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Multi-parametric monitoring and assessment of High Intensity Focused Ultrasound (HIFU) boiling by Harmonic Motion Imaging for Focused Ultrasound (HMIFU): An *ex vivo* feasibility study

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Abstract

Harmonic Motion Imaging for Focused Ultrasound (HMIFU) is a recently developed high-intensity focused ultrasound (HIFU) treatment monitoring method with feasibilities demonstrated *in vitro* and *in vivo*. Here, a multi-parametric study is performed to investigate both elastic and acoustics-independent viscoelastic tissue changes using the Harmonic Motion Imaging (HMI) displacement, axial compressive strain and change in relative phase-shift during high energy HIFU treatment with tissue boiling. Forty three (n=43) thermal lesions were formed in *ex vivo* canine liver specimens (n=28). Two dimensional (2D) transverse HMI displacement maps were also obtained before and after lesion formation. The same method was repeated in 10-s, 20-s and 30-s HIFU durations at three different acoustic powers of 8, 10, and 11W, which were selected and verified as treatment parameters capable of inducing boiling using both thermocouple and Passive Cavitation Detection (PCD) measurements. Although a steady decrease in the displacement, compressive strain, and relative change in the focal phase shift (ϕ) were obtained in numerous cases, indicating an overall increase in relative stiffness, the study outcomes also showed that during boiling, a reverse lesion-to-background displacement contrast was detected, indicating potential change in tissue absorption, geometrical change and/or, mechanical gelatification or pulverization. Following treatment, corresponding 2D HMI displacement images of the thermal lesions also mapped consistent discrepancy in the lesion-to-background displacement contrast. Despite unpredictable changes in acoustic properties with boiling, the relative change in phase shift showed a consistent decrease, indicating its robustness to monitor biomechanical properties independent of the acoustic property change throughout the HIFU treatment. In addition, the 2D HMI displacement images confirmed and indicated the increase in the thermal lesion size with treatment duration, which was validated against pathology. In conclusion, multi-parametric HMIFU was shown capable of monitoring and mapping tissue viscoelastic response changes during and after HIFU boiling, some of which were independent of the acoustic parameter changes.

Keywords

Elasticity Imaging; Harmonic Motion Imaging for Focused Ultrasound; High intensity focused ultrasound monitoring; Multi-parametric HIFU monitoring; Therapeutic ultrasound; Tissue boiling

Introduction

High Intensity Focused Ultrasound (HIFU) treatment is a rapidly emerging technology in the field of non-invasive tumor treatment (Ter Haar, 1995; Kennedy, 2005). As a promising non-ionizing and cost effective thermal ablation modality, HIFU is capable of targeting and inducing a contained thermal lesion, i.e., cell necrosis embracing its focal spot within a tumor while sparing the majority of the peripheral tissue. To date, numerous studies have demonstrated the capability of HIFU for the treatment of local diseases in organs such as the brain, liver, uterus, kidney, prostate, bone and breast (Al-Bataineh *et al.*, 2012). As is the case for every treatment technique, there are three stages involved: planning, monitoring, and assessment follow-up. One of the potential areas of improvement is the maturation of cost-effective, precise and accurate assessment technologies at all stages, which can effectively open the door towards the full clinical translation of HIFU worldwide.

HIFU treatment planning and assessment

For the treatment planning and assessment stages, an extensive amount of studies have been carried out, leading to different techniques that have been coupled with HIFU. Magnetic Resonance Imaging (MRI) has been shown capable of localizing tumors and assessing thermal lesions formed based on the changes in the tissue water content (Cline *et al.*, 1995; Hynynen *et al.*, 2001; Gianfelice *et al.*, 2003; Huber *et al.*, 2001). In addition, MRI has also been recently shown capable of localizing the HIFU focus (Grissom *et al.*, 2009; Kaye *et al.*, 2011). Conventional B-mode ultrasound imaging can serve as a viable option for detecting and assessing the thermal lesion formed through their distinctive echogenicity with respect to the surrounding medium (Lele, 1966; Ter Haar *et al.*, 1989; Yang *et al.*, 1993; Chavrier *et al.*, 2000). Noninvasive echo-shift based thermography provides a high resolution (sub-millimeter) HIFU beam guidance and localization utilizing the tissue echo shifts due to changes in the speed of sound upon temperature rise (Seip and Ebbini, 1995; Pernot *et al.*, 2004; Casper *et al.*, 2012). Other ultrasound-based techniques have utilized changes in the spectral characteristics of backscattered signals in order to detect the thermal lesion (Zheng and Vaezy, 2010). Recently, acoustic radiation force (Nightingale *et al.*, 2001; Fatemi and Greenleaf, 1999; Sarvazyan *et al.*, 1998), static (Ophir *et al.*, 1991) and dynamic (Parker *et al.*, 1990) elasticity imaging techniques have also been shown capable of visualizing tumors (Bercoff *et al.*, 2003; Zhai *et al.*, 2012; Alizad *et al.*, 2004; Thitaikumar *et al.*, 2008) and the induced thermal lesions (Mitri *et al.*, 2008; Lizzi *et al.*, 2003; Souchon *et al.*, 2003; Chenot *et al.*, 2010; Curiel *et al.*, 2005; Kallel *et al.*, 1999; Righetti *et al.*, 1999; Stafford *et al.*, 1998; Fahey *et al.*, 2004; Bharat *et al.*, 2005; Thittai *et al.*, 2011) based on their distinctive mechanical properties.

HIFU treatment monitoring

Monitoring of HIFU treatment remains as the most challenging and crucial aspect of its clinical translation requiring both high frame rate and spatial resolution within the localized focal zone. To date, several techniques have been developed with an interest in monitoring the focal tissue environment under HIFU treatment. MRI-guided Focused Ultrasound (MRgFUS) (Cline *et al.*, 1995; Huber *et al.*, 2001; Hynynen *et al.*, 2001; Gianfelice *et al.*, 2003; Furusawa *et al.*, 2006; Smith *et al.*, 2000) is the current standard monitoring modality which provides a focal temperature map at a feed-back frame rate of 0.1 to 2 Hz and millimeter resolution. It is based on changes in the tissue proton-resonance frequency, which is associated with the water proton chemical shift resulting from rupture, stretching, or bending of hydrogen bonds in a temperature elevated environment (Ishihara *et al.*, 1995). Acousto-optic sensing is a recently developed, cost-effective modality capable of monitoring the change in tissue optical absorption and scattering using a modulated light with HIFU beams during treatment (Lai *et al.*, 2011; Cui and Yang, 2011). Several acoustic echo signal-based techniques (Nandlall *et al.*, 2011; Anand and Kaczkowski, 2004) have also utilized either changes or rise in harmonics through spectral analysis of the backscattered signals in order to detect thermal lesion formation.

HIFU tissue elasticity imaging focuses on detecting and monitoring the onset and progress of tissue elasticity and/or viscosity throughout the entire treatment. Currently, several techniques have investigated and proven its potential in HIFU monitoring including Magnetic Resonance Elastography (MRE) (Lewa, 1991; Multhupillai R., 2001; Sinkus *et al.*, 2000; Kruse SA, 2000), Supersonic Shear Wave Imaging (SSI) (Arnal *et al.*, 2011a, b), Acoustic Radiation Force Impulse (ARFI) Imaging (Bing *et al.*, 2011), and Harmonic Motion Imaging for Focused Ultrasound (Maleke and Konofagou, 2008, 2010). Both MRE and SSI are capable of monitoring the change of tissue mechanical properties through estimation of the shear wave velocity, where the tissue motion is induced either by an external mechanical exciter (MRE) or *in situ* plane wave generated using a series of focused acoustic beams (SSI). ARFI has recently shown feasibility in ablating and monitoring formation of thermal lesions through operation of a customized beam sequence using a conventional curvilinear imaging probe (Bing *et al.*, 2011). Each of the aforementioned monitoring technique possesses unique advantages: MRE is capable of quantitatively monitoring shear modulus changes with sub-millimeter spatial resolution through the entire ablation sequence, SSI is capable of assessing the shear modulus change of high frame rates under a frame acquisition rate up to 10,000 frames/sec and a shear modulus mapping rate up to 0.333 frames/sec (Arnal *et al.*, 2011), and ARFI imaging is capable of utilizing a cost-effective conventional imaging system to induce and monitor lesion formation. Nevertheless, MRE can be costly while operating at frame rates of 0.5-10 Hz and one of the primordial unsolved issues of HIFU, lies with the long duration of the procedures. Therefore, real-time feedback on the effectiveness of lesioning is warranted. This is achieved by providing information on the success of the treatment (i.e., coagulation) in real time, i.e., fast and before having moved to the next site of treatment. Therefore, it is important to develop monitoring techniques that can achieve the cost-effectiveness without the use of MRI, providing true real time capability in ideal registration with the treatment, i.e., maintaining high frame rate at kHz range in localized HIFU focal zone, while not

interrupting or slowing down the HIFU treatment Harmonic Motion Imaging for Focused Ultrasound (HMIFU) couples a HIFU transducer emitting an Amplitude-modulated (AM) beam for inducing stable oscillatory tissue probing at its focal zone while the response is acquired through a confocally-aligned pulse-echo imaging transducer (Maleke and Konofagou, 2008). Band-pass filtering is performed on the RF signals from pulse-echo imaging transducer in order to remove the interference due to HIFU echo, and the oscillatory tissue motion is then estimated using a 1D cross-correlation method.

