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High Intensity Focused Ultrasound Monitoring using Harmonic Motion Imaging for Focused Ultrasound (HMIFU) under boiling or slow denaturation conditions

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Abstract

Harmonic Motion Imaging for Focused Ultrasound (HMIFU) is a recently developed High-Intensity Focused Ultrasound (HIFU) treatment monitoring method that utilizes an amplitude-modulated therapeutic ultrasound beam to induce an oscillatory radiation force at the HIFU focus and estimates the focal tissue displacement to monitor the HIFU thermal treatment. In this study, the performance of HMIFU under acoustic, thermal and mechanical effects were investigated. The performance of HMIFU was assessed in *ex vivo* canine liver specimens (n=13) under slow denaturation or boiling regimes. Passive Cavitation Detector (PCD) was used to assess the acoustic cavitation activity while a bare-wire thermocouple was used to monitor the focal temperature change. During lesioning with slow denaturation, high quality displacements (correlation coefficient above 0.97) were observed under minimum cavitation noise, indicating tissue the initial-softening-then-stiffening property change. During HIFU with boiling, HMIFU monitored a consistent change in lesion-to-background displacement contrast (0.46 ± 0.37) despite the presence of strong cavitation noise due to boiling during lesion formation. Therefore, HMIFU effectively monitored softening-then-stiffening during lesioning under slow denaturation, and detected lesioning under boiling with a distinct change in displacement contrast under boiling in the presence of cavitation. In conclusion, HMIFU was shown effective in HIFU monitoring and lesioning identification without being significantly affected by cavitation noise.

Keywords

Elasticity Imaging; Therapeutic ultrasound; Harmonic Motion Imaging; High intensity focused ultrasound monitoring; Passive Cavitation Detection

Introduction

High Intensity Focused Ultrasound is a novel thermal ablation treatment capable of noninvasively treating tumors while sparing the majority of the peripheral tissue using a set

of focused sound waves [1, 2]. Historically, extensive studies have been aimed at treating local tumors in organs such as the brain, liver, uterus, kidney, prostate, bone and breast [3]. Although HIFU treatment is advantageous over the present cancer therapy techniques such as chemotherapy or cryoablation, Radio Frequency (RF) ablation, or microwave ablation in terms of its noninvasive and non-ionizing nature, numerous challenges remain in the development of HIFU in order to achieve further advancement towards its full clinical implementation. Some of the major challenges for clinical translation of HIFU including, but not limited to: Adaptive targeting to ensure a clear acoustic path to the target under breathing and other tissue movements, detection of the entire treated tissue volume, real-time monitoring of the treatment procedure without interrupting the ablation sequence, and quantitative assessment of the treated versus untreated regions.

Guidance and assessment for HIFU treatment have been studied extensively under numerous techniques: Magnetic Resonance Imaging (MRI) is capable of localizing tumors, assessing thermal lesions formed on the changes in the tissue water content [4, 5], B-mode ultrasound imaging is capable of detecting and assessing the thermal lesion formed through their distinctive echogenicity contrast (i.e., change in tissue acoustic absorption value) [6–8]. Noninvasive echo-shift-based thermography is capable of sub-millimeter mapping of HIFU focal zone based on the tissue echo shifts induced by changes in speed of sound with temperature rise [9–11]. Other ultrasound-based techniques have also investigated the distinctive spectral characteristics from the backscattered signals of the thermal lesion [12], as well as assessment of elasticity properties with mechanical excitation using static [13], dynamic [14], or acoustic radiation force [15–17] for visualizing treatment targets and the induced thermal lesions [18–29].

