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An All-Ultrasound-Based System for Real-Time Monitoring and Sonication of Temperature Change and Ablation

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Abstract— **Previously, we introduced a new Harmonic Motion Imaging (HMI) technique for simultaneous monitoring and generation of ultrasound therapy treatment using a single element focused-ultrasound and one pulse-echo transducer. The new HMI technique uses an amplitude-modulated beam (instead of using two beams) that has a stable focal zone for the applied harmonic radiation force. The harmonic radiation force was generated by a 4.68 MHz focused transducer and a 7.5 MHz pulse-echo transducer was used to acquire RF echoes. The RF echoes were recorded and used to estimate tissue displacements during sonication. The new HMI technique has been shown to provide tissue displacement information during ultrasound therapy. In this paper, a study on the temperature dependence of the new HMI method is presented. The sonication time used applied was approximately equal to 80 seconds at maximum acoustic intensity of 658 W/cm^2 at the focus. The experiments were performed on bovine tissues *in vitro*. The results show that the temperature elevation at the focal zone during sonication rises rapidly until it reaches a temperature higher than 50^{o}C, which produces tissue damage. The new HMI technique provides temperature-related tissue displacement changes using the same transducer, which makes it simple for monitoring temperature rise and lesions formation during High Intensity Focused Ultrasound (HIFU) treatment.**

I. INTRODUCTION

Over the past 50 years, researchers have investigated the potential of High Intensity Focused Ultrasound (HIFU) for non-invasive or minimally invasive modalities for cancer treatment. HIFU produces an acoustic wave that propagates through tissue and deposits a high acoustic energy only at the localized focus of the transducer. The focal spot size is approximately 1 to 3 mm^3. High acoustic energy at the localized focus can cause temperature elevation that is sufficient to initiate coagulation necrosis in tissue (lesions), while the surrounding tissues remain unheated. The ability of HIFU to cause irreversible cell damage in tissues has received attention from researchers as a potential technique for non-invasive cancer treatment.

In 1942, Lynn et al. introduced the first application of HIFU for local modification of brain functioning in five live animals, three cats and two dogs [1]. Fry et al. (1950) continued the development of the HIFU application, where they produced lesions deep in the brain tissue of cats and monkeys [2,3]. Research on HIFU applications in neurosurgery continued during the 1950s and 1960s, but practical and technological limitations restricted their progress [4].

The application of HIFU was introduced for cancer treatment in 1956 [5,6], and since then, the effects on ultrasound tissue during HIFU treatment has continued to be investigated into the present [4,7-11].

In HIFU treatments, focused ultrasound induces a high acoustic intensity at a localized focus for a short time while the temperature at the focus rises significantly and reaches a thermal dose that causes local irreversible cell damage (coagulation necrosis). The key limitations of HIFU treatment are the difficulty in monitoring change of temperature and tissue mechanical properties, and the lack of ability to optimally stop HIFU upon lesion formation.

Harmonic Motion Imaging (HMI) is a radiation-force-based technique that induces oscillatory displacements in the focal zone of a focused transducer for the detection of localized stiffness changes [12]. We recently introduced a new HMI method that produced the harmonic radiation force locally by a single focused ultrasound element using an amplitude-modulated (AM) signal [13,14]. An AM beam offered the advantage of a sustained application of the radiation force at a constant stable focus within the tissue region *and* a simpler transducer design. The new HMI technique could potentially be used for real-time monitoring of the mechanical properties of tissues during HIFU treatment [13,14]. One major advantage of this technique is that the tissue displacements are measured during the application of the acoustic radiation force and HIFU ablation.

The purpose of this study was to investigate the temperature effects during heating and tissue ablation using the new HMI technique. The preliminary results were completed in bovine tissues *in vitro*.

II. NON AMPLITUDE-MODULATED AND AMPLITUDE-MODULATED TECHNIQUE

A. METHOD

A 4.68 MHz focused transducer (Riverside Research Institute, New York, NY, USA) generated the acoustic radiation force using a low-frequency amplitude-modulated RF signal. The intensity at the focus was equal to 658 W/cm^2. The experimental setup is shown in (Fig 1). A

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function generator (Agilent (HP) 33120A, Palo Alto, CA, USA) was used to produce the RF signal at 4.68 MHz. The amplitude of the RF signal was then modulated using a second function generator (Agilent 33220A) that generated a low frequency modulation at 50 Hz.

