Single-Element Focused Ultrasound Transducer Method for Harmonic Motion Imaging

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The harmonic motion imaging (HMI) technique for simultaneous monitoring and generation of ultrasound therapy using two separate focused ultrasound transducer elements was previously demonstrated. In this study, a new HMI technique is described that images tissue displacement induced by a harmonic radiation force using a single focused-ultrasound element. A wave propagation simulation model first indicated that, unlike in the two-beam configuration, the amplitude-modulated beam produced a stable focal zone for the applied harmonic radiation force. The AM beam thus offered the unique advantage of sustaining the application of the spatially-invariant radiation force. Experiments were performed on gelatin phantoms and ex vivo tissues. The radiation force was generated by a 4.68 MHz focused ultrasound (FUS) transducer using a 50 Hz amplitude-modulated wave. A 7.5 MHz pulse-echo transducer was used to acquire rf echoes during the application of the harmonic radiation force. Consecutive rf echoes were acquired with a pulse repetition frequency (PRF) of 6.5 kHz and 1D cross-correlation was performed to estimate the resulting axial tissue displacement. The HMI technique was shown capable of estimating stiffness-dependent displacement amplitudes. Finally, taking advantage of the real-time capability of the HMI technique, temperature-dependent measurements enabled monitoring of HIFU sonication in ex vivo tissues. The new HMI method may thus enable a highly-localized force and stiffness-dependent measurements as well as real-time and low-cost HIFU monitoring.

Key words: Ablation; amplitude modulated; displacement; FUS; HIFU; harmonic motion imaging; monitoring; oscillatory; radiation force.

INTRODUCTION

Palpation is routinely used by physicians to distinguish cancerous tissues from normal tissues in organs such as the breast and the prostate. This technique is effective because cancerous tissues typically have higher stiffness compared to that of normal soft tissues such as the breast. Over the past 20 years, researchers have developed elasticity imaging techniques with various forms of tissue perturbation methods for detection of tissue response or tissue elasticity.

The tissue perturbation methods can be divided into two groups: external and internal stimulus methods. In the external methods, the tissues are externally compressed (static) or dynamically excited using a vibratory device. Krouskop et al. applied an external vibration at low frequency (10 Hz) to the surface of muscle tissue and estimated the resulting tissue velocity using a Doppler-based technique. A similar approach was later used in MR imaging. The difficulties in the external method are the fact that they rely upon knowledge of the boundary conditions for modulus reconstructions and the induced motion may not efficiently propagate to deeper tissues, such as the liver.
On the other hand, the internal methods can produce a concentrated force in a targeted region, deep inside the tissue, and can be used for probing and analyzing tissue properties point-by-point directly or remotely within the targeted region. In 1990, Sugimoto et al. were the first to use a focused transducer to produce an impulse radiation force that caused a localized static compression deep inside tissue specimens, such as the human liver, kidney and heart muscle. Their objective was to evaluate localized tissue stiffness. The tissue displacement was measured as a function of time by using pulse-echo methods and exhibited an exponential decay over time after the applied force was removed. This measurement technique first introduced the idea of employing a focused transducer to generate a force deep inside the tissue. Some years later, several research groups proposed the use of an impulse radiation force to induce brief mechanical excitations locally and image the resulting tissue response while rf data were collected during tissue relaxation (ARFI) or shear wave propagation, i.e., supersonic shear imaging and shear wave elasticity imaging (SWEI).

In 1998, Fatemi and Greenleaf introduced ultrasound-stimulated acoustic emission (USAE) that used two confocal transducer elements of a spherically-focused annular array driven at slightly different frequencies, $f_1$ and $f_2$. The transducer they designed produced a sinusoidal modulation of acoustic energy at the focus that resulted in a local oscillatory radiation force. The resulting tissue displacement produced a localized acoustic source that emitted an acoustical signal recorded by a hydrophone. Following Fatemi and Greenleaf’s discovery, further studies have shown that an oscillatory acoustic radiation force can be generated in biological soft tissues at variable depths within the tissue.