Nevertheless, the monitoring aspect of the HIFU treatment remains a key area which still requires optimization in order to both accurately detect and assess the progress and onset of thermal lesion formation. Over the past, numerous monitoring techniques have been developed and implemented for monitoring of the HIFU treatment procedure: MRI-guided Focused Ultrasound (MRgFUS) [4, 5] serves as the current standard monitoring modality which provides a thermal dosage map with a feedback frame rate of 0.1 to 2 Hz at high spatial resolution. The temperature map by MRgFUS is estimated 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 [30]. Acousto-optic sensing is another cost-effective modality capable of monitoring the change in tissue optical absorption and scattering using a modulated beam under HIFU beams during the treatment [31, 32]. Other backscattered signal-based techniques have also utilized either the change [33] or rise [34] in harmonics using spectral analysis in order to detect the onset of thermal lesion formation.

Elasticity-based HIFU monitoring aims at detecting and tracking the relative changes in tissue elasticity upon formation of thermal lesion with several modalities have been developed and implemented thus far to achieve this goal: Magnetic Resonance Elastography (MRE) [35–38] reconstructs both the storage and loss modulus through mapping of the shear wave propagation with sub-millimeter spatial resolution induced by an external mechanical exciter, whereas Supersonic Shear Imaging (SSI) [39, 40] is capable of providing high frame

rates and mapping the local shear modulus through an *in situ* plane shear wave induced by a focused acoustic radiation force [39]. Acoustic Radiation Force Impulse (ARFI) Imaging has recently shown feasibility in ablating and monitoring formation of thermal lesions using a cost-effective conventional imaging platform in combination with a curvilinear imaging probe operating under a customized beam excitation sequence [41]. Nevertheless, MRE relies on the costly MRI system with limited frame rate of 0.5–10 Hz and the limited accuracy of estimating focal thermal dosage under boiling condition [42]. On the other hand, both SSI and ARFI require the HIFU treatment to be turned off during its imaging sequences in spite of the fact that one of the primordial unsolved issues of HIFU is the long duration of its procedures. It therefore becomes imperative to implement a monitoring technique capable of providing high frame rate, real-time feedback without interrupting the treatment.

Harmonic Motion Imaging for Focused Ultrasound (HMIFU) is an acoustic radiation force based technique developed to address the aforementioned shortfalls. The HMIFU system couples a HIFU transducer emitting an amplitude-modulated (AM) beam for inducing stable oscillatory tissue motion within its focal zone while the response is acquired through a confocally-aligned single element pulse-echo imaging transducer [43] during the progression of the HIFU treatment. The RF signals from the pulse-echo imaging transducer are band-pass filtered in order to remove the interference with the HIFU beam before the oscillatory tissue motion is estimated using a 1D cross-correlation method [44]. Despite the extensive previous studies in HMIFU in terms of concept development [45], system feasibility [43, 46], and application feasibility [47], the principal objective of HMIFU is to achieve consistent monitoring of progressive tissue elasticity phase change, i.e., initial softening-then-stiffening, due to the progressive process of protein denaturation, as previously proposed and investigated [43, 48, 49]. Nevertheless, there has yet to be a comprehensive study on assessing and validating the reliability of HMIFU in monitoring of this stiffness phase change under both slow denaturation and boiling regimes, i.e., simultaneously monitoring both focal acoustic and thermal property changes in addition to mechanical property changes.

In this study, acoustic emission monitoring is performed using passive cavitation detection (PCD) [50–52], which has been a standard approach to detecting the presence and activities of cavitation under HIFU treatment based on the characteristics of the backscattered HIFU signal spectrum [53]. For HIFU treatment, it has been known that focal tissue heating by the energy deposition of the HIFU beam introduces cavitation activities, and such bubble-driven mechanisms play a critical role in the formation of the thermal lesion [54, 55]. Previously studies have also investigated such relationship between the cavitation dosage and the formation of thermal lesion, indicating an important relationship between the treatment thermal dosage and the level of focal cavitation activities [56, 57]. Moreover, broadband noise is also known to be present during tissue boiling with presence of strong bubble dynamics [58–60]. In addition to acoustic emission monitoring, focal temperature measurements were also applied in tandem in order to provide quantitative information regarding the thermal property change and the delivered thermal dosage. Therefore, the present study is a continuing effort from our previous work on multi-parametric assessment of HMIFU [61], where we demonstrated only the feasibility of HMIFU in monitoring HIFU