Several HMIFU feasibility studies have been completed for *in vitro* (Maleke et al., 2006; Konofagou and Hynynen, 2003), *ex vivo* (Maleke and Konofagou, 2008), and *in vivo* (Maleke and Konofagou, 2009; Curiel *et al.*, 2009) applications. However, monitoring HIFU ablation with boiling was not studied using this technique. In HIFU treatment, tissue boiling usually occurs at the focal region when tissue is being exposed at the highest acoustic intensity, where bubbles may form from thermal mechanisms such as boiling of fluid in blood or tissue, or mechanical mechanisms such as growth of tiny cavitation nuclei inside the tissue by the negative pressure of the induced nonlinear acoustic waves (Bailey *et al.*, 2003; Khokhlova *et al.*, 2009). Occurrence of the formation of such boiling bubbles is unpredictable and the nonlinear wave induced at high intensities may lead to an increased absorption, i.e., higher thermal dosage, thus presenting a potential challenge for the current existing temperature estimation-based monitoring modalities. Nevertheless, in the literature of HIFU treatment on cancerous tissues, numerous studies have indicated the importance of high intensities (2-20 kW/cm²) capable of inducing boiling (Ter Haar *et al.*, 1991; Wu *et al.*, 2001a; Wu *et al.*, 2005) given the resistive nature and proliferated vasculature among cancerous cells (Wu *et al.*, 2003). Additionally, a group of studies have investigated the histological changes between normal and cancerous cells following HIFU treatment and inferred that effective cell death in cancerous tissues requires higher intensities compared to those under normal conditions (Chen *et al.*, 1999; Chen *et al.*, 1993). Despite this interesting aspect, the performance of current clinical monitoring techniques using B-mode or MRI is limited under HIFU treatment with boiling. The B-mode is only capable of indicating hyperechoic regions denoting formation of bubbles, yet the bubbles are unstable and do not necessarily delineate the entire lesion extent (Jensen *et al.*, 2012). On the other hand, the temperature monitoring using MRI loses its accuracy as the initiation of boiling is unlikely to be registered as 100 °C or above, which could potentially question the accuracy of any ablation volume calculation using MR-based thermal dosage (Khokhlova *et al.*, 2009).

Therefore, it is crucial to assess the performance of HMIFU under such boiling conditions using high acoustic power levels where HIFU treatment is proposed to be more effective and efficient through both thermal (protein denaturation due to heat-shock) and mechanical (cavitation) damage. Moreover, amongst the previous studies, focal displacement has been the only tracking parameter representing a qualitative and relative change of stiffness of focal tissue accounting for both acoustic and mechanical changes under HIFU treatment. To further improve the assessment quality of HMIFU, therefore, requires a comprehensive and complementary assessment of focal tissue mechanical properties. Here, we propose a multi-parametric monitoring study combining four different parameters, namely displacement, phase shift, compressive strain, and 2D mapping to monitor and assess the tissue stiffness

change during and following HIFU treatment. From our previous work (Maleke et al., 2008), the peak-to-peak amplitude of HMI focal displacement first increases then decreases as tissue undergoes softening-followed by-stiffening during slow thermal ablation, which is the pattern of stiffness change under slow denaturation (Marquet *et al.*, 2012; Hou *et al.*, 2013b). Nevertheless, lesions induced by high power with boiling forms much more rapidly thus stiffening occurs much earlier in time during treatment period. We therefore hypothesize that a multi-parametric monitoring approach would improve the HMIFU reliability in the sense that 1) focal phase shift (ϕ) will serve to decouple changes in mechanical and acoustical tissue responses; 2) compressive strains would serve to confirm the displacement assessment within the focal region, and 3) the 2D HMI displacement image will accurately delineate the lesion margins. In this study, we present a multi-parametric approach to enhance the reliability of the HMIFU technique for real-time HIFU treatment with the capability of 1) monitoring thermal lesion formation under HIFU-induced boiling, 2) comprehensive lesion assessment using three main HMI parameters, and 3) decoupling changes in mechanical from those in acoustical tissue properties under HIFU treatment.

Methods

1. HMIFU Monitoring parameters

1a. HMI focal Displacement—In HMIFU, the amplitude-modulated HIFU beams induce a sinusoidal displacement profile at the geometric focus. The motion originates from the acoustic radiation force generated due to the energy absorption from the HIFU beam, which was previously derived and indicated as follows (Nyborg, 1958; Palmeri *et al.*, 2005):

$$F = \frac{2\alpha I}{c}, \quad (1)$$

where I is the *in situ* acoustic intensity field, α is the acoustic absorption coefficient, and c is the speed of sound. The relationship between induced displacement and excitation force can be described from the general theory of wave propagation within a linear elastic medium:

$$\rho \frac{\partial^2 u}{\partial t^2} = \left(K + \frac{\mu}{3} \right) \nabla (\nabla \cdot u) + \mu \Delta u + \rho F \quad (2)$$

where ρ is the density of the medium, K is the bulk modulus, μ is the shear modulus, F is the volumetric force, and u is the induced displacement. Note that in this study, we focus our investigation along the propagation direction (z), i.e., $F = F(z)$, and $u = u(z)$. In HMIFU, an oscillatory response is induced at the HIFU focal zone due to the AM-HIFU excitation (Figure 1(d)), namely the HMI displacement. Although the displacement may also arise from thermal expansion and variation in speed of sound, they are considered to be much smaller than the oscillatory mechanical motion generated by the acoustic radiation force from the AM-HIFU beam in the case of HMI as we have reported elsewhere (Maleke and Konofagou, 2008). This HMI displacement is monitored throughout the entire HIFU treatment duration. The relative change of the peak-to-peak HMI displacement amplitude with respect to the displacement at the baseline, i.e., at the beginning of the HIFU treatment, can be correlated with the relative change in local tissue stiffness as the thermal lesion

develops. Until now, the displacement parameter has been the main parameter used; nevertheless, displacement is a qualitative parameter which accounts for changes in both the acoustic and mechanical properties at the focus during HIFU treatment. For example, displacement may not clearly reveal the relative changes in tissue stiffness when stiffening occurred along with increase of acoustic absorption, i.e., increased displacement amplitude. Therefore, complementary approaches are required to improve the reliability of HMIFU.

1b. Relative change in phase shift—Within the acoustic focal zone where displacement is monitored, another parameter, phase shift, can also be monitored (Figure 1). The phase shift refers to the phase angle difference between the applied force and induced displacement profile. In the frequency domain, the complex modulus can be derived from calculating the ratio between the oscillatory excitation force and the induced displacement with a delay ϕ (Vappou *et al.*, 2009),

$$\frac{F(\omega)}{u(\omega)} = \frac{F_0 e^{i\omega t}}{u_0 e^{i(\omega t - \phi)}} = G' + iG'', \quad (3)$$

where F_0 is the force amplitude, ω is the modulation frequency, u_0 is the displacement amplitude, $i^2 = -1$, G' is the shear storage modulus, G'' is the shear loss modulus, ϕ is the phase angle between force and displacement profile, and t is the time. The phase angle between these two functions is simply the ratio between G' (elasticity) and G'' (viscosity).

$$\frac{G'}{G''} = \frac{1}{\tan(\phi)} \quad (4)$$

$$\phi = \phi_{\text{displacement}} - \phi_{\text{force}} \quad (5)$$

$$\Delta\phi = \phi(t) - \phi(t_0) \quad (6)$$

The phase shift is capable of providing the ratio of the shear storage to the shear loss modulus, i.e., the ratio of the tissue elasticity to the viscosity. Although phase shift by itself requires quantification using shear or Young's modulus, it nevertheless represents a standard biomechanical parameter independent of changes in the tissue acoustic properties. As the Young's modulus represents tissue elasticity, the phase shift is a model-independent biomechanical parameter that can be used to assess the tissue viscoelasticity. Also, the HMI phase shift is a localized parameter that is estimated using the only the phase of focal displacement and force during the force application. In this study, we will investigate the relative change in the difference of phase shift degree across the monitoring stage with respect to starting time of treatment (t_0), namely ϕ , or namely, the relative change in focal phase shift (ϕ). The reader is referred to Vappou *et al.*, (2009) for a comprehensive viscoelasticity investigation using HMI.