In addition to measuring tissue displacements, the use of a focused transducer can be advantageous for an all-ultrasound-based technique that can both generate and monitor the treatment during high intensity focused ultrasound (HIFU) ablation. In a previous study, the UAE technique was applied for monitoring of HIFU therapy using two separate focused ultrasound transducer elements at different frequencies ($f_1$ and $f_2$). Lizzi et al. also developed a method to monitor the formation of lesions during HIFU therapy using the impulse radiation force. They estimated the tissue displacement during HIFU ablation using the ARFI technique and showed that the displacement induced by the radiation force was much smaller in the coagulated tissue than in the normal tissue. A limitation of both aforementioned techniques for ultrasound therapy monitoring lies in the requirement to interrupt the treatment in order to estimate the tissue displacements.

In 2002, we developed a new technique called harmonic motion imaging (HMI) that utilized the same transducer configuration as that used for UAE but used a pulse-echo transducer and rf tracking to acquire the echoes during oscillation of the tissue and estimate the corresponding displacements. The advantage of this technique is that it does not depend on the acoustic properties or is not as affected by the acoustic noise during signal acquisition, as the UAE technique may be. Michishita et al. used a similar pulse-echo technique to estimate small cyclical displacements of the silicone rubber phantom in order to locally measure its complex elastic modulus. The intended goal of this technique was to measure the complex elastic modulus of tissues on or close to the surface such as the skin and the breast. The ultrasonic transducer produced a low acoustic intensity ($\leq 1\text{W/cm}^2$) for force generation and was paused when displacement was measured. Thus, the measurement of the silicone rubber motion was not obtained during force activation.

Recently, an improvement of the original HMI technique was shown using a single-element FUS that was amplitude-modulated (AM) as opposed to two separate elements previously used. Thus, the new HMI technique could require a single high power FUS beam for sonication and radiation force generation and for estimation of the displacements during the application of the radiation force. To our knowledge, this is the only technique that can measure the mechanical response during the application of the force.
In this paper, the potential for the use of the HMI method for HIFU treatment monitoring is examined. First, simulations are performed showing that the AM beam offers the advantage of sustaining the application of the radiation force at a constant, stable focus within the tissue region, unlike with the previously-used two-transducer configuration. Second, experiments are performed in gelatin phantoms and \textit{ex vivo} porcine liver. This is to test whether HMI is capable of mapping the displacement amplitude and phase shift of the material at high resolution. The displacement amplitudes are measured at the location of the applied force using a pulse-echo transducer. Given that the mechanical properties of biological tissues change during HIFU ablation,\textsuperscript{22-24} this technique could potentially be used for real-time monitoring of the mechanical properties of tissues during HIFU treatment.\textsuperscript{21} One major advantage of this technique is that the displacement is measured during the application of the acoustic radiation force and HIFU ablation so that no interruption of the treatment is required.

**METHODS**

In order to first identify the advantages of using an amplitude-modulated FUS transducer versus the two-transducer configuration, simulations of the pressure field were performed. The pressure fields were calculated using the Field II simulation package.\textsuperscript{25} Two different types of transducers were designed. The first was a single-element transducer operating at 1 MHz central frequency with a 70 mm diameter and a focal length of 100 mm. A 1 MHz continuous wave with sinusoidal amplitude modulation at 50 Hz was simulated for this transducer.

The second transducer was a confocal and concentric transducer. It had two separate elements: the first element had a diameter of 50 mm and a focal length of 100 mm. It was surrounded by the second annular element that had an inner diameter of 50 mm, an outer diameter of 70 mm and a focal length of 100 mm. A 1 MHz continuous wave was simulated for the first element and a 1.00005 MHz continuous wave was simulated for the second element. Both transducer types had the same total surface.

For both simulations, the sampling frequency was 100 MHz and the pressure field $p(x,z)$ was calculated in a region around the focus of 40 mm (lateral) $\times$ 60 mm (axial) with a pitch of 0.1 mm and a bandwidth for both AM and continuous waves of approximately 100%.