treatment with presence of boiling. In this study, our objective is to further investigate the performance of HMIFU monitoring under slow denaturation (low treatment power and long treatment duration) as well as boiling (high treatment power and short treatment duration) regime based on the changes in focal displacement, focal displacement contrast, phase shift (ϕ), and correlation coefficients during HIFU. We couple both thermal and acoustic emission monitoring using respectively the thermocouple and PCD based measurements during HIFU treatment in order to provide focal medium information during the HMIFU treatment under both slow denaturation and boiling conditions. We hypothesize that HMIFU can effectively differentiate and monitor both HIFU treatment under slow denaturation and boiling. More specifically, we expect the slow denaturation sequence will enable a consistent monitoring of initial-softening-then-stiffening elasticity changes and reliable displacement as well as phase shift (ϕ) estimation during lesion formation. In addition, the change in displacement contrast will serve as a robust indicator of lesion formation in the boiling sequence despite the underlying effects on displacement and phase shift (ϕ) estimation due to strong thermal and acoustical changes in the presence of boiling.

Materials and Methods

Canine livers (subject=12, lobes = 13, Treatment location = 70) 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 placed inside of a de-ionized and degassed PBS container. The HMIFU system was comprised of a 4.75 MHz 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 providing HIFU treatment and radiation force based tissue probing 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 signal acquisition for both imaging tissue displacement and cavitation detection at a pulse repetition frequency (PRF) of 1 kHz. Note that the Compared to our previous HMIFU studies with a limited RF acquisition window [43, 61], we have expanded our 1-D HMIFU system such that RF signals can now be acquired and stored continuously throughout the entire treatment window, which allows us to further investigate the tissue property change in detail. The HMIFU system was mounted onto, and controlled by, a 3D translational system (Velmex Inc., Bloomfield, NY, U.S.A.) for targeting purpose (Figure 1). The received RF signals were band-pass filtered (Model #SN05-1, Reactel, Inc., Gaithersburg, Maryland, USA) with cutoff frequencies of $f_{c1} = 5.84$ MHz and $f_{c2} = 8.66$ MHz (at -60 dB) and recorded along with the excitation signal representing the force profile by a dual-channel data acquisition unit (Gage applied, Lockport, IL, U.S.A.) at a sampling frequency of 100 MHz (Figure 1). Subsequently, a 1-D normalized cross-correlation (window size of 3.85 mm and 90% overlap) technique [44] was used to estimate the axial displacement and phase shift (ϕ) with the recorded input voltage as the applied force (Figure 1). Regarding the method for estimation of phase shift (ϕ), the reader is referred to the prior literature [61]. The Peak-to-peak values of the focal oscillatory displacements for each treatment case were tracked

throughout the treatment window using a customized peak-detection algorithm. The displacement waveforms were divided into non-overlapping time segments of 1s. For each segment, the local maxima and minima were calculated. The collected local maxima and minima were linearly interpolated, respectively, and the resulting waveforms were smoothed using a moving average filter of 100 points. Constant extrapolation was used to fit and align the resulting waveforms with the displacement waveform. Finally, the peak-to-peak amplitude was calculated by subtracting the smoothed local minima waveform from the local maxima waveform. In order to assess the presence of tissue boiling at the proposed treatment level, PCD monitoring was also performed by operating the conically-aligned pulse-echo transducer in passive mode under the same PRF (1 kHz) and also operating the data acquisition unit under same RF signal sampling rate (100 MHz) in conjunction with thermocouple measurement. Focal temperature monitoring was performed by inserting a T-type bare wire thermocouple with a diameter of 25 μm (Omega Inc., Stamford, CT) inside the tissue through a customized needle gauge. The diameter of the thermocouple was selected to be smaller than 1/10 of the wavelength of the carrier frequency in order to minimize reflection and viscous heating artifacts [62]. Four additional parameters are introduced in this study to assess the performance of HMIFU monitoring in this study: displacement contrast, mean correlation coefficient, minimum correlation coefficient, and PCD broadband energy. The displacement contrast is defined as:

$$\frac{Disp_{\max} - Disp_{\min}}{Disp_{\max} + Disp_{\min}} \quad (1)$$

Where the $Disp_{\max}$, $Disp_{\min}$, are the maximum and minimum displacement during any monitoring displacement profile during a single treatment window. The mean correlation coefficient ρ_{mean} and minimum correlation coefficient $\rho_{\min}$ are defined as the average and minimum cross-correlation coefficient value for the estimated displacement during a single treatment window:

$$\rho_{mean} = \frac{\sum_t^T \rho(t)}{T} \quad (2)$$

$$\rho_{\min} = \min(\rho(0); \rho(T)), \quad (3)$$

Lastly, the PCD Broadband Energy is obtained simply by subtracting both the harmonic energy (at frequencies of 9.51 MHz, 14.3 MHz, 19.0 MHz, 23.9 MHz, 28.5 MHz, 33.3 MHz, 38.0 MHz, 42.8 MHz, and 47.6 MHz) and ultra-harmonic energy (at frequencies of 9.26 MHz, 14.0 MHz, 18.8 MHz, 23.5 MHz, 28.3 MHz, 33.0 MHz, 37.8 MHz, 42.5 MHz, and 47.3 MHz) from the total energy quantified across the PCD frequency response. Two HMIFU monitoring sequences were performed for HIFU treatment: slow denaturation and boiling, respectively. Monitoring HIFU treatments with slow denaturation was completed by exciting the 4.75 MHz therapeutic transducer with sequences composed of treatment duration between 120 to 240 s under extrapolated *in situ* focal peak negative pressure of

−2.74 MPa, −3.42 MPa, −4.11 MPa, acoustic intensity (I_{sptp}) of 2773 W/cm², 3582 W/cm², 5803 W/cm², and total acoustic power of 4W, 5W, and 7W, respectively. Monitoring HIFU treatments with boiling consisted of sequences with a treatment duration of 30 s under extrapolated *in situ* focal peak negative pressure of −4.79 MPa, −5.78 MPa, −6.16 MPa, acoustic intensity (I_{sptp}) of 5546 W/cm², 7164 W/cm², and 9067 W/cm², and total acoustic power of 8W, 10W, and 11W for treatment sequence with boiling, respectively.