1c. Compressive Strain—In the presented HMIFU study, compressive strains can be estimated at adjacent regions of the focal zone in the axial direction (ϵ_{zz}), which can be estimated through calculation of the spatial derivative of the displacement:

$$\varepsilon_{zz} = \frac{\varphi u_z}{\varphi x_z} \quad (5)$$

Compared to the displacement, the strain has higher spatial resolution, i.e., measurement across a tissue depth of 1 to 2 mm compared to 5 to 7 mm for displacement (Figure 1). In this study, we studied three cases of the axial compressive strains during monitoring for treatment of 10W at 10, 20, and 30 seconds, respectively. Strain monitoring cases from other treatment parameters were not included due to poor signal to noise ratio (SNR) amongst the estimated focal displacements.

2. Experimental protocol

Canine livers (subject=7, lobes = 28) were excised immediately upon animal sacrifice and immersed into a degassed Phosphate buffered saline (PBS) solution bath maintained at room temperature. All procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of Columbia University. Each specimen was fixed using metallic needles onto an acoustic absorber submerged in a de-ionized and degassed PBS tank. The HMIFU system was comprised of a 4.75MHz focused Lead Zirconate Titanate (PZT) (outer diameter 80 mm, inner diameter 16.5 mm, focal depth 9 cm) transducer (Riverside Research Institute, New York, NY) for probing tissue with an AM frequency of 25 Hz, and a confocal 7.5 MHz single-element pulse-echo transducer (Olympus-NDT, Waltham, MA, U.S.A.) with a diameter of 15 mm and a focal length of 6 cm for simultaneous RF signals acquisition at a frame rate of 4 kHz. Raster scans were completed by mechanically moving the transducers through a 3D translational system (Velmex Inc., Bloomfield, NY, U.S.A.) for targeting and raster scan purposes (Figure 2). The extrapolated *in situ* focal acoustic intensity and power was equal to 5546 W/cm², 7164 W/cm², and 9067 W/cm², at 8W, 10W, and 11W, respectively. The treatment power and duration were selected to fall within the boiling regime range and so as to investigate the performance of HMI under different power and duration as typically used in HIFU (Hou *et al.*, 2013a). The received RF signals were band-pass filtered (Reactel, Inc., Gaithersburg, Maryland, USA) with cutoff frequencies of $f_{c1} = 5.84$ MHz and $f_{c2} = 8.66$ MHz (at -60dB) and recorded along with the excitation signal representing the force profile and a dual-channel data acquisition unit (Gage applied, Lockport, IL, U.S.A.) at a sampling frequency of 80 MHz (Figure 2). Subsequently, a 1-D normalized cross-correlation (window size of 3.85 mm and 90% overlap) technique (Luo and Konofagou, 2010) was used to estimate the displacement and axial compressive strains were estimated using a least-square estimator on the RF signals (Kallel and Ophir, 1997). In each HMIFU treatment, 2D transverse HMI displacement maps were also obtained through raster scan acquisition before and after lesion formation. A 3 × 3 median filter was applied on the displacement profiles in order to enhance the SNR of the displacement map. Lesion-to-displacement contrast values were assessed by taking the ratio of HMI focal displacement outside to inside of the mapped thermal lesion on the 2D transverse HMI displacement map after the HIFU treatment. In order to confirm the presence of tissue boiling at the proposed treatment level, Passive Cavitation Detection (PCD) monitoring was also performed by operating the conically-aligned pulse-echo transducer in passive mode in conjunction with thermocouple measurement. Focal temperature monitoring was performed by inserting a T-

type bare wire thermocouple with diameter of 25 μm (Omega Inc., Stamford, CT) inside the tissue. The diameter of the thermocouple was chosen to be smaller than 1/10 of the carrier wavelength in order to minimize reflection and viscous heating artifacts (Wang *et al.*, 2011).

Results

First, PCD monitoring were investigated at the three acoustic power levels of 8, 10, and 11 W for 30 seconds, respectively, where all spectrograms detected significant increase in broadband noise, indicating formation of strong bubble dynamics likely to be induced by tissue boiling (Figures 3a, 3b, 3c) (Hou *et al.*, 2013a). The thermocouple temperature measurement at the minimum power case of 8W also confirmed the presence of boiling; display of a sharp exponential increment followed by an unsteady trend around 100° C, which is a result of the shielding effect due to bubble formation at the focal region (Figure 3d). Consequentially, forty-three HIFU lesions were induced across all of the treatment power levels with the presence of boiling throughout this study. We first investigated our studies on nine HMIFU treatments on three pieces of *ex vivo* canine livers where HIFU treatments were repeated under acoustic intensity and power of 7164 W/cm² and 10 W for durations of 10-, 20-, and 30-s. As the treatment duration increased, both the relative change in peak-to-peak value of HMI focal displacement (-8.67 ± 4.80 , -14.44 ± 7.77 , -24.03 ± 12.11 μm) and peak axial compressive strain (-0.16 ± 0.06 , -0.71 ± 0.30 , -0.68 ± 0.36 %) exhibited decrease throughout the treatment, whereas the ϕ showed slight increase at 10 s and significant decrease at 20, 30-s cases ($+1.80 \pm 6.80^\circ$, $-15.80 \pm 9.44^\circ$, $-18.62 \pm 13.14^\circ$) (Figures. 4 and 5) with a few monitoring time points around the focal zone where ϕ exhibited an increase in spatial variation. The standard deviation of both HMI focal displacement and phase shift monitoring curve refers to the average of measurements across the focal zone (2 mm) at the HIFU focusing depth inside the tissue. The 2D HMI displacement images also mapped an increase in lesion-to-background displacement contrast (1.34 ± 0.19 , 1.98 ± 0.30 , 2.26 ± 0.80) and lesion size with treatment time (40.95 ± 8.06 , 47.6 ± 4.87 , 52.23 ± 2.19 mm²), which was verified with pathology results (25.17 ± 6.99 , 42.17 ± 1.77 , 47.17 ± 3.10 mm²) (Figures. 5 and 6.1).

However, during the reproducibility studies as we repeated our multi-parametric HMIFU protocol across three different acoustic powers (8 W, 10 W, and 11 W) under treatment durations of 10-, 20-, and 30-s, there was a discrepancy in the distribution of the HMI lesion maps consisting of reversed lesion-to-background HMI displacement contrast, namely blue (HMI focal displacement decrease) lesion cases [Figure 6.1], where the 2D HMI displacement contrast map (c,h,m) showed a decrease of displacement inside the thermal lesion and red (HMI focal displacement increase) [Figure 6.2] lesion cases were found [Figure 6.3]. In addition, these results also confirmed that such a discrepancy was observed across all of the investigated treatment power and duration range where boiling was present [Figure 7a]. The magnitude change of HMI displacement spanned from decreased (blue) to increased (red) cases amongst the 8W, 10W treatment cases and only increased cases were detected at 11 W under 10, 20, and 30 seconds treatment, respectively [Figures 7a, Table 1, 2, 3]. For the ϕ , the range of the observed values also spanned across increased and decreased cases at 8W, 10W, whereas only decreased displacement and phase shift cases were detected at 11W treatment cases under 10, 20, and 30 seconds treatment [Figure 7b,

Table 1,2,3]. For the estimated lesion-to-background contrast, both increased and decreased cases were observed across all the treatment power levels [Figure 7c, Table 1,2,3]. Lastly, the mapped lesion size from the constructed 2D HMI image increased with treatment duration across all 8W, 10W, then slightly decreased for 11W treatment cases [Figure 7d, Table 1,2,3], confirmed with similar trends in gross pathology assessment [Figure 7e, Figure 7f Table 1,2,3].