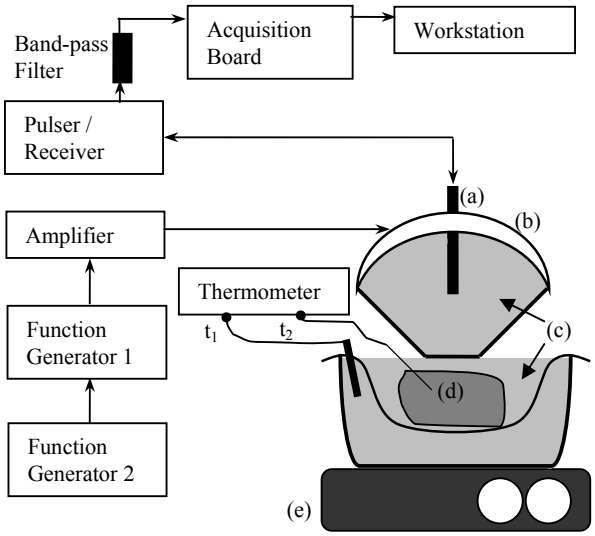

Fig 1. Experiment setup. (a) Pulse-echo transducer, (b) HIFU transducer, (c) Degassed water, (d) Tissue *in vitro*, (e) Hot plate, and t_1 measures degassed water temperature, t_2 measures tissue temperature

The real-time monitoring was driven by two different input signals. The first generated a 2-second sonication time using a continuous wave (Fig 2(a)), and this was immediately followed by a 100-millisecond amplitude-modulated RF signal to estimate tissue displacements (Fig 2(b)). The continuous wave and amplitude-modulated RF signals were adjusted to have the same level of acoustic intensity at the focus. This sequence was repeated until the total sonication time was equal to approximately 80 sec with an acoustic intensity of 658 W/cm^2 at the focus. Therefore, 40 cycles of what is shown in figure 2 were used.

A pulse-echo transducer (Panametrics, Waltham, MA, USA) with a center frequency of 7.5 MHz was placed in the center of the focused transducer so that the beams of the two transducers were properly aligned. A pulser/receiver (Panametrics 5051PR, Waltham, MA, USA) was used to acquire consecutive filtered RF signals at a Pulse Repetition Frequency (PRF) of 6.5 kHz. A bandpass analog filter (Reactel, Inc., Gaithersburg, Maryland, USA) with cutoff frequencies of fc_1 = 5.84 MHz and fc_2 = 8.66 MHz was used to filter out the FUS spectrum. An acquisition board (CS14200, Gage Applied Technologies, Lachine, Canada) was used to capture the filtered RF data with a sampling frequency of 80 MHz.

A type T thermocouple (MT-29, Physitemp Instruments, Inc., Clifton, New Jersey, USA) with a diameter of 0.33 mm was inserted into tissue *in vitro* close to the focus area to monitor temperature changes during sonication. The thermometer (HH506A, Omega Engineering, Stamford, CT, USA) recorded the temperature every second before, during, and after sonication. A hot plate was positioned underneath the glass beaker and a magnetic stirrer was placed on the side to maintain a homogeneous temperature of 37^{o}C throughout the entire tissue specimen to simulate human body temperature.

The time-shift occurring between two successively acquired Radio-Frequency (RF) images was calculated using a speckle tracking technique: a one-dimensional cross-correlation was performed along the ultrasound beam axis with a small data window of 1.2 mm and 85% overlap.

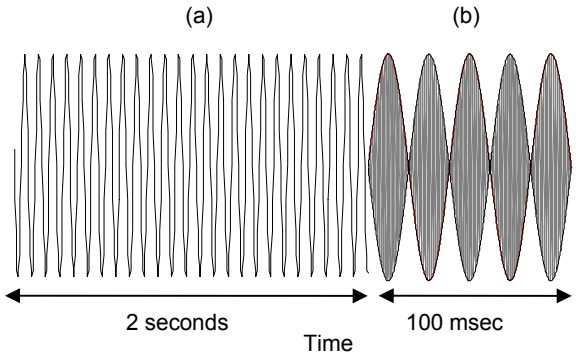

Fig 2. One cycle of the real-time monitoring method used in the tissue *in vitro* experiment. (a) Continuous wave at f=4.68 MHz for 2-sec, (b) Amplitude-modulated frequency at f= 50 Hz for 100-milliseconds. Sequence (a) denotes the sonication period and sequence (b) denotes the imaging period. Both of the sequences are repeated for the entire sonication time.