Results

In this study, a total of 70 HIFU treatments (43 HIFU treatments with only HMIFU monitoring and 27 HIFU treatments with only PCD monitoring) were performed on freshly excised canine liver *ex vivo* (Table 1). Of the 43 HIFU treatments with only HMIFU monitoring, 34 treatments were completed using the slow denaturation treatment sequence and 9 treatments were completed using the boiling treatment sequence (Table 1). For all HMIFU monitoring cases, displacement, cross-correlation coefficient, and phase shift (ϕ) was monitored across the entire treatment window. Sixty-two percent (21/34) of all the cases under slow denaturation sequence exhibited displacement decrease following HIFU treatment. Furthermore, there were also 9 treatments completed using the HIFU treatment with boiling, where 6 cases exhibited displacement increase and 3 cases exhibited displacement decrease following HIFU treatment without any exhibiting initial increase in displacement. Clear differentiations were observed across all HMIFU monitoring parameters between HIFU treatment cases with slow denaturation or boiling conditions. The averaged displacement change, displacement contrast, and phase shift (ϕ) were $-36.7 \pm 15\%$, 0.34 ± 0.18 , and $12.8 \pm 2.0^\circ$ during the slow denaturation HIFU treatment cases (Figure 2a,d,g). The mean correlation and minimum correlation during the slow denaturation HIFU treatment cases were 0.97 ± 0.079 and 0.81 ± 0.19 (Figure 2b,e,h, Figure 6) (Table 2), which were performed under *in situ* focal acoustic intensity (I_{sptp}) of 2773 W/cm², 3582 W/cm², 5803 W/cm² at acoustic power ranging between 4W, 5W, and 7W, respectively. The averaged displacement change, displacement contrast (Eq. 1), and phase shift (ϕ) were $197.4 \pm 315.3\%$, 0.46 ± 0.37 , and $7.0^\circ \pm 16.3^\circ$ during HIFU treatment with boiling. The mean correlation, and minimum correlation during HIFU treatment with boiling cases were 0.81 ± 0.14 , and 0.26 ± 0.40 (Figure 3,6) (Table 2), which were performed under *in situ* focal acoustic intensity (I_{sptp}) of 5546 W/cm², 7164 W/cm², and 9067 W/cm² at acoustic power ranging between 8W, 10W, and 11W, respectively. PCD monitoring was also performed on 27 cases from both treatment sequences (21 cases using slow denaturation sequences and 6 using boiling sequences); No significant broadband noise was detected on slow denaturation HIFU treatment sequences (Figure 2c,f,i)(Figure 4a), where HIFU treatment with boiling cases observed the presence of broadband noise from the backscattered signal on PCD frequency response with energy levels reaching the saturation point of the 40-dB detection limit as temperature increased (Figure 3c,f,i)(Figure 4b). Note that temperature measurements were Monitoring of PCD and displacement with temperature monitoring was also performed. Insignificant broadband noise (−30 to −40 dB) was shown during HIFU treatment with slow denaturation (Figure 4b), whereas HIFU treatment with boiling indicated 40-dB increase in level of broadband noise up to around 100 °C (Figure 4c). All of the 21 cases under the slow denaturation HIFU regime with displacement decrease also

exhibited an increase-then-decrease displacement trend, i.e., the positive slope was equal to $0.072 \pm 0.2 \mu\text{m/sec}$ while the negative slope equaled $-0.0025 \pm 0.03 \mu\text{m/sec}$, whereas none of the cases under boiling HIFU regime with displacement decrease exhibited such trend. The displacement increase reached a peak range around $50\text{--}60^\circ\text{C}$ followed by a stiffening phase, and the formed thermal lesion was relatively uniform in contrast to the pulverized lesions formed by the boiling regime (Figure 5a,b). Both the focal displacement and temperature monitoring were highly variable in the HIFU treatment with boiling regime, where no consistent pattern between displacement variation and change in temperature was observed, especially reaching the boiling temperature range (Figure 5c,d). Nevertheless, the average change in focal displacement contrast after lesion formation remained consistently high (0.46 ± 0.37), in comparison with that of the slow denaturation cases (0.34 ± 0.18) (Figure 6) (Table I).

Discussion

HIFU has shown great promise in the field of noninvasive ablation treatment with its cost-effective, non-ionizing, extracorporeal procedural advantages. Critical challenges still remain in the treatment monitoring stage of HIFU, including lacking modalities capable of quantitative, localized, and real-time feedback information in order to facilitate the physician with reliable indication of completion, i.e., performing effective ablation in all cancerous tissues while sparing the surrounding normal tissue. Elasticity imaging techniques such as MRE [35–38], ARFI [41], SSI [39, 40], and acousto-optic imaging [31, 32] have shown promising quantitative assessment of underlying mechanical property changes but require the interruption of HIFU treatment, whereas MRI-based techniques can map temperature and thermal dosage mapping but are costly and cannot reliably monitor the treatment under boiling condition [42], which are considered to be more effective in inducing necrosis in cancerous cells [63].