The average acoustic intensity ($I_{ave}$) was then calculated using the equation\textsuperscript{26}

$$I_{ave} = \frac{1}{\lambda} \int_0^\lambda p^2 \, dz = \frac{k}{2\pi} \int_0^{2\pi/k} p^2 \frac{1}{Z} \left(\cos^2(2\pi f_z t - kz) \cos^2(2\pi f_z t - k\bar{z})\right) dz = \frac{kp^2}{2\pi Z} \frac{2\pi}{4k} = \frac{p^2}{4Z}$$

where $p$ denotes the pressure and $Z$ denotes the impedance. Thus, the intensity of the high power FUS beam with AM wave is half of the maximum allowable intensity of the transducer. Figure 1 shows the acoustic intensities emitted by the two types of transducer configurations over one period of oscillation. Since the acoustic radiation force is linearly related to the acoustic intensity, these results show that, in the two-beam configuration (Fig. 1(a)), the overlapping, focused beams produced an acoustic radiation force field continuously moving across the focal region at the difference frequency ($\Delta f$). On the other hand, the AM beam offered the advantage of sustaining the application of the radiation force at the same stable focus within the tissue through the entire excitation time (Fig. 1(b)).

Our experiments were performed on tissue-mimicking phantoms and \textit{ex vivo} tissues. Gelatin material (Gelatin 50 bloom, MP Biomedicals, Irvine, CA, USA) was used to construct
the tissue-mimicking phantoms. Five homogeneous phantoms with different elastic moduli (20 kPa, 30 kPa, 40 kPa, 50 kPa, and 60 kPa) and a 20 kPa tissue mimicking phantom with a 40 kPa cylindrical inclusion were constructed.

Phantom preparation was completed using the following steps: degassed, de-ionized water and gelatin powder were mixed in a 500 ml solution. The amount of gelatin powder was calculated according to reference 27:

\[
E_{\text{gelatin}} = 0.003C^{2.09}
\]  

(2)

where \(E_{\text{gelatin}}\) denotes the Young’s modulus of the gelatin in kPa and \(C\) denotes the concentration of gelatin powder in g/L. The concentration was varied between 63 g/L and 107 g/L in order to obtain stiffnesses between 20 kPa and 60 kPa (Eq. 2). The mixture was constantly stirred and heated until the temperature reached 50°C. The gelatin powder was assumed to have been uniformly dissolved at this state. The mixture was then placed into a waterbath for cooling until the temperature decreased to 35°C. Isopropanol and agar powder were then added to the mixture. Isopropanol was added to increase cross-linking and thus increase the
melting point of the gelatin while solid agar powder was added to induce scattering. Note that agar only bloomed at temperatures above 80 °C; thus, it did not contribute significantly to the increase of the phantom stiffness. The amount of agar powder (Acros Organics, Geel, Belgium) was equal to 10% of the total gelatin powder added. The stirrer was removed from the mixture when the temperature reached 30 °C. The solution was covered with plastic wrap to minimize dehydration and was placed in a refrigerator for approximately 12 hours. Similarly, *ex vivo* porcine liver was submerged in a phosphate buffered saline (PBS) solution and degassed for 30 minutes prior to use for the experiments.

The experimental setup is shown in figure 2. The harmonic radiation force was generated by a 4.68 MHz FUS transducer using an amplitude-modulated wave. The diameter of the FUS transducer (Riverside Research Institute, New York, NY) and the radius of curvature were 84 mm and 90 mm respectively. A 7.5 MHz pulse-echo transducer with diameter of 12 mm was placed through the center of the FUS transducer.

This transducer design is safe because the FUS transducer is not directly facing the pulse-echo transducer. The pulse-echo transducer has a smaller diameter by seven times compared to that of the FUS transducer; this will decrease the probability of damage by a high power FUS beam. In addition, a silicon rubber/absorber (McMaster-Carr, Dayton, New Jersey, USA) was placed beneath the specimen in order to reduce specular reflections at the interface between the specimen and the bottom of the container. Therefore, no heating of the pulse-echo transducer by the high power FUS beam was observed in all the experiments performed.