B. RESULTS

Figure 3 shows the tissue displacement image during 80 seconds of sonication in the middle of the tissue specimen (Fig 1(d)). The tissue displacement amplitude increases during lesion formation, while the surrounding tissue displacement amplitudes remain invariable.

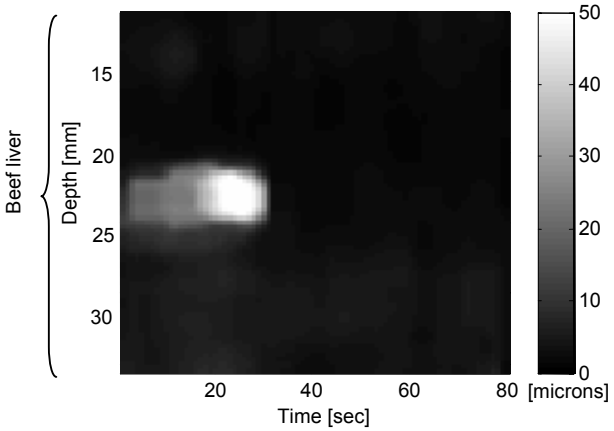

Fig 3. Real-time monitoring results in the tissue *in vitro* during 80 sec sonication. HMI displacement amplitudes at the focus with a depth equal to 22 mm.

The focus was located at a depth equal to 22 mm. The temperature during sonication rose from 34°C up to 55.2°C, causing irreversible cell damage in the tissue. In the figure 4, the values (-x-) are the estimated tissue displacement in the focal region with average standard deviation (SD) is 1.6% and the values (-●-) are the estimated tissue displacement in the surrounding tissue with SD is 0.14%. There was a sudden decrease in tissue displacement above 40°C that suggests that the tissue became stiffer (lesion) (Fig 4). Moreover, steady increase of displacement amplitudes indicated that tissue softening occurred during the experiment. Figure 5 shows a picture of the lesion induced at the end of one of the experiments.

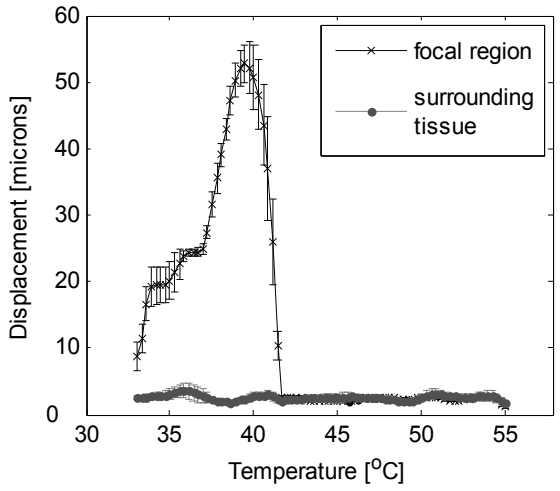

Fig 4. Tissue displacement plotted against temperature during sonication.

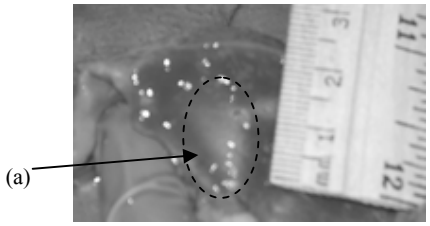

Fig 5. Photograph of beef liver after 80 seconds sonication. (a) shows lesion.

III. AMPLITUDE-MODULATED HMI TECHNIQUE

A. METHOD

In the amplitude-modulated HMI technique, we used the same HIFU transducer, to generate amplitude-modulated RF signal for the entire sonication time (Fig. 6). In this technique, we decreased the sonication time to approximately 20 sec and maintained the acoustic intensity equal to 658 W/cm² at the focus. The advantage of using uniform amplitude modulated RF signal during the entire sonication time is that we can follow the speed of sound changes due to heating during HIFU therapy. The speed of sound changes is simply indicated by the echoes shift in tissue displacement. Therefore, by measuring the shift of the displacement, the temperature from a region of interest can be predicted.