HMIFU is a dynamic ultrasound-based elasticity imaging technique based on a dual-configuration of HIFU and imaging transducer that can provide and track a stable focal oscillatory motion, which can be used to investigate the underlying local tissue mechanical property in real time without stopping the HIFU treatment. Despite the fact that HMIFU has also been shown feasible in monitoring lesion formation under boiling [61], the detailed relationship between the underlying mechanical property change and the associated simultaneous changes in acoustical and thermal properties during HIFU treatment remains unknown. Previous studies have shown that cavitation activities and broadband noise associated bubble dynamics at boiling [58–60] are present at the focal region during HIFU treatment [54, 55], and the level of focal cavitation activities can in turn facilitate the estimation and optimization of the guidance and thermal dose delivery of HIFU treatment [56, 57]. Nevertheless, there has yet to be a comprehensive HMIFU-based study where tissue mechanical property change, thermal dosage, and cavitation level were simultaneously monitored during HIFU treatment. Therefore, it is important to perform an investigation on the effect of the changes in focal acoustic and thermal properties on the monitoring assessment by HMIFU. In other words, understanding the level of acoustic property change, i.e. cavitation and other bubble-dynamics driven mechanism as well as thermocouple based measurement can in turn, assist in optimization of the stability of

HMIFU performance under HIFU treatment with both slow denaturation and boiling condition. Such comprehensive assessment will further facilitate the translation of HMIFU technique towards clinical settings.

Hence, the objective of this study is to perform a comprehensive investigation in understanding the relationship of HMIFU monitoring under both slow denaturation (low treatment power and long treatment duration) and boiling (high treatment power and short treatment duration) regimes. HMIFU parameters (i.e., focal axial displacement, phase shift (ϕ), mean cross-correlation coefficient, and minimum cross-correlation coefficient) were studied along with the associated underlying acoustic and thermal property changes during HIFU treatment. Bare-wire thermocouple and PCD monitoring were used to monitor thermal and acoustic cavitation activities, respectively. We expected that HMIFU could differentially monitor HIFU treatment with slow denaturation and boiling conditions. That is, monitoring a stable change, or a progressive tissue softening-then-stiffening indicated by displacement increase-then-decrease will likely constitute the result during slow denaturation condition, where the changes in acoustic and thermal property are minimum. For HIFU treatment with boiling conditions, we expected the HMIFU to be robust in detecting the formation of lesion based on the increase of focal displacement contrast. In addition, we expect HMIFU to be capable of monitoring changes in the focal displacements despite the strong thermal and cavitation noise at the focal region.

In the case of slow denaturation, correlation coefficient (Figure 2a,d,g), focal displacement (Figure 2b,e,h) and PCD frequency response (Figure 2c,f,i) were monitored under treatment protocol between 120 to 240s with *in situ* focal acoustic intensity (I_{sptp}) and power ranging between 2773 W/cm², 3582 W/cm², 5803 W/cm², at 4W, 5W, 7W, respectively. As we hypothesized, it was clear that all of the HMIFU parameters showed consistent trend across the HIFU treatment window: Both the mean (Figure 5a, blue) and minimum correlation coefficients (Figure 5a, green) remained high (Figure 2a,d,g) throughout the entire treatment window, while focal displacement exhibited an increase-then-decrease trend, indicating tissue softening followed by stiffening mechanical property change (Figure 2b,e,h). Also, consistent increases were observed in phase shift (ϕ) across all cases, indicating consistent changes in the viscoelasticity of the focal medium throughout the HIFU treatment, which were in agreement with mechanical testing assessment in our previous studies [64]. PCD frequency response of the slow denaturation cases showed minimized presence of boiling-associated bubble dynamics (Figure 2c,f,i)(Figure 4a), which is represented by the minimized level of broadband noise (Figure 4a). In the case of boiling, correlation coefficient (Figure 3a,d,g), focal displacement (Figure 3b,e,h) and PCD frequency response (Figure 3c, f, i) were monitored under treatment protocol of 30 seconds with *in situ* focal acoustic intensity (I_{sptp}) and total acoustic power ranged between 5546 W/cm², 7164 W/cm², and 9067 W/cm², at 8W, 10W, and 11W, respectively. In contrast to the slow denaturation treatment cases, significant variations were observed amongst the HMIFU parameters across the treatment window for the cases of HIFU treatment with boiling. The focal displacement exhibited either relatively no significant changes (Figure 2b), or significant increases (Figure 2e,h) following the HIFU treatment onset. In addition, the PCD frequency responses showed significant presence of boiling-associated bubble dynamics

