demonstrated recently, TA can be explained by irregular scattering of the Doppler ensemble pulses from the fluctuating microbubbles trapped in crevices of the kidney stone. In this work, TA was used to detect cavitation in tissue and in polyacrylamide gel phantoms during pulsed 1 MHz HIFU exposures with different peak negative pressures (1.5-11 MPa). At each pressure level, the probability of cavitation occurrence was characterized using TA and the broadband signals recorded by PCD, aligned confocally with the HIFU transducer. The results indicate that TA is more sensitive to the onset of cavitation than conventional PCD detection, and allows for accurate spatial localization of the bubbles. Work supported by RFBR and NIH (EB007643, 1K01EB015745, R01CA154451).

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INTRODUCTION

In many modern applications of ultrasound in medicine it is important to know whether microbubbles are present in tissue that is exposed to ultrasound. Those bubbles can be preexisting, artificially introduced for a specific application (*e.g.*, ultrasound contrast agents), or initiated by intense ultrasound. If the bubbles are present in the region of interest of tissue, they could strongly affect ultrasound imaging or therapy, because they are efficient acoustic scatterers, and can also behave violently, oscillating and collapsing and thus creating significant bioeffects in tissue. In particular, pulsed high intensity focused ultrasound (HIFU) exposures designed to promote the cavitation effects while minimizing the thermal effects, have been extensively used to enhance drug/gene delivery to tumors with and without the assistance of microbubbles.[1-3] However, although cavitation can be beneficial, it may cause undesired tissue damage if it is out of control.

Passive cavitation detection (PCD) is considered to be the most reliable, cost-effective and sensitive means of real-time cavitation detection method.[4] In that method, broadband emissions resulting from bubble collapses, are detected by a single-element focused hydrophone, aligned confocally with the HIFU transducer. However, this technique does not allow one to monitor the spatial distribution of the bubbles. Recently, a passive method for monitoring cavitation emissions with multi-element ultrasound arrays has been proposed.[5] However, the image reconstruction technique requires a large aperture transducer in order to achieve the reasonable image quality. Another widespread way of cavitation detection is B-mode imaging.[6] However, this method has limited sensitivity, especially to small-size and non-violently-collapsing microbubbles.

Here, we propose to use a so-called Twinkling Artifact (TA) of Doppler imaging for cavitation detection during HIFU treatment. The TA occurs when one uses Color Doppler ultrasound, which is usually employed to display moving blood, to image a kidney stone. The artifact appears in the images of calcifications in soft tissue, kidney stones or other hard concretions, and edges of the medical instruments. The TA is displayed as brightly colored spots on a black-and-white background of imaging area of tissue. The mechanism for the appearance of the TA during Doppler imaging of kidney stones was recently investigated.[7] It was demonstrated that strong evidence exists that irregular scattering of the Doppler ensemble pulses from the submicron-size fluctuating microbubbles, that are often trapped in cracks and crevices on solid objects, gives rise to the TA. Therefore, the TA can be used not only to detect hard concretions in tissue, but also to visualize bubbles that exist or appear in the bulk of soft tissue. Because the Doppler imaging is designed to detect scattering from weak scatterers (*viz*, red blood cells), it is likely to be very sensitive to the presence of small-size bubbles.

MATERIALS AND METHODS

A customized pre-clinical system VIFU-2000 (Alpinion US Inc, Kirkland, WA), was used for the pulsed HIFU exposures of polyacrylamide gel phantoms and *ex-vivo* bovine liver. The exposures were performed in a tank filled with degassed water. As shown in Fig.1a, the system included a 1.1-MHz HIFU transducer (64 mm aperture and radius of curvature) with a central circular opening of 38 mm in diameter. The transducer was powered by a computer-controlled combination of a power amplifier and a function generator. Before the experiments, the focal pressures produced by the transducer at different power levels were characterized by a fiber optic probe hydrophone (FOPH 2000; RP Acoustics, Leutenbach, Germany) in water. The peak negative pressures used in the studies were 4.6 MPa for the gel phantom and 11 MPa for the *ex-vivo* bovine liver samples. These pressure levels were chosen so that the probability of cavitation occurrence was over 50%, according to the preliminary measurements. A focused ring PCD (outer diameter 38 mm, inner diameter 33 mm), made of 70 μm PVDF film was built into the central opening of the HIFU transducer and positioned confocally with it. The signals received by the PCD were increased by 20 dB with an amplifier (Panametrics PR5072, Waltham, MA, USA) and then recorded by a digital oscilloscope at the sampling frequency of 50 MHz. The bandwidth of the PCD at –6 dB level was 2.3 – 8.8 MHz. The gel phantoms containing 7% bovine serum albumin and *ex-vivo* tissue samples were sized to fit the sample holder, which was attached to a 3D positioning system.

For ultrasound imaging of the HIFU exposures, the Verasonics Ultrasound Engine (VUE, Verasonics, Redmond, WA) was used, with a clinical probe ATL/Philips HDI L7-4 (Bothell, WA). The probe was aligned with the axis of the HIFU transducer as shown in Fig.1. The imaging was performed in “flash” transmitting mode when all the array elements were excited simultaneously to emit a quasi-plane wave in the direction orthogonal to the radiating surface (zero degrees incident angle). Both B mode and Doppler mode were employed. In the Doppler mode the array elements were excited by a series of 14 identical pulses emitted with a pulse repetition frequency (PRF) of 30 kHz.

The imaging system was triggered by the trailing edge of the HIFU pulse to acquire one Doppler image and one B-mode image. This triggering approach allowed to avoid the saturation of the receive channels by scattered HIFU waves. As in conventional ultrasound imagers, the scattered acoustic signals were received by the same array, digitized and then processed in MatLab by the VUE software.