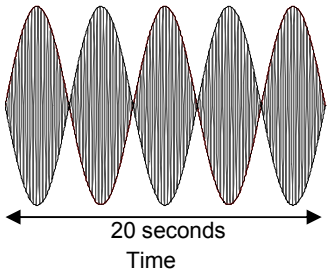

Fig 6. The real-time monitoring method a in the tissue *in vitro* experiment using Amplitude Modulated RF signal for the entire sonication time.

B. RESULTS

Figure 7 shows the tissue displacement image during 20 seconds of sonication. The tissue displacement amplitudes increase during lesion formation, while the surrounding tissues remain constant.

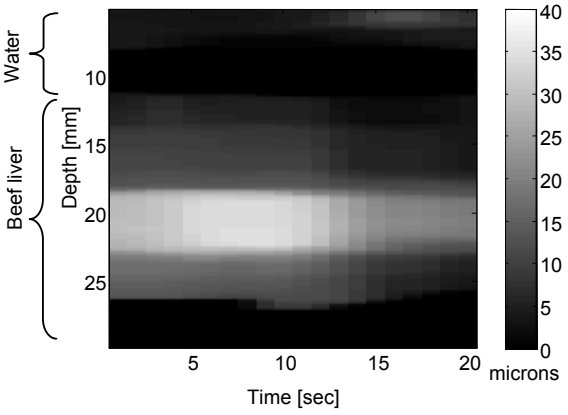

Fig 7. Real-time monitoring results using amplitude modulated HMI technique in the liver during 20 sec sonication. HMI displacement amplitudes at the focus with a depth equal to 22 mm.

In this experiment, the temperature during sonication rose from 36°C up to 47°C, produces protein-denatured lesion in the tissue. The average standard deviation (SD) of the estimated tissue displacement in the focal region and in the surrounding tissue are 0.17%(-*-) and 0.05% (-◊-) respectively (Fig. 8). A decrease in tissue displacement above 40°C indicates lesion formation (Fig 8).

The tissue displacements at the focus in figure 4 reach the same level as those of surrounding tissue, but the tissue

displacements in figure 8 do not, because of the shorter sonication time.

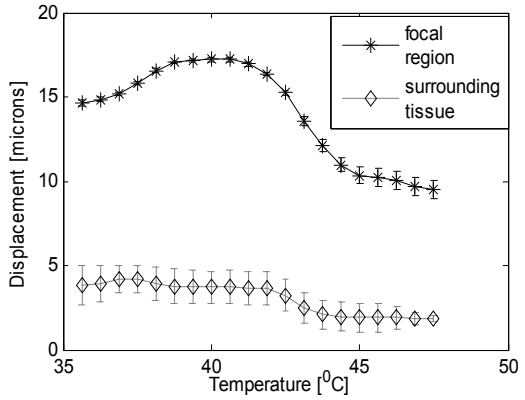

Fig 8. Tissue displacement plotted against temperature during sonication using amplitude modulated HMI technique.

IV. SUMMARY

In this study, we present tissue displacement variations due to temperature elevation during HIFU ablation. Figure 3 and figure 7 suggest that we could potentially observe the occurrence of protein-denatured lesion due to large changes in tissue displacement amplitudes. Tissue displacement rapidly decreases to approximately 3 microns, after 30 seconds sonication, indicate lesion formation (Fig. 4). Similarly, in the amplitude modulated HMI technique, tissue displacements increase and then decrease because of changes in tissue properties (lesion) within a shorter sonication time (Fig. 8). The separately-acquired temperature and tissue displacement variations show a linear relationship during heating and prior to lesion formation (Fig. 4, 7), and thus by monitoring the temperature changes, physicians can predict the tissue thermal changes during hyperthermia. These results are comparable with the MR elastography technique (MRE), where the displacements increase up to 55 microns in the beginning of tissue ablation, then decrease to 15 microns during cooling [15]. The new HMI method has simpler design, low-cost and portable device. Moreover, this presented technique is able to accurately monitor when the protein-denatured lesions will form, although there are several frequency-dependent factors that also determine lesion rate, such as: sonication time, maximum acoustic power, attenuation, tissue absorption, etc.. Further investigation needs to be performed in order to consider these factors, especially the exposure time and acoustic power intensity to control the size of lesion.

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