(Figure 2c,f,i), which is represented by an elevated level of broadband energy (Figure 4b) across the entire treatment window. Note the monitored broadband energy changed very disruptively with temperature due to the degraded quality of thermocouple measurement under strong bubble shielding effect from cavitation and boiling during the HIFU treatment inside the focal zone. The characteristics between displacement variation and temperature were also studied, where a gradual displacement increase-then-decrease trend was observed for HIFU treatment with slow denaturation, where the displacements reached a maximum around 55 °C following tissue softening, then following a decreasing trend indicating tissue softening (Figure 5a). This observation is consistent with previous findings from both our group and others [39, 40, 43, 65, 66]. Nevertheless, as expected, the temperature reading was strongly affected by the bubble dynamics and shielding effects from the boiling mechanism, thus exhibiting a chaotic trend with non-monotonic increase with treatment time (Figure 5b). Additionally, there is a distinct characteristic difference between lesions formed at gross pathology after two different HIFU treatment sequences. The lesion formed under slow denaturation was relatively uniform in shape and boundaries (Figure 5b), whereas the lesion formed under HIFU treatment with boiling contained cavities, which can be due to either strong mechanical and thermal effects due to the boiling mechanisms around 100 °C (Figure 5d). The mean correlation coefficients remained high throughout the treatment duration for both HIFU treatment with slow denaturation and HIFU treatment with boiling (Figure 6a,b). Nevertheless, the average minimum correlation decreased significantly down to 0.26 amongst the cases of HIFU treatment with boiling (Figure 6b) compared to the slow denaturation cases, where it remained on average above 0.8 (Figure 6a).

Despite the fact that majority of the HIFU treatment with boiling exhibited increase of peak-to-peak focal displacement (Figure 6c), it is noteworthy that a clear change in the contrast of the monitoring displacement profiles was observed across all cases with boiling (Figure 6d), indicating that the robustness of HMIFU's focal displacement even in the presence of strong broadband noise induced by the boiling bubble dynamics. From the present study, it was demonstrated that the slow denaturation regime was more suitable in monitoring a steady viscoelasticity change under HIFU treatment using HMIFU, because of its advantage in maintaining a high cross correlation coefficient while minimizing the disturbance due to the mechanical and acoustical noise induced by boiling where temperatures reached around or above 100 °C. In addition, this study also demonstrated the robustness of HMIFU in monitoring HIFU lesion formation based on the change of displacement contrast throughout the treatment window, which further validated our previous finding on monitoring HIFU treatment with boiling condition [61].

While there could potentially be other factors that can affect the level and occurrence of boiling such as the degassing time, depth-dependent attenuation effect, which are still being investigated, the fact that the displacement contrast was shown feasible to monitor the formation of HIFU lesion in the presence of strong broadband noise and low correlation coefficients validated the robustness of HMIFU to detect the formation of lesions even under strong boiling regime. More importantly, it is also noteworthy that previous reports in the field mainly focused either on the monitoring of tissue thermal property [4, 5, 9–11], elasticity property [39–41, 49, 65, 66], or acoustic or optical response [31, 50, 53, 56, 57, 60] based on a limited range of HIFU treatment powers and durations. The present study