For HIFU exposures, the samples were positioned so that the HIFU focus was 15 mm below the tissue surface. A series of twenty 100-microsecond pulses with 1 Hz PRF were delivered, and the PCD signals and ultrasound images were acquired for each pulse. The PCD signals were then filtered in the frequency domain using a combination of a notch filter (MATLAB function *lirnotch*, notch width 100 kHz), to filter out the harmonics of the HIFU wave, and a band-pass filter with 2.3-8.8 MHz band (MATLAB function *fir1*). The resulting signal, representing the broadband noise emitted by the collapsing bubbles, was then integrated in the frequency domain and used as a metric to quantify the cavitation activity and to verify the TA method.

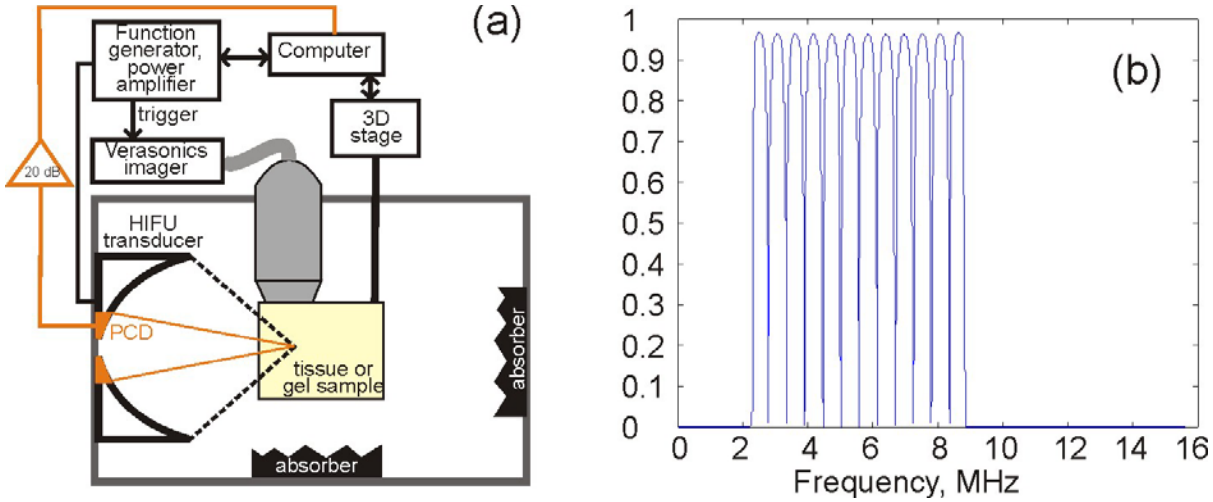

FIGURE 1. (a) Schematic illustration of the experimental setup. (b) The combination of the band-pass and notch filters applied to the PCD signals in the frequency domain.

RESULTS

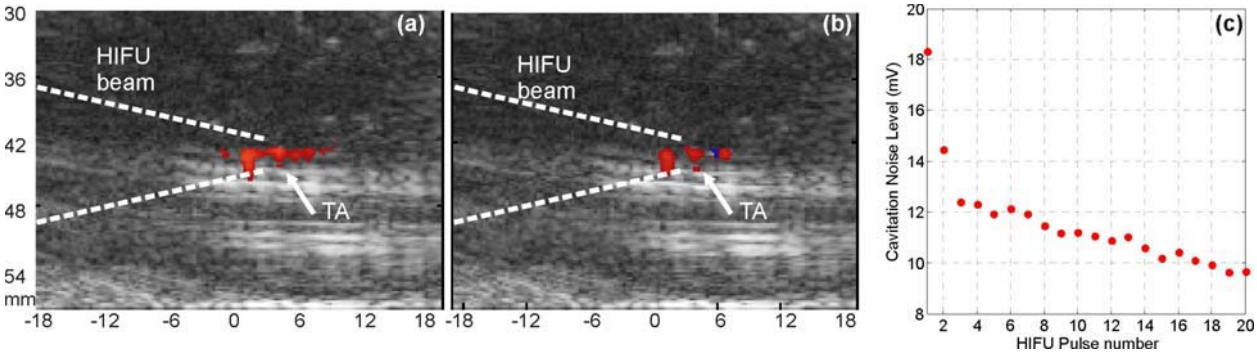

FIGURE 2. Ultrasound images (Doppler and B-mode) acquired during a single 20-pulse HIFU exposure of a polyacrylamide gel phantom after the 1st HIFU pulse (a) and after the 11th HIFU pulse (b). Cavitation noise level detected by the PCD during the exposure (c). Over the course of the exposure, the cavitation activity declined, and so did the brightness and the size of the TA. Note, that the brightness of the B-mode image did not change.

Figure 2 (a) and (b) shows an example of the two ultrasound images acquired after 1st and 11th HIFU pulses of a 20-pulse exposure of the polyacrylamide gel phantom. Cavitation was present in the focal region throughout the exposure, but according to the amplitude of the signal received by the PCD (Fig.2c), cavitation activity gradually

declined over the course of the exposure, and so did the brightness and area of the TA. This effect of cavitation decline over the course of the pulsed HIFU exposure is often observed in gels and some *ex-vivo* tissues.[8]

Similar results were obtained with the *ex-vivo* liver samples.

DISCUSSION AND CONCLUSIONS

The preliminary results presented here indicate that the TA is a more sensitive technique for bubble detection than B-mode ultrasound. The intensity of the TA, at least qualitatively, corresponds well to the readings of the PCD. The location of the cavitation bubbles within the imaging plane of the ultrasound probe can also be determined using the TA. In order to optimize this method of cavitation detection and make it quantitative, the raw signals received by the imaging probe should be analyzed and processed, which will be done in our future work.

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