Discussion

HIFU is an emerging technology that holds great promise as a cost effective, noninvasive, non-ionizing, extracorporeal tumor ablation method with a short recovery period. Across its three procedural stages, i.e., treatment planning, treatment monitoring, and treatment assessment, numerous assistive techniques have been developed in the field of MRI, ultrasound, and acousto-optics. Despite recent advancements for such guidance and assessment techniques, the treatment monitoring stage of HIFU especially during boiling remains as a critical challenge with respect to quantitative, localized, reliable, and real-time feedback requirements. HMIFU is a dynamic ultrasound-based elasticity imaging technique using a pair of confocally-aligned HIFU and pulse-echo transducers for inducing and tracking a stable focal oscillatory motion, which is directly related to the local mechanical property. This has provided the HMIFU with the capability of performing localized HIFU monitoring without interrupting the treatment. In the past, the HMIFU feasibility was shown in the assessment of tissue relative stiffness as well as HIFU monitoring based on the displacement amplitude change. Throughout this study, we investigated the feasibility of a comprehensive HMIFU monitoring method with high energy HIFU treatment that induced boiling, which incorporated a multi-parametric monitoring method including focal displacement, focal compressive axial strain, and relative change in focal phase shift (ϕ). We hypothesized the multi-parametric monitoring method improves the monitoring quality of HMIFU, i.e., 1) under boiling at high energy HIFU treatment 2) providing complementary analysis with each parameter for indication of various tissue response changes upon formation of a thermal lesion, 3) decoupling of acoustic and mechanical tissue parameters. Multi-parametric HMIFU was applied on HIFU treatment monitoring and assessment under three different acoustic powers (8W, 10W, and 11W) and durations (10 s, 20 s, and 30 s).

Although the previous literature and our assessment of *ex vivo* liver showed a slow progressive elasticity decay under HIFU treatment with progressive decay in displacement or shear modulus (Maleke and Konofagou, 2008; Sapin-de Brosses *et al.*, 2010; Sapin-de Brosses *et al.*, 2011; Wu *et al.*, 2001b), we found that across the HIFU treatment cases with boiling, the 2D HMI displacement images displayed reverse lesion-to-background displacement contrast. Figures 6.1-6.3 demonstrate a case of displacement discrepancy between lesions with increased and decreased displacement under same HIFU treatment sequence. For HIFU treatment under 10W and lasting 10 second (a-e), 20 second (f-j), and 30 second (k-o), there were discrepancies where some cases exhibited a decrease trend in focal monitoring displacement during treatment (6.1 d,i,n) whereas others exhibited an increase trend (Figure 6.2 d,i,n). The corresponding displacement contrast images of each treatment also mapped the consistent change of displacement increase (6.1 c,h,m) and

decrease (6.2 c,h,m), accordingly. We summarized our finding amongst the 10 W treatment cases, and found out that such discrepancies were present across all treatment durations where cases of both increase and decrease displacement were detected (Figure 6.3). Throughout our reproducibility studies, we also confirmed the consistency of such observation across all the treatment powers we have investigated in this study. Additionally, it is noteworthy that the changes in displacement were always consistent with its corresponding displacement monitoring curves across all of the treatment cases.

Figure 7 plots the outcome distribution of each parameter for all HIFU treatment cases performed at 8W (blue), 10W (magenta), and 11W (red). In Figure 7a and 7c, it was shown that, depending on the case, the HMI displacement will increase or decrease after lesioning but always reflect a change as a result of treatment regardless of the treatment or duration, indicating the consistent effect of boiling. Nevertheless, HMI was capable of detecting the lesion at all treatment durations and powers, i.e., the HMI displacement contrast ratio was different from one in every case where lesion was formed. The phase shift (Figure 7b), on the other hand remained relatively consistent, despite a few outliers, indicating a consistent decrease trend (Table 1,2,3). In addition, the mapped lesion sizes from HMI contrast maps (Figure 7d) were consistent with the measurements in gross pathology findings (Figure 7e). A good correlation was found between the thermal lesion sizes as mapped by HMI and gross pathology findings (Figure 7f). In addition, there was an increase of lesion size from 8W to 10W then decrease in lesion size from 10W to 11W possibly due to the shielding effect associated with attenuation under strong boiling activity (Table 1, 2, 3). There can be several reasons for such reversal of displacement outcomes: Based on the measured focal temperature curve and PCD spectrograms, it was found that the focal region reaches boiling within first few seconds of the treatment window. That said, there have been discussions that beyond a certain temperature threshold, e.g., boiling, as well as the mechanism such as tissue pulverization(Shahmirzadi *et al.*, 2012), gelatification (Kiss *et al.*, 2009; Sapin-de Broses *et al.*, 2010; Sapin-de Broses *et al.*, 2011), or shielding due to bubble occurrence and increase of acoustic absorption (Damianou *et al.*, 1997) can occur with continuous delivery of high thermal dosage (Ter Haar *et al.*, 1989). More importantly, the increase in attenuation can be due to either boiling and/or formation of thermal lesion(Sokka *et al.*, 2003), resulting an enhanced radiation force, i.e., higher displacement inside the lesion that creates an opposite lesion-to-background contrast. It is therefore concluded that the blue (or, displacement decrease) lesion maps may have been obtained in cases where the mechanical response change dominated (stiffening) over the structural and/or absorption change whereas the red lesion maps represented cases where the acoustic response change dominated (increase in attenuation). This finding can be supported from the aspect of change in the relative phase shift: It is noteworthy that the average phase shifts exhibited decrease with heating, especially for the 20 and 30 second treatment cases with the 2D HMI maps having either blue or red lesion-to-background displacement ratio, indicating a consistent tissue mechanical response change during acoustic property changes. Furthermore, we have completed a rheometer based mechanical testing study on HIFU lesions induced on *ex vivo* canine liver using the same treatment settings as previously described. In turn, we found the shear modulus of HIFU lesions samples to range between 10 to 15 times compared to that of the untreated samples(Shahmirzadi *et al.*, 2012). Therefore, this validates the fact that all

lesions investigated in this study did undergo mechanical stiffening, i.e., absorption changes were likely to be dominant amongst the cases where displacement increased.

In addition to displacement monitoring, we also investigated changes in strain during monitoring on a total number of nine treatment cases at 10W treatment, where we found a decrease in the axial compressive strain, which proved the feasibility of HMIFU to confirm relative stiffness monitoring at a finer spatial resolution. However, not only does strain estimation rely on the displacement SNR, but also the SNR of the displacement profile across the focal zone inside the tissue, i.e., the end of the focal excitation zone must be clearly mapped in order to estimate for the axial compressive strain by calculating the spatial derivative. In this study, the strains were found to be noisier at other powers and the performance of HMI strain estimation is part of ongoing efforts in our group. The ϕ also showed an interesting trend, where the 10-sec cases indicated a slight increase whereas both the 20 and 30 second cases indicated a significant decrease following an initial increase (Figure 7b, Table 1,2,3). Nevertheless, ϕ consistently decreased amongst all lesions detected a with reverse displacement trend under the same treatment, confirming its strength as an independent biomechanical property marker. Additionally, the 2D HMI displacement images clearly mapped the relative increase of the lesion size and lesion-to-background contrast, which were comparable to previous studies (Hou et al., 2010; Dasgupta et al., 2010; Kun and Wan, 2005; Chenot et al., 2010). There was a slight decrease from the cases of treatment under 20 to 30 seconds, which could stem from either reduced thermal ablation at the pre-focal shielding effects (Table 1, 2, 3).

Despite the unpredictable change in acoustic properties in the presence of boiling, our results in treatment assessment also indicated the capability of HMIFU in displacement mapping across all treatment power levels and durations reaching boiling, demonstrating the robustness of HMIFU under high energy HIFU treatment. Moreover, the consistent trend decrease in ϕ amongst all of the formed lesion cases proved its usefulness as an independent biomechanical parameter for both monitoring and assessment. However, the strains were not estimated for lesion mapping during post-assessment phase due to the low SNR of the displacement when short lower pulse sequences were used compared to that of the monitoring study. Nevertheless, HMIFU was shown robust and reliable in mapping HIFU lesions formed with boiling despite the change in acoustic absorption. Ongoing and future investigations include the study of the slow denaturation treatments where HMIFU monitoring showed a consistent trend where displacement increased then decreased, indicating tissue softening and stiffening (Hou *et al.*, 2012), and the change in tissue stiffness such as gelatification and pulverization at various thermal dose levels (Shahmirzadi *et al.*, 2012). Furthermore, additional studies are being performed to study the relationship between the proposed monitoring parameters to both the PCD-based cavitation level as well as thermocouple-based focal temperature profile under the HIFU slow denaturation regime (Hou *et al.*, 2013a). Thermocouple measurements are not deemed reliable in the presence of boiling.