The goal of the new HMI technique is to produce a single oscillatory frequency at the modulation frequency $f_m$. The modulation index ($m$) is defined as the ratio of the maximum to the minimum voltage of the modulated signal. The conventional amplitude modulation has modulation index $m$ equal to 1 (i.e. 100% modulation), which indicates that the magnitude of the modulating signal is equal to that of the carrier signal. If this conventional amplitude modulation is applied to generate the radiation force, the resulting acoustic pressure at the fo-
cus would consist of three oscillatory frequencies, i.e., $f_c, f_c \pm f_m$, where $f_c$ and $f_m$ represent the carrier and modulation frequency, respectively. The carrier signal was thus overmodulated ($m \geq 50$) to induce oscillation of the resulting acoustic pressure at the only desired frequency, i.e., $f_m$ (Fig. 3(c)).

Therefore, the single-element FUS transducer was driven by a 50 Hz amplitude-modulated wave with a high modulation index ($m \geq 50$) in order to produce an acoustic pressure oscillating at the modulation frequency $f_m$ at the focus. The first function generator (Agilent (HP) 33120A, Palo Alto, Ca, USA) generated the carrier signal given by

$$X_c(t) = X_c \times \sin(2\pi f_c t)$$  \hspace{1cm} (3)

where $f_c$ was at 4.68 MHz and $X_c$ was the carrier signal amplitude (Fig. 3(a)). The second function generator (Agilent 33220A) generated the low-frequency modulation signal given by

$$X_m(t) = m \times \sin(2\pi f_m t)$$  \hspace{1cm} (4)

where $f_m$ was equal to 50 Hz and $X_m$ was a modulation signal amplitude (Fig. 3(b)). The resulting modulated signal was then equal to

$$X(t) = X_c(t) \times (1 + X_m(t))$$  \hspace{1cm} (5)

or,

$$X(t) = X_c \times \left(1 + m \times \sin(2\pi f_m t)\right) \times \sin(2\pi f_c t)$$  \hspace{1cm} (6)

FIG. 3 Illustration of amplitude-modulated signal process. (a) High-frequency input, (b) low-frequency modulation ($m \geq 50$), (c) AM signal output of the function generator and (d) acoustic intensity generated at the focus.
Therefore, the pressure field (Fig. 3(c)) and acoustic intensity (Fig. 3(d)) oscillated at the desired modulation frequency $f_m$ of 50 Hz at the focus.

Note that the excitation parameters, such as the modulation frequency and input power, affect the radiation force profile, which in turn also relates to the displacement distribution in the tissue. Therefore, a preliminary experiment was performed using ex vivo porcine liver, where the modulation frequency $f_m$ was varied from 20 Hz to 300 Hz using a frequency sweep for 10 seconds. The intensity of the high power FUS beam was set to 237 W/cm$^2$. If the amplitude modulation frequencies were below 20 Hz, the estimated displacement amplitudes would be at significantly low resolution and, thus, higher amplitude modulation frequency was preferred. The preliminary experiment showed that the displacement amplitudes at the focus decreased rapidly at frequencies above 74 Hz, thereby making it very difficult to accurately estimate displacement amplitudes at higher frequencies, possibly due to higher damping effects. This preliminary study provided the relationship between the frequency modulation and the tissue response. Hence, the optimal modulation frequency $f_m$ can be selected. A frequency of 50 Hz was thus chosen for the amplitude modulation frequency in this experiment. The output of the function generator was varied from 100 to 600 mVpp and then amplified by a 50 dB rf amplifier (ENI 3100L, ENI Products division of MKS instruments Inc., Rochester, NY, USA). The two function generators were connected in series and controlled automatically using Matlab 7.0 (MathWorks Inc., Natick, MA, USA) to generate sequences of continuous and AM waves. The real-time monitoring method was adjusted to induce a two-second continuous wave sonication (Fig. 4(a)), immediately followed by a 100 ms amplitude-modulated wave for radiation force generation (Fig. 4(b)). Both the continuous and amplitude-modulated waves were manually adjusted to have the same intensity at the focal zone, i.e., the heating was not interrupted. This sequence was repeated until the total sonication time was approximately 80 seconds at 100% duty cycle (Fig. 4). The sonication time of 80 s was used to ensure that a cigar-shaped lesion with a diameter of 1 cm was well formed.

