Abstract— Over the past years, researchers have investigated the potential of focused ultrasound surgery for non-invasive or minimally invasive modalities for cancer treatment. Focus ultrasound (FUS) transducer induces a high acoustic intensity at the localized focus for a short time period 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 FUS surgery are the difficulty of monitoring temperature and tissue mechanical properties as well as potential requirement of interrupting the FUS exposure during surgery. Amplitude-modulated Harmonic Motion Imaging (AM-HMI) technique for simultaneous monitoring and generation of ultrasound surgery using a single-element FUS transducer was formerly introduced [1]. The uniqueness of this technique is that the focused transducer is driven by a low AM wave with high modulation index. This produces a stable harmonic radiation force oscillating at a low modulation frequency (25 Hz). This paper presents the effect of thermal ablation using the AM-HMI technique in in vitro bovine liver. The temperature and RF echoes were recorded during FUS ablation. The tissue displacement was estimated using a speckle tracking technique based on the one-dimensional cross-correlation to estimate the resulting axial tissue displacement. The temperature elevation at the focal zone throughout sonication was over 50°C that produced tissue damage. During FUS ablation, the temperature rose significantly while the tissue stiffness decreased resulting in higher tissue displacements. The results show a linear relationship between the temperature and tissue displacements during lesion formation (<53°C). The AM-HMI technique was able to accurately detect the protein-denatured lesion according to variation in the tissue displacement. In this conclusion, the technique could be potentially used for real-time monitoring of the temperature and mechanical properties of tissues during FUS surgery.

Keywords: Displacement, FUS, Harmonic Motion Imaging, HIFU, Noninvasive measurement, Oscillatory, Radiation force.

I. INTRODUCTION

Over the past 60 years, researchers have investigated the potential of focused ultrasound (FUS) for non-invasive or minimally invasive modalities for cancer treatment. FUS 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 mm³. There is no heating along the beam path. High acoustic energy at the localized focus can cause temperature elevation that is sufficient to initiate coagulation necrosis in tissue (thermal lesions), while the surrounding tissues remain unheated. The ability of FUS 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 FUS for local modification of brain functioning in five live animals, three cats and two dogs [2]. Fry et al. (1950) continued the development of the FUS application, where they produced lesions deep in the brain tissue of cats and monkeys [3, 4]. Research on FUS applications in neurosurgery continued during the 1950s and 1960s, but practical and technological limitations restricted their progress [5]. The application of FUS was introduced for cancer treatment in 1956 [6, 7], and since then, the effects on ultrasound in tissue during FUS surgery has continued to be investigated into the present [5, 8-12].

In FUS surgery, 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. The limitations of FUS surgery are the difficulty in monitoring the change of temperature and tissue mechanical properties, and the lack of ability to optimally stop FUS upon lesion formation.

Harmonic Motion Imaging (HMI) is a radiation-force-based technique that induces oscillatory displacements in the focal zone of a FUS transducer for the detection of localized stiffness changes [13]. We recently introduced AM-HMI method that produced the harmonic radiation force locally by a single element FUS transducer using an amplitude-modulated (AM) wave [1]. 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 [1]. The presented technique could potentially be used for real-time monitoring of the mechanical properties of tissues during FUS surgery. One major advantage of this technique is that the tissue displacements are measured during the application of the acoustic radiation force and FUS ablation. The purpose of this study was to investigate the temperature effects during FUS ablation in in vitro tissue using the AM-HMI technique. The preliminary results were completed in four in vitro bovine liver specimens with three different locations for each liver i.e. twelve locations total.
Sample preparations
Sample tissue (i.e. *in vitro* bovine liver) was degassed in Phosphate Buffered Saline (PBS) solution for 30 minutes prior to the experiment. The specimen was then placed into a glass beaker and submerged in a PBS solution. 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°C throughout the entire tissue specimen to simulate human body temperature.