Conclusion

A multi-parametric HMIFU framework using focal displacement, relative change in phase shift, and compressive strain was developed to independently track the change in acoustic and viscoelastic tissue response under high energy HIFU treatment with boiling. Despite all studies were performed under boiling where displacement monitoring and lesion map contrast showed a consistent reversal trend between increase and decrease, every parameter underwent a clear change in absolute magnitude upon lesion formation, indicating its feasibility in monitoring the drastic change of acoustic and/or mechanical property change throughout formation of HIFU lesion. In addition, relative change in phase shift showed a consistent decrease at longer treatment duration, indicating acoustically-independent mechanical change. Transverse 2D HMI images were also investigated and showed feasibility in mapping the increase in lesion size and lesion-to-background contrast.

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Appendix

In this study, 2D transverse HMI displacement maps were obtained before and after lesion formation through raster scanning on all treatment cases, where we utilized the displacement distribution for mapping both the lesion size and lesion-to-background displacement contrast. In addition to use of displacement, we also investigated the feasibility of mapping the lesion using the relative change in phase shift taken from the same displacement and input force acquired at the corresponding raster scan coordinate. Despite the changes in lesion-to-background displacement contrast across all of the treatment durations [Figure A1. (a,d,g) vs. Figure A2 (a,d,g)], ϕ shows a consistent decrease within the thermal lesion [Figure A1. (b,e,h) vs. Figure A2. (b,e,h)], which indicates a consistent change in viscosity-to-elasticity ratio and its robustness as an independent biomechanical parameter.

Figure A1.

Displacement map (a,d,g) and corresponding ϕ maps (b,e,h) for lesions with decreased displacement. Note when displacement decays, the ϕ maps also indicates decrease in phase shift change within area of formed lesion (c,f,i).

Figure A2.

Displacement contrast map (a,d,g) and corresponding ϕ maps (b,e,h) for lesions with increased displacement. Despite when displacement showed reversal trend, i.e., increase, the ϕ maps still showed consistent decrease inside the lesion (c,f,i), indicating a consistent biomechanical property change.

References

- Al-Bataineh O, Jenne J, Huber P. Clinical and future applications of high intensity focused ultrasound in cancer. *Cancer Treatment Reviews*. 2012; 38:346–53. [PubMed: 21924838]
- Alizad A, Fatemi M, Whaley DH, Greenleaf JF. Application of vibro-acoustography for detection of calcified arteries in breast tissue. *Journal of Ultrasound in Medicine*. 2004; 23:267–73. [PubMed: 14992365]
- Anand A, Kaczkowski PJ. Monitoring formation of high intensity focused ultrasound (HIFU) induced lesions using backscattered ultrasound. *Acoustics Research Letters Online-Arlo*. 2004; 5:88–94.
- Arnal B, Pernot M, Tanter M. Monitoring of Thermal Therapy Based on Shear Modulus Changes: I. Shear Wave Thermometry. *Ieee T Ultrason Ferr*. 2011a; 58:369–78.
- Arnal B, Pernot M, Tanter M. Monitoring of Thermal Therapy Based on Shear Modulus Changes: II. Shear Wave Imaging of Thermal Lesions. *Ieee T Ultrason Ferr*. 2011b; 58:1603–11.
- Bailey MR, Khokhlova VA, Sapozhnikov OA, Kargl SG, Crum LA. Physical mechanisms of the therapeutic effect of ultrasound - (A review). *Acoustical Physics*. 2003; 49:369–88.
- Bercoff J, Chaffai S, Tanter M, Sandrin L, Catheline S, Fink M, Gennisson JL, Meunier M. In vivo breast tumor detection using transient elastography. *Ultrasound in Medicine and Biology*. 2003; 29:1387–96. [PubMed: 14597335]
- Bharat S, Techavipoo U, Kiss M, Liu W, Varghese T. Monitoring stiffness changes in lesions after radiofrequency ablation at different temperatures and durations of ablation. *Ultrasound in Medicine and Biology*. 2005; 31:415–22. [PubMed: 15749565]
- Bing KF, Rouze NC, Palmeri ML, Rotemberg VM, Nightingale KR. Combined Ultrasonic Thermal Ablation with Interleaved ARFI Image Monitoring Using a Single Diagnostic Curvilinear Array: A Feasibility Study. *Ultrasonic Imaging*. 2011; 33:217–32. [PubMed: 22518953]
- Casper A, Liu DL, Ebbini ES. Realtime Control of Multiple-focus Phased Array Heating Patterns Based on Noninvasive Ultrasound Thermography. *Ieee Transactions on Biomedical Engineering*. 2012; 59:95–105. [PubMed: 21768037]
- Chavrier F, Chapelon JY, Gelet A, Cathignol D. Modeling of high-intensity focused ultrasound-induced lesions in the presence of cavitation bubbles. *Journal of the Acoustical Society of America*. 2000; 108:432–40. [PubMed: 10923905]
- Chen LL, Rivens I, Terhaar G, Riddler S, Hill CR, Bensted JPM. Histological-Changes in Rat-Liver Tumors Treated with High-Intensity Focused Ultrasound. *Ultrasound in Medicine and Biology*. 1993; 19:67–74. [PubMed: 8456530]
- Chen LL, ter Haar G, Robertson D, Bensted JPM, Hill CR. Histological study of normal and tumor-bearing liver treated with focused ultrasound. *Ultrasound in Medicine and Biology*. 1999; 25:847–56. [PubMed: 10414902]
- Chenot J, Melodelima D, WA. ND, Souchon R, Rivoire M, JY. C. Intra-operative ultrasound hand-held strain imaging for the visualization of ablations produced in the liver with a toroidal HIFU transducer: first in vivo results. *Phys Med Biol*. 2010; 55:3131–44. [PubMed: 20479514]
- Cline HE, Hynynen K, Watkins RD, Adams WJ, Schenck JF, Ettinger RH, Freund WR, Vetro JP, Jolesz FA. Focused US System for MR Imaging-Guided Tumor Ablation. *Radiology*. 1995; 194:731–7. [PubMed: 7862971]
- Cui HZ, Yang XM. Real-time monitoring of high-intensity focused ultrasound ablations with photoacoustic technique: An in vitro study. *Medical Physics*. 2011; 38:5345–50. [PubMed: 21992353]
- Curiel L, Chopra R, Hynynen K. In vivo monitoring of focused ultrasound surgery using local harmonic motion. *Ultrasound in Medicine and Biology*. 2009; 35:65–78. [PubMed: 18805626]
- Curiel L, Soucho R, Rouvère O, Gelet A, JY. C. Elastography for the follow-up of high-intensity focused ultrasound prostate cancer treatment: Initial comparison with MRI. *Ultrasound in Medicine and Biology*. 2005; 31:1461–3. [PubMed: 16286025]
- Damianou CA, Sanghvi NT, Fry FJ, MaassMoreno R. Dependence of ultrasonic attenuation and absorption in dog soft tissues on temperature and thermal dose. *Journal of the Acoustical Society of America*. 1997; 102:628–34. [PubMed: 9228822]

- Dasgupta S, Wansapura J, Harihara P, Pratt R, Witte D, Myers M, Banerjee R. HIFU volume as function of time, as determined by MRI, histology, and computations. *Journal of Biomechanical Engineering*. 2010; 132:081055.
- Fahey BJ, Nightingale KR, Stutz DL, Trahey GE. Acoustic radiation force impulse imaging of thermally- and chemically-induced lesions in soft tissues: Preliminary ex vivo results. *Ultrasound in Medicine and Biology*. 2004; 30:321–8. [PubMed: 15063514]
- Fatemi M, Greenleaf JF. Vibro-acoustography: An imaging modality based on ultrasound-stimulated acoustic emission. *Proceedings of the National Academy of Sciences of the United States of America*. 1999; 96:6603–8. [PubMed: 10359758]
- Furusawa H, Namba K, Thomsen S, Akiyama F, Bendet A, Tanaka C, Yasuda Y, Nakahara H. Magnetic resonance-guided focused ultrasound surgery of breast cancer: Reliability and effectiveness. *Journal of the American College of Surgeons*. 2006; 203:54–63. [PubMed: 16798487]
- Gianfelice D, Khiat A, Amara M, Belblidia A, Boulanger Y. MR imaging-guided focused ultrasound surgery of breast cancer: correlation of dynamic contrast-enhanced MRI with histopathologic findings. *Breast Cancer Research and Treatment*. 2003; 82:93–101. [PubMed: 14692653]
- Grissom WA, Kerr AB, Holbrook AB, Pauly JM, Butts-Pauly K. Maximum Linear-Phase Spectral-Spatial Radiofrequency Pulses for Fat-Suppressed Proton Resonance Frequency-Shift MR Thermometry. *Magnet Reson Med*. 2009; 62:1242–50.
- Hou, G.; Marquet, F.; Wang, S.; Konofagou, E. Optimization of Real-Time Acoustical and Mechanical Monitoring of High Intensity Focused Ultrasound (HIFU) treatment using Harmonic Motion Imaging for High Intensity Focused Ultrasound (HMIFU); 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society; Osaka, Japan. 2013a.
- Hou, GY.; Jianwen, L.; Maleke, C.; Konofagou, EE. Simulation of HMIFU (Harmonic Motion Imaging for Focused Ultrasound) with in-vitro validation. *Bioengineering Conference, Proceedings of the 2010 IEEE 36th Annual Northeast*; 2010. p. 1-2.
- Hou GY, Marquet F, Wang S, Konofagou EE. Performance optimization of High Intensity Focused Ultrasound (HIFU) treatment monitoring using Harmonic Motion Imaging for Focused Ultrasound (HMIFU). *Phys Med Biol*. 2012
- Hou, GY.; Marquet, F.; Wang, S.; Konofagou, EE. Optimization of Real-Time Acoustical and Mechanical Monitoring of High Intensity Focused Ultrasound (HIFU) treatment using Harmonic Motion Imaging for High Intensity Focused Ultrasound (HMIFU). 2013b. (In preparation)
- Huber PE, Jenne JW, Rastert R, Simiantonakis I, Sinn HP, Strittmatter HJ, von Fournier D, Wannenmacher MF, Debus J. A new noninvasive approach in breast cancer therapy using magnetic resonance imaging-guided focused ultrasound surgery. *Cancer Research*. 2001; 61:8441–7. [PubMed: 11731425]
- Hynynen K, Pomeroy O, Smith DN, Huber PE, McDannold NJ, Kettenbach J, Baum J, Singer S, Jolesz FA. MR imaging-guided focused ultrasound surgery of fibroadenomas in the breast: A feasibility study. *Radiology*. 2001; 219:176–85. [PubMed: 11274554]
- Ishihara Y, Calderon A, Watanabe H, Okamoto K, Suzuki Y, Kuroda K, Suzuki Y. Precise and Fast Temperature Mapping Using Water Proton Chemical-Shift. *Magnet Reson Med*. 1995; 34:814–23.
- Jensen CR, Ritchie RW, Gyongy M, Collin JRT, Leslie T, Coussios CC. Spatiotemporal Monitoring of High-Intensity Focused Ultrasound Therapy with Passive Acoustic Mapping. *Radiology*. 2012; 262:252–61. [PubMed: 22025731]
- Kallel F, Ophir J. A least squares estimator for elastography. *Ultrasonic Imaging*. 1997; 19:195–208. [PubMed: 9447668]
- Kallel F, Stafford RJ, Price RE, Righetti R, Ophir J, Hazle JD. The feasibility of elastographic visualization of HIFU-induced thermal lesions in soft tissues. *Ultrasound in Medicine and Biology*. 1999; 25:641–7. [PubMed: 10386741]
- Kaye EA, Chen J, Pauly KB. Rapid MR-ARFI Method for Focal Spot Localization During Focused Ultrasound Therapy. *Magnet Reson Med*. 2011; 65:738–43.
- Kennedy JE. High-intensity focused ultrasound in the treatment of solid tumours. *Nature Reviews Cancer*. 2005; 5:321–7.

- Khokhlova TD, Canney MS, Lee D, Marro KI, Crum LA, Khokhlova VA, Bailey MR. Magnetic resonance imaging of boiling induced by high intensity focused ultrasound. *Journal of the Acoustical Society of America*. 2009; 125:2420–31. [PubMed: 19354416]
- Kiss MZ, Daniels MJ, Varghese T. Investigation of temperature-dependent viscoelastic properties of thermal lesions in ex vivo animal liver tissue. *Journal of Biomechanics*. 2009; 42:959–66. [PubMed: 19362313]
- Konofagou EE, Hynynen K. Localized harmonic motion imaging: Theory, simulations and experiments. *Ultrasound in Medicine and Biology*. 2003; 29:1405–13. [PubMed: 14597337]
- Kruse SASJ, Lawrence AJ, Dresner MA, Manduca A, Greenleaf JF, Ehman RL. Tissue characterization using magnetic resonance elastography: preliminary results. *Phys Med Biol*. 2000; 45:1579–90. [PubMed: 10870712]
- Kun G, Wan MX. A comparison of HIFU-induced lesion size measurement based on gross histological examination and image of bovine thigh in vitro. *Ultrasonics*. 2005; 43:351–5. [PubMed: 15737385]
- Lai PX, McLaughlan JR, Draudt AB, Murray TW, Cleveland RO, Roy RA. Real-Time Monitoring of High-Intensity Focused Ultrasound Lesion Formation Using Acousto-Optic Sensing. *Ultrasound in Medicine and Biology*. 2011; 37:239–52. [PubMed: 21208729]
- Lele PP. Concurrent detection of the production of ultrasonic lesions. *Med Biol Eng*. 1966; 4:451–6. [PubMed: 5975870]
- Lewa CJ. Magnetic-resonance-imaging in the presence of mechanical waves. *Spectroscopy Letters*. 1991; 24:55–67.
- Lizzi FL, Muratore R, Deng CX, Ketterling JA, Alam SK, Mikaelian S, Kalisz A. Radiation-force technique to monitor lesions during ultrasonic therapy. *Ultrasound in Medicine and Biology*. 2003; 29:1593–605. [PubMed: 14654155]
- Luo JW, Konofagou EE. A Fast Normalized Cross-Correlation Calculation Method for Motion Estimation. *Ieee T Ultrason Ferr*. 2010; 57:1347–57.
- Maleke C, Konofagou EE. Harmonic motion imaging for focused ultrasound (HMIFU): a fully integrated technique for sonication and monitoring of thermal ablation in tissues. *Phys Med Biol*. 2008; 53:1773–93. [PubMed: 18367802]
- Maleke C, Konofagou EE. In vivo feasibility of real-time monitoring of focused ultrasound surgery (FUS) using Harmonic Motion Imaging (HMI). *IEEE Transactions on biomedical Engineering*. 2009; 57:7–11. [PubMed: 19643703]
- Maleke C, Konofagou EE. In Vivo Feasibility of Real-Time Monitoring of Focused Ultrasound Surgery (FUS) Using Harmonic Motion Imaging (HMI). *IEEE Transactions on biomedical Engineering*. 2010; 57:7–11. [PubMed: 19643703]
- Maleke C, Pernot M, Konofagou EE. Single-element focused ultrasound transducer method for harmonic motion imaging. *Ultrasonic Imaging*. 2006; 28:144–58. [PubMed: 17147056]
- Marquet, F.; Wang, S.; Hou, GY.; Konofagou, EE. Boiling Effects on the Performance of Harmonic Motion Imaging for Focused Ultrasound. *IEEE International Ultrasonics Symposium*; Dresden, Germany. 2012.
- Mitri F, Davis B, Alizad A, Greenleaf J, Wilson T, Mynderse L, Fatemi M. Prostate cryotherapy monitoring using vibro-acoustography: Preliminary results of an ex vivo study and technical feasibility. *IEEE Transactions on biomedical Engineering*. 2008; 55:2584–92. [PubMed: 18990628]
- Multhupillai RLD, Rossman PJ, Greenleaf JF, Manduca A, Ehman RL. Magnetic resonance elastography by direct visualization of propagating acoustic strain waves. *Science*. 2001; 269:1854–7.
- Nandlall SD, Jackson E, Coussios CC. Real-Time Passive Acoustic Monitoring of Hifu-Induced Tissue Damage. *Ultrasound in Medicine and Biology*. 2011; 37:922–34. [PubMed: 21601136]
- Nightingale KR, Palmeri ML, Nightingale RW, Trahey GE. On the feasibility of remote palpation using acoustic radiation force. *Journal of the Acoustical Society of America*. 2001; 110:625–34. [PubMed: 11508987]
- Nyborg WL. Acoustic Streaming near a Boundary. *Journal of the Acoustical Society of America*. 1958; 30:329–39.

- Ophir J, Cespedes I, Ponnekanti H, Yazdi Y, Li X. Elastography: A quantitative method for imaging the elasticity of biological tissues. *Ultrasonic Imaging*. 1991; 13:111–34. [PubMed: 1858217]
- Palmeri ML, Sharma AC, Bouchard RR, Nightingale RW, Nightingale KR. A finite-element method model of soft tissue response to impulsive acoustic radiation force. *Ieee T Ultrason Ferr*. 2005; 52:1699–712.
- Parker KJ, Huang SR, Musulin RA, Lerner RM. Tissue response to mechanical vibrations for Sonoelasticity Imaging. *Ultrasound Med. Biol*. 1990; 16:241–6. [PubMed: 2194336]
- Pernot M, Tanter M, Bercoff J, Waters KR, Fink M. Temperature estimation using ultrasonic spatial compound imaging. *Ieee T Ultrason Ferr*. 2004; 51:606–15.
- Righetti R, Kallel F, Stafford RJ, Price RE, Krouskop TA, Hazle JD, Ophir J. Elastographic characterization of HIFU-induced lesions in canine livers. *Ultrasound in Medicine and Biology*. 1999; 25:1099–113. [PubMed: 10574342]
- Sapin-de Broses E, Gennisson JL, Pernot M, Fink M, Tanter M. Temperature dependence of the shear modulus of soft tissues assessed by ultrasound. *Phys Med Biol*. 2010; 55:1701–18. [PubMed: 20197599]
- Sapin-de Broses E, Pernot M, Tanter M. The link between tissue elasticity and thermal dose in vivo. *Phys Med Biol*. 2011; 56:7755–65. [PubMed: 22094357]
- Sarvazyan AP, Rudenko OV, Swanson SD, Fowlkes JB, Emelianov SY. Shear wave elasticity imaging: a new ultrasonic technology of medical diagnostics. *Ultrasound in Medicine and Biology*. 1998; 24:1419–35. [PubMed: 10385964]
- Seip R, Ebbini ES. Noninvasive Estimation of Tissue Temperature Response to Heating Fields Using Diagnostic Ultrasound. *Ieee Transactions on Biomedical Engineering*. 1995; 42:828–39. [PubMed: 7642197]
- Shahmirzadi D, Hou GY, Konofagou EE. Ex Vivo Characterization of Canine Liver Tissue Viscoelasticity Following High Intensity Focused Ultrasound (HIFU) Ablation. *Ultrasound in Medicine and Biology*. 2012
- Sinkus R, Lorenzen J, Schrader D, Lorenzen M, Dargatz M, Holz D. High-resolution tensor MR elastography for breast tumour detection. *Phys Med Biol*. 2000; 45:1649–64. [PubMed: 10870716]
- Smith DN, Hynynen KH, Pomeroy OH, Huber PE, McDannold NJ, Kettenbach J. MRI guided focused ultrasound surgery (FUS) of fibroadenomas in the breast. *Radiology*. 2000; 217:268.
- Sokka SD, King R, Hynynen K. MRI-guided gas bubble enhanced ultrasound heating in in vivo rabbit thigh. *Phys Med Biol*. 2003; 48:223–41. [PubMed: 12587906]
- Souchon R, Rouviere O, Gelet A, Detti V, Srinivasan S, Ophir J, Chapelon JY. Visualisation of hifu lesions using elastography of the human prostate in vivo: Preliminary results. *Ultrasound in Medicine and Biology*. 2003; 29:1007–15. [PubMed: 12878247]
- Stafford RJ, Kallel F, Price RE, Cromeens DM, Krouskop TA, Hazle JD, Ophir J. Elastographic imaging of thermal lesions in soft tissue: A preliminary study in vitro. *Ultrasound in Medicine and Biology*. 1998; 24:1449–58. [PubMed: 10385966]
- Ter Haar G. Ultrasound Focal Beam Surgery. *Ultrasound in Medicine and Biology*. 1995; 21:1089–100. [PubMed: 8849823]
- Ter Haar G, Rivens I, Chen L, Riddler S. High-Intensity Focused Ultrasound for the Treatment of Rat-Tumors. *Phys Med Biol*. 1991; 36:1495–501. [PubMed: 1754620]
- Ter Haar G, Sinnott D, Rivens I. High-Intensity Focused Ultrasound - a Surgical Technique for the Treatment of Discrete Liver-Tumors. *Phys Med Biol*. 1989; 34:1743–50. [PubMed: 2685839]
- Thitaikumar A, Mobbs LM, Kraemer-Chant CM, Garra BS, Ophir J. Breast tumor classification using axial shear strain elastography: a feasibility study. *Phys Med Biol*. 2008; 53:4809–23. [PubMed: 18701768]
- Thittai AK, Galaz B, Ophir J. Visualization of Hifu-Induced Lesion Boundaries by Axial-Shear Strain Elastography: A Feasibility Study. *Ultrasound in Medicine and Biology*. 2011; 37:426–33. [PubMed: 21276656]
- Vappou J, Maleke C, Konofagou EE. Quantitative viscoelastic parameters measured by Harmonic Motion Imaging. *Phys Med Biol*. 2009; 54:3579–94. [PubMed: 19454785]

- Wang ST, Frenkel V, Zderic V. Optimization of pulsed focused ultrasound exposures for hyperthermia applications. *Journal of the Acoustical Society of America*. 2011; 130:599–609. [PubMed: 21786925]
- Wu F, Chen WZ, Bai J, Zou JZ, Wang ZL, Zhu H, Wang ZB. Pathological changes in human malignant carcinoma treated with high-intensity focused ultrasound. *Ultrasound in Medicine and Biology*. 2001a; 27:1099–106. [PubMed: 11527596]
- Wu F, Wang ZB, Cao YD, Chen WZ, Zou JZ, Bai J, Zhu H, Li KQ, Jin CB, Xie FL, Su HB, Gao GW. Changes in biologic characteristics of breast cancer treated with high-intensity focused ultrasound. *Ultrasound Med Biol*. 2003; 29:1487–92. [PubMed: 14597346]
- Wu F, Wang ZB, Zhu H, Chen WZ, Zou JZ, Bai J, Li KQ, Jin CB, Xie FL, Su HB. Extracorporeal high intensity focused ultrasound treatment for patients with breast cancer. *Breast Cancer Research and Treatment*. 2005; 92:51–60. [PubMed: 15980991]
- Wu T, Felmlee JP, Greenleaf JF, Riederer SJ, Ehman RL. Assessment of thermal tissue ablation with MR elastography. *Magnet Reson Med*. 2001b; 45:80–7.
- Yang R, Kopecky KK, Rescorla FJ, Galliani CA, Wu EX, Grosfeld JL. Sonographic and Computed-Tomography Characteristics of Liver Ablation Lesions Induced by High-Intensity Focused Ultrasound. *Investigative Radiology*. 1993; 28:796–801. [PubMed: 8225883]
- Zhai L, Polascik TJ, Foo WC, Rosenzweig S, Palmeri ML, Madden J, Nightingale KR. Acoustic Radiation Force Impulse Imaging of Human Prostates: Initial in Vivo Demonstration. *Ultrasound in Medicine and Biology*. 2012; 38:50–61. [PubMed: 22104533]
- Zheng XL, Vaezy S. An Acoustic Backscatter-Based Method for Localization of Lesions Induced by High-Intensity Focused Ultrasound. *Ultrasound in Medicine and Biology*. 2010; 36:610–22. [PubMed: 20211516]

Figure 1.

(a) The schematic description of HMIFU multi-parametric framework. (b) 1-cycle of HMI focal displacement M-mode. Both ϕ and displacement are estimated from values extracted within the focal region. (c) Strain distribution estimated using least square estimation on the same 1-cycle HMI focal displacement M-mode as (b). Note that only compressive strain is being investigated here. (d) ϕ corresponds to the phase angle difference between the registered input force (Blue curve) and induced focal displacement (Red). The D indicated here refers to the HMI focal displacement, which is the peak-to-peak displacement in the oscillatory response under AM-HIFU beam excitation.