In the new AM-HMI technique, the high power FUS beam is used to generate a radiation force at the targeted region in the tissue below the damage threshold and the tissue response is imaged at the same time using a diagnostic (pulse-echo) transducer. A pulse-echo transducer with a center frequency of 7.5 MHz, a diameter of 12.5 mm and a focal length of 60 mm (Panametrics, Waltham, MA, USA) was placed through the center of the FUS so that the beams of the two transducers were properly aligned. Consecutive, filtered rf signals were acquired at a pulse repetition frequency of 6.5 kHz (Panametrics 5051PR, Waltham, MA, USA). A bandpass analog filter (Reactel, Inc., Gaithersburg, Maryland, USA) with cut-off
frequencies of \( f_1 = 5.84 \text{ MHz} \) and \( f_2 = 8.66 \text{ MHz} \) was used to filter out the spectrum of the high power FUS beam prior to displacement estimation.

In order to study the interference between the diagnostic and high power FUS beams, the spectra of the two beams in \textit{in vitro} bovine liver tissue are shown before (Fig. 5(a)) and after (Fig. 5(b)) bandpass filtering using the analog filter as described in the previous paragraph. Figure 5(c) shows the corresponding rf signals before and after bandpass filtering.

It can clearly be seen that the fundamental frequency \( (f = 4.68 \text{ MHz}) \) and the harmonics of the FUS transducer have been successfully filtered. Figure 5 therefore demonstrates that the rf signal can be fully recovered after the high power FUS beam spectrum has been removed, indicating low interference between the two beams.

An acquisition board (CS14200, Gage Applied Technologies, Lachine, Canada) was used to capture filtered rf data with a sampling frequency of 80 MHz. For the raster-scanned process, the transducer was moved along a 2D grid using a computer-controlled positioner (Velmex Inc., Bloomfield, NY, USA) with a step size of 1 mm.

The time shift occurring between the two consecutively acquired rf echoes was calculated using a speckle-tracking technique. One-dimensional cross-correlation was performed along the ultrasound beam axis with a small data window of 1.3 mm and 85% overlap. This method is simple to implement, computationally efficient and provides an accurate estimation of small displacements (on the order of 1-10 \( \mu \text{m} \) at 7.5 MHz).

The displacement amplitude and phase shift between the input force and resulting displacement at the frequency of amplitude modulation (or vibration) were extracted for each region where displacements were estimated. These two parameters were obtained by computing the frequency response of the estimated time-shift at the frequency of modulation. The phase shift \( (\phi) \) between the radiation force and estimated displacement was calculated (Fig. 6). The phase shift has been shown to relate more closely to the viscosity of the tissues than does the displacement amplitude.

\[ \text{RESULTS} \]

1. Tissue-mimicking phantom experiments

In order to investigate the stiffness-dependence of the tissue displacement, this experiment was first performed in five gelatin phantoms of different stiffnesses. The intensity of the high power FUS beam used in this experiment was 658 W/cm\(^2\) and the AM frequency was 50 Hz.

Figure 7(a) shows that the average displacement amplitude decreases from 10.3 \( \mu \text{m} \) to 4.15 \( \mu \text{m} \) as the gelatin stiffness increases from 20 kPa to 60 kPa. The HMI displacements clearly indicate the stiffness variation. The average force-displacement phase shift decreases from \(-66.4^\circ\) to \(-30.4^\circ\), potentially consistent with decreasing gel viscosity (Fig. 7(b)).

Inhomogeneous phantom experiments were then performed in a 20 kPa gelatin phantom with a 40 kPa cylindrical inclusion (Fig. 8(a)). Two-dimensional maps of the displacement amplitudes and force-displacement phase shifts are shown in figures 8(b) and (c), respectively. The average displacement in the inclusion is 3.3 \( \mu \text{m} \) (Fig. 8(b)) and the average phase shift is \(-34^\circ\) (Fig. 8(c)) while in the surrounding gel the displacement is 6.1 \( \mu \text{m} \) (Fig. 8(b)) and the phase shift is \(-65.9^\circ\) (Fig. 8(c)). Note that the average displacement amplitude in the 20 kPa region is twice as high as the average displacement amplitude in the 40 kPa cylindrical inclusion region. These results are consistent with the inverse relationship between the displacement and elastic modulus during harmonic excitation.
FIG. 5 Spectra of the high power FUS beam (dotted line) and diagnostic beam (solid line) before (a) and after (b) bandpass filtering. Dotted line spectrum indicates presence of high power FUS beam with the highest peak indicating fundamental frequency followed by its harmonic peak. Solid line shows reflection of tissue response with no high power FUS beam present. Spectra after filtering at frequency 7.5 MHz demonstrate that the tissue response is imaged at diagnostic frequency ($f_c = 7.5$ MHz). (c) RF signal before (dotted line) and after (solid line) removal of high power FUS beam in in vitro bovine liver: (c₁) PBS solution, (c₂) specimen and (c₃) silicon rubber/absorber.
2. Monitoring HIFU ablation

A 20 x 20 x 30 mm³ piece of ex vivo porcine liver was submerged in phosphate-buffered saline (PBS) solution and degassed for 30 minutes. The 20 x 20 mm² area was ras-
ter-scanned before and after the lesion formation. The intensity of the FUS used in the raster-scan process was 237 W/cm² with an am frequency of 50 Hz. The displacement amplitudes at the focus of the ex vivo porcine liver, before and after the lesion formation, were approximately equal to 25 μm (Fig. 9(a)) and 10 μm (Fig. 9(b)), respectively. The image resulting from the subtraction of the image after, from the image before the lesion formation is shown in figure 9(c). The negative displacement amplitude (≤ −5 μm) defines a circular lesion with a diameter of 10 mm (Fig. 9(c)). These results indicate that the displacement amplitude decreases after lesion formation due to the associated higher tissue stiffness. They also reveal an inhomogeneous lesion with two separate zones with the central zone having the lowest displacement. In this case, the difference image was necessary to highlight the ablated, or stiffer, region unlike in the case of the gels where the HMI amplitude image was sufficient (Fig. 8(b)). This is most likely due to increased post-ablation absorption that has the opposite effect, i.e., of increasing the applied force and therefore, estimated displacement, after coagulation.  

For the real-time monitoring application, the experiment was completed in an ex vivo porcine liver with a sonication time of a total of 80 seconds. Figure 10(b) shows the tissue displacement amplitude at the focal depth versus sonication time. The focus is located at 16.5 mm and has displacement amplitude of 50 μm, which then decreases to about 15 μm (Fig. 10(c)). The regions above and below the focus have approximately constant displacements (Fig. 10(c)). This indicates that the acoustic radiation force is produced and maintained at the focus and that after 20 seconds of sonication time, the properties of the liver tissue irreversibly changes due to tissue coagulation (Fig. 10(a)).
Furthermore, it should be noted that the effect on the echoes induced by the increase in the speed of sound with temperature also introduced a linear shift in the HMI displacement in time (Fig. 11(a)). The linear shift was then separated from the HMI displacement by removing the linear slope incurred (Fig. 11(c)). The result is shown in Fig. 11(b). This technique is therefore able to accurately monitor the stiffness-related heating process, possibly detecting the time of coagulation as well as separating the speed-of-sound effect from stiffness-related changes.

**DISCUSSION AND SUMMARY**

Experimental results of the HMI technique in the tissue-mimicking phantoms and ex vivo porcine liver were shown in relation to the potential for the use of the HMI technique for monitoring HIFU treatment. Low interference between the high power FUS and diagnostic beams is achieved after bandpass filtering and, thus, tissue displacements using the filtered rf signals can be accurately estimated. Although the tissue-mimicking phantoms might present small discrepancies in an absolutely uniform stiffness reported, the new HMI technique is still capable of detecting the displacement changes caused by changes in the material stiffness.

Our technique indicates that the HMI displacement amplitude and force-displacement phase shift vary with material stiffness and viscosity. The maximum temperature change measured during HMI was 1°C. The phase shift might be beneficial for estimating the vis-
cosity of the medium in the future. The relationship between the displacement amplitude and the phase shift is a topic of ongoing investigation.

A phantom with a cylindrical inclusion was generated to mimic HIFU lesions and a 2D raster-scanned process was performed to obtain an HMI image. The cylindrical inclusion was accurately mapped using the displacement amplitude and phase shift. The phase shift map shows an artifact below the inclusion (Fig. 8(c)). This variation could be the result of temperature, attenuation or tissue absorption change during the radiation force application. In addition, we obtained consistent real-time monitoring of tissue ablation in the \textit{ex vivo} porcine liver tissue. The tissue displacement amplitude initially increased and then decreased at the onset of the lesion formation. A continuous wave was generated during the sonication period in order to accelerate the lesion formation and reduce the HIFU therapy duration.

Despite the fact that the HMI technique shows a high potential for elasticity imaging, this method was primarily designed for real-time monitoring of tissue properties during HIFU treatment. The acoustic intensity of the high power FUS beam (600-1,000 W/cm\(^2\)) is well adapted for both acoustic radiation force generation and HIFU therapy, allowing displacement amplitude of 1 to 10 \(\mu\)m in the gelatin and tissue and 10 to 50 \(\mu\)m in the tissue ablation experiments.

Thus, the ablation of the tissue and the monitoring can be performed at the same time, which may prove to be a major advantage for efficient HIFU application and real-time monitoring compared with other radiation-force-based monitoring techniques that require interruption of the treatment to measure the mechanical responses. This is an important contribution in the area of noninvasive or minimally-invasive thermal therapy.

In this method, it was also assumed that the variation of the elasticity during HIFU ablation is the main effect that produces the displacement amplitude variation. However, for a given transducer and intensity, the acoustic radiation force generated in biological tissues depends on several parameters that can also vary during HIFU ablation, such as the density and the ultrasound absorption of the tissue. It has been shown, in particular, that the attenuation, and tissue absorption, of ultrasound increases significantly during heating.\textsuperscript{30} If this effect were

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig11.png}
\caption{Illustration of removal of temperature-dependent speed of sound effect on the displacement as a result of temperature change that induces (a) a linear shift, which can then be successfully separated (b) from the HMI displacement variation. (c) Slope of the HMI displacement shift.}
\end{figure}
predominant, it would increase the radiation force and consequently the amplitude of the tissue displacement. However, we have shown here that the displacement amplitude decreases consistently during ablation, which suggests that this variation is mainly due to the elasticity change.

The choice of the modulation frequency plays an important role in this method. It is possible to induce mechanical oscillations in a 1 to 3 mm³ region of the tissue due to the large attenuation of low frequency shear waves. Since the attenuation increases with frequency, a higher frequency modulation (>100 Hz) would allow the oscillations to be contained in a smaller region in the vicinity of the focus. However, at high frequencies, the viscosity of the tissue becomes very important and the oscillation of the tissue decreases rapidly. For example, below 10 Hz and above 74 Hz, it becomes very difficult to detect the tissue oscillations in ex vivo porcine liver using an acoustic intensity of 237 W/cm². At this frequency, the tissue oscillations are limited to a region of about 10 mm around the focal spot. In conclusion, the feasibility of using an amplitude-modulated radiation force for harmonic motion imaging (HMI) and simultaneous monitoring of tissue stiffness variation during ultrasound therapy was shown in phantoms and ex vivo tissues. Since it uses oscillatory techniques, the HMI technique could be used for the estimation of mechanical properties, such as stiffness and viscosity, as well as their separation from acoustical property changes with temperature, such as those from the speed of sound and absorption. Further investigations will focus on the estimation of those aforementioned properties together with the precise quantification of the size of the oscillating region and the frequency-dependence of the response.

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