Experimental setup
A 4.68 MHz FUS transducer (Riverside Research Institute, New York, NY, USA) was used to generate the acoustic radiation force using a low-frequency amplitude-modulated RF signal. The acoustic intensities at the focus were 1086 W/cm² during FUS ablation and 231 W/cm² before and after FUS ablation. For this study, a continuous AM wave was applied for FUS ablation and a burst of AM signal was applied before and after FUS ablation (Fig. 1) in order to estimate displacement without significant temperature rise. The advantage of calculating displacements during FUS ablation was that the resulting tissue displacements could indicate when the thermal lesion was formed. By examining amplitude displacements before and after FUS ablation, one can study tissue stiffness after FUS ablation. The AM wave generated a lower acoustic intensity (Iave) compared with conventional sinusoidal wave [14]

\[ I_{ave} = \frac{1}{\pi} \int_{0}^{\lambda_0} p^2 dz = k \frac{2\pi}{\lambda_0} \frac{Z_p^2}{Z} \left( \cos^2(2\pi f_1 - kZ) \cos^2(2\pi f_2 - kZ) \right) = \frac{\lambda_0^2}{2\pi} \frac{Z_p^2}{Z} \left( \cos^2(2\pi f_1 - kZ) \cos^2(2\pi f_2 - kZ) \right) \]

and therefore a longer FUS ablation time is required. In this experiment, the FUS ablation time was approximately equal to 45 sec. The experimental setup was shown in (Fig 2). A 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, Palo Alto, CA, USA) that generated a low frequency modulation at 25 Hz and burst of 30 cycles/duty cycle of 25%.

The advantage of using uniform amplitude-modulated RF signal during the entire FUS ablation was that the speed of sound changes can be followed. The speed of sound changes is simply indicated by the echoes shift in tissue displacements (Fig 3(b)).

A pulse-echo transducer (Panametrics, Waltham, MA, USA) with a center frequency of 7.5 MHz and a diameter of 12 mm was placed in the center of the FUS transducer hence 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 5.4 kHz. A bandpass analog filter (Reactel, Inc., Gaithersburg, Maryland, USA) with cutoff frequencies of fc1 = 5.84 MHz and fc2 = 8.66 MHz was used to filter out the high focused beam.

A silicone rubber/absorber (McMaster-Car, Dayton, NJ, USA) was placed beneath the specimen to further reduce the specular reflection from the bottom of the glass container. An acquisition board (CS14200, Gage Applied Technologies, Lachine, Canada) was used to capture the filtered RF data with a sampling frequency of 80 MHz.

Data processing
In this method, M-mode frames were acquired before, during and after FUS ablation. Each M-mode frame had period of 111 msec, where \( \tau = \frac{N}{PRF} \), with N is number of RF lines (N=600) and PRF of 5.4 kHz.

The resulting axial tissue displacement was estimated using one-dimensional cross-correlation consecutive RF lines for each collected M-mode frame with a data window equal to 0.47 mm. The window overlap equaled to 90%. The resulting axial displacement from each M-mode frame consisted of superposition and shifted echoes of the tissue response (Fig 3(b)). The echo shift appeared because of speed of sound variation in tissue due to temperature change.

The Fourier transform of the RF input signal (Fig. 4(a)) and the resulting displacement (Fig. 4(b)) represent the frequency dependence associated with scattering tissue reflection.

\[ \text{Fig 1. The real-time monitoring method in the tissue *in vitro* experiment using AM wave for before, during, and after FUS ablation (FUS ablation).} \]

\[ \text{Fig 2. Experimental setup.} \]

\[ \text{Band-pass Filter} \]
\[ \text{Acquisition Board} \]
\[ \text{Workstation} \]
\[ \text{Pulser / Receiver} \]
\[ \text{Amplifier} \]
\[ \text{Function Generator 1} \]
\[ \text{Function Generator 2} \]
\[ \text{Thermometer} \]
\[ t_1 \quad t_2 \quad (a) \quad (b) \quad (c) \quad (d) \quad (e) \]

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The highest peak of the RF input spectrum locates the modulated frequency \( f_{AM} = 25 \text{Hz} \) (Fig. 4(c)). In order to find an amplitude displacement at the same modulation frequency independently, the peak of amplitude displacement at \( f_{AM} \) was selected and divided based on the number of samples (Fig. 4(b)). The calculated displacement was normalized to compensate two different radiation force amplitudes. Therefore, for each M-mode frame yields one amplitude displacement. The amplitude displacement was then plotted against time to understand the relationship between tissue response and temperature during FUS ablation.

**Temperature measurement**

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 near the focus area to monitor temperature changes before, during, and after FUS ablation. The thermometer (HH506A, Omega Engineering, Stamford, CT, USA) recorded the temperature every second accordingly.

### III. RESULTS

It is important to verify that no changes in tissue properties or minimum temperature elevation before and after FUS ablation. Modulated wave in burst mode \( V_{\text{input}} = 300 \text{mVpp} \) was used to generate low acoustic intensity at the focus in liver specimens. The results showed that temperature rose within 1°C and the resulting tissue displacement were between 8 and 11 microns indicating constant tissue properties. Thus, the modulated wave in burst mode can be used to quantitatively evaluate tissue stiffness before and after FUS ablation.

Figure 5 shows tissue amplitude displacement plotted in time and photograph of in vitro bovine liver. The size of each liver specimen was approximately equal to 15 mm. Tissue displacements increased up to 30 microns (Fig. 5(a),(c),(e)) within the first 20s of FUS ablation, indicating a decrease in tissue stiffness, i.e. softening. For the remaining 25 s of FUS ablation, a rapid decline in tissue displacement occurred due to coagulation necrosis (thermal lesion). The lesion size varied between 8 and 12 microns. Although axial tissue displacement was calculated based on RF lines at one location for each acquisition, a relationship between lesion location and size (Fig. 5(a),(c),(e)), complied with the calculated tissue displacement and photograph images (Fig. 5(b),(d),(f)). Therefore, one can predict the lesion formation according to the tissue displacement. Since there are relatively low temperature differences between FUS ablation without AM burst (Fig. 6(a)1) and with AM burst (Fig. 6(a)2), the temperature difference during AM burst will not change the tissue properties.

In order to study the relationship between temperature and tissue stiffness during FUS ablation, average of tissue displacements and temperature before, during, and after FUS ablation are shown in figure 7.
Tissue displacement increases and then decreases because of coagulation necrosis during FUS ablation indicated by temperature elevation above 50°C. From this experiment lesion-formation rate of 0.405 mm/s can be calculated. After FUS ablation, tissue displacements are two times lower compared to before ablation. These results indicate that lesion has a stiffer tissue property compared to normal tissue (before FUS ablation).

IV. Conclusion

In this study, we present and evaluate AM-HMI based monitoring due to temperature elevation during FUS ablation. Figure 5 and figure 6 suggest that we could potentially observe the occurrence of protein-denatured lesion due to large changes in tissue displacement amplitudes. AM-HMI tissue displacements rapidly decreased to approximately 8 microns, after 45 s of FUS ablation, indicating lesion formation (Fig. 6(b)). The separately-acquired temperature and tissue displacement variations (Fig. 6(a)) show a linear relationship during FUS ablation and following lesion formation (Fig. 6(b)) with a rate of 0.405 mm/s (Fig. 7). By monitoring the temperature changes, physicians can predict the tissue thermal changes during hyperthermia. Moreover, this presented technique is able to monitor the speed of sound effect using the shifted tissue displacements. This effect can be potentially used to calculate temperature non-invasively during FUS surgery [15]. There are several frequency-dependent factors that also determine lesion formation, such as attenuation and tissue absorption. Further investigation needs to be performed in order to consider these factors for modulus reconstruction.

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