Figure 2.

HMIFU experimental set up and data flow. The focal depth of the HIFU is 9 cm and the focal spot lies at 3.4 cm below of the tip of the coupling cone containing degassed water. Note the 3D positioning system is responsible for HMI raster scan.

Figure 3.

Passive Cavitation Detection (PCD) Spectrograms at acoustic power of 8W (b), 10W (c), and 11W (d) all showed significant increase in broadband noise energy, confirming formation of strong bubble dynamics due to boiling. (d) Representative temperature monitoring using T-type bare-wire thermocouple indicates boiling within the first several seconds from treatment onset, indicating presence of unsteady state throughout each monitoring case.

Figure 4.

Example cases of multi-parametric HMIFU monitoring from first set of investigations. HIFU treatment of acoustic power were all set to be 10 W for 10 (a-d), 20 (e-h), and 30 second (i-l), respectively. Mean displacement, strain, and phase shift values were estimated across the HIFU focal zone (placed at approximately 10 mm from the surface of liver) as indicated by the gray line on the ϕ M-mode (c,g,k). As shown, decrease trends were observed for both displacement (a,e,i) and strain. ϕ was observed to increase slightly amongst the 10 second cases but decrease significantly amongst the 20 and 30 second cases. The decorrelation points throughout the 2D phase shift M-mode (c,g,k), as well as phase shifts at the focal zone (d,h,l), are likely to be linked to boiling.

Figure 5.

Statistical summary of the investigated treatment cases under 10W. Between three cases of HIFU treatments under 10, 20, and 30 seconds, decrease trend was observed in the peak-to-peak HMI focal displacement value (a) and compressive strain (c). ϕ (b) had a relatively increase, though unstable, amongst the 10 second treatment cases but showed clear decrease trends amongst the 20 and 30 second treatment cases. 2D HMI displacement images observed increase in lesion-to-background displacement contrast (d) and lesion size (e), which was confirmed with pathology (f).

Figure 6.1.

HMIFU monitoring and assessment images for cases with displacement decrease. HIFU treatment of acoustic power were set to be 10 W for 10 (a-e), 20 (f-j), and 30 second (k-o), respectively. The displacement contrast maps (c,h,m) are estimated from subtracting the displacement maps after lesion formation (b,g,l) from that of before (a,f,k) and displayed along with their corresponding monitoring curves (d,i,n). Both the lesion size and contrast increases with treatment time, lastly the increase in size was confirmed with corresponding gross pathology (e,j,o).

Figure 6.2.

HMIFU monitoring and assessment images for cases with displacement increase. HIFU treatment of acoustic power were also set to be 10 W for 10 (a-e), 20 (f-j), and 30 second (k-o), respectively. The displacement contrast maps (c,h,m) along with their corresponding displacement monitoring curves (d,i,n) had reversed displacement-to-background contrast in comparison with Figure 6.1 across all of the treatment cases. Nevertheless, the mapped lesion sizes increased with treatment time and were confirmed with pathology images (e,j,o).

Figure 6.3.

Statistical summary change in HMIFU displacement monitoring and contrast map for all treatment cases investigated under power of 10W. Each treatment time duration comprised of cases with both decrease (blue) and increase (red) displacement within the lesion compared to before treatment.

Figure 7.

Statistical distribution of all of the investigated case at acoustic power of 8W (blue), 10W (Magenta) and 11W (Red) for 10 (square), 20 (circle), and 30 (star) seconds. Trend for focal displacement (a) varied between increase and decrease across all treatment levels. However, the group of 10W seemed to host most of the decrease cases whereas 11W only had increase cases. Also, the magnitude of change increased as function of treatment time. Trends for ϕ (b) showed a relatively unstable trend amongst the 10 sec cases with both increase and decrease trend, whereas decrease trend was observed amongst all other cases across all power levels. (c) Lesion-to-background contrast showed a reversed change, among the 8 W and 10 W cases whereas 11 W only consisted of increase trend (i.e., contrast < 1). (d) Lesion size increased with treatment time across all the investigated powers, which was confirmed with gross pathology results (e). (f) Linear regression analysis for comparing the thermal lesion size estimated with gross pathology and HMI mapping. It can be depicted that the HMI mapped size is well correlated with the pathological findings.

Table 1

Quantification of monitoring and assessment parameters across different acoustic powers for 10 seconds treatment duration. Note that red indicates cases where displacement increased and blue indicates cases where displacement decayed inside the thermal lesion, respectively.

Acoustic Power Parameter	8W		10W		11W
% of Displacement change during treatment (%)	4.9±0.0 (n=1)	2.3±2.3 (n=4)	13.2± 6.0 (n=3)	27.3±6.0 (n=2)	50.0±23.6 (n=2)
Phase shift during treatment (°)	-2.6±0.0 (n =1)	-2.9±7.4 (n=4)	4.5±6.9 (n=3)	1.7±6.1 (n=2)	-35.8±28.1 (n=2)
Lesion-to-background contrast after treatment	1.3±0.0 (n=1)	0.7±0.2 (n=4)	1.4±0.2 (n=3)	0.65±0.04 (n=3)	0.77±0.04 (n=2)
Mapped HMI Lesion size (mm ²)	34.0±0.0 (n=1)	42.7±8.1 (n=4)	36.9±1.1 (n=3)	18.6±1.2 (n=3)	18.3±4.0 (n=2)

Table 2

Quantification of monitoring and assessment parameters across different acoustic powers for 20 seconds treatment duration. Note that red indicates cases where displacement increased and blue indicates cases where displacement decayed inside the thermal lesion, respectively.

<div> <div>Acoustic Power</div> <div>Parameter</div> </div>	8W		10W		11W
Displacement during treatment (μm)	24.3 $\pm$ 15.5 (n=2)	49.9 $\pm$ 48.9 (n=3)	17.8 $\pm$ 21.6 (n=4)	73.3 $\pm$ 23.3 (n=4)	111.7 $\pm$ 40.1 (n=2)
Phase shift during treatment ($^{\circ}$)	-6.4 $\pm$ 18.2 (n=2)	-2.1 $\pm$ 15.3 (n=3)	-22.2 $\pm$ 8.1 (n=4)	13.0 $\pm$ 7.1 (n=4)	-13.5 $\pm$ 1.6 (n=2)
Lesion-to-background contrast after treatment	1.4 $\pm$ 0.04 (n=2)	0.77 $\pm$ 0.05 (n=3)	1.98 $\pm$ 0.3 (n=4)	0.64 $\pm$ 0.07 (n=4)	0.70 $\pm$ 0.04 (n=2)
Mapped HMI Lesion size (mm^2)	55.7 $\pm$ 1.4 (n=2)	26.6 $\pm$ 5.8 (n=3)	45.0 $\pm$ 2.9 (n=4)	38.9 $\pm$ 9.9 (n=4)	47.7 $\pm$ 9.9 (n=2)

Table 3

Quantification of monitoring and assessment parameters across different acoustic powers for 30 seconds treatment duration. Note that red indicates cases where displacement increased and blue indicates cases where displacement decayed inside the thermal lesion, respectively.

Acoustic Power Parameter	8W		10W		11W
Displacement during treatment (μm)	19.0 $\pm$ 0.0 (n=1)	73.2 $\pm$ 54.1 (n=5)	61.4 $\pm$ 31.1 (n=4)	118.9 $\pm$ 61.4 (n=5)	48.3 $\pm$ 25.9 (n=3)
Phase shift during treatment ($^{\circ}$)	-1.9 $\pm$ 0 (n=1)	-14.7 $\pm$ 10.6 (n=5)	-18.5 $\pm$ 10.1 (n=4)	-14.6 $\pm$ 18.3 (n=5)	-22.8 $\pm$ 9.4 (n=3)
Lesion-to-background contrast after treatment	1.7 $\pm$ 0.0 (n=1)	0.76 $\pm$ 0.05 (n=5)	2.3 $\pm$ 0.8 (n=4)	0.7 $\pm$ 0.05 (n=5)	0.76 $\pm$ 0.04 (n=3)
Mapped HMI Lesion size (mm^2)	44.1 $\pm$ 0.0 (n=1)	43.3 $\pm$ 4.8 (n=5)	52.1 $\pm$ 2.4 (n=4)	43.6 $\pm$ 11.2 (n=5)	43.4 $\pm$ 6.1 (n=3)