provided insightful information on the relationship between the simultaneous changes of underlying tissue stiffness, the performance of the elasticity assessment by HMI, and the acoustic response during HIFU treatment with slow denaturation and boiling. Consequently, the present study examined on the advantage of HMIFU in simultaneously monitoring both mechanical and acoustic responses during HIFU treatment under either slow denaturation or boiling regimes. Nevertheless, there are areas of improvement that remain including the capability of simultaneously monitoring all of the PCD, thermocouple, and HMIFU measures. Here, the PCD and temperature measurements were monitored separately during HMIFU. Ongoing efforts include translating the acquisition sequences presented herein onto the recently developed 2D platform [67] in order to perform multi-dimensional and parametric studies, such as real-time mapping of the focal cavitation response as well as quantitative mapping of depth-dependent attenuation change during HIFU [68]. Other application-specific ongoing studies include HMIFU monitoring assessment in pathological tissues such as breast [69] and pancreatic tumors detection and monitoring *in vivo* [70].

Conclusion

In this paper, a comprehensive monitoring study was performed in order to investigate the relationship between the HMIFU parameters of focal displacement and phase shift (ϕ) and the tissue thermal, acoustical, and mechanical properties in liver specimens *ex vivo* under two HIFU treatment regimes: slow denaturation and boiling. During slow denaturation, a consistent displacement increase-then-decrease trend was obtained in all cases, indicating tissue softening-then-stiffening, and phase shift (ϕ) increased with treatment time in agreement with mechanical testing outcomes. Under boiling, HMIFU was shown to be robust in monitoring the lesion formation in the presence of strong cavitation events with good displacement contrast across the entire treatment window. The study presented herewith validated that HMIFU could differentiate between slow denaturation and boiling, capable of consistently monitoring the softening-then-stiffening elasticity change during lesioning for HIFU treatment with slow denaturation under minimum effects of boiling-induced noise in focal acoustic and thermal property changes, and monitoring the formation of thermal lesions through the resulting displacement contrast despite the focal displacement variations in the presence of boiling associated high cavitation noise.

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Figure 1.

HMIFU experimental setup and flowchart. 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 relocating transducers between treatment locations.

Figure 2.

Multi-parametric monitoring of both focal HMIFU parameters and acoustic response under HIFU treatment with slow denaturation. The sub-figures (a,d,g) indicate the change of HMIFU correlation coefficient during HIFU treatment at 4W (a), 5W (d), and 7W (g). The sub-figures (b,e,h) indicate the change of focal axial displacement (at 10 mm) during HIFU treatment at 4W (b), 5W (e), and 7W (h). Sub-figures (c,f,i) are the respective PCD frequency response observed during HIFU treatment at 4W (c), 5W (f), and 7W (i).

Figure 3.

Multi-parametric monitoring of both focal HMIFU parameters and acoustic response under HIFU treatment with boiling. The sub-figures (a)–(h) indicate the change of HMIFU correlation coefficient and focal axial displacement (at 10 mm) during HIFU treatment at 8W (a), 10W (d), and 11W (g) as well as focal displacement at 8W (b), 10W (e), and 11W (h). Sub-figures (c,f,i) are the respective PCD frequency response observed during HIFU treatment at 8W (c), 10W (f), and 11W (i).

Figure 4.

Quantification of broadband energy for PCD monitoring of both HIFU treatment with slow denaturation (a) and boiling (b) sequences, as well as the respective thermocouple measurements (c,d) for the same treatment cases. The solid and dash curves (a,c) represent the cases of 4W and 7W, respectively, whereas the solid and dot curves (b,d) represent the HIFU treatment cases of 8W, and 11W, respectively.

Figure 5.

Comparative display between the change of peak-to-peak HMIFU focal displacements with temperature during monitoring, and gross pathology of thermal lesion for both HIFU treatment with slow denaturation (a,b) and boiling (c,d) sequences, respectively.

Figure 6.

Quantification of HMIFU parameters used in this study for both HIFU treatment with slow denaturation and boiling: Mean correlation coefficient ('mean corr') and minimum correlation coefficient ('min corr') across the entire treatment window for HIFU treatment cases with slow denaturation (a) and boiling (b). (c) Percentages of HIFU treatment cases with decrease or increase-then-decrease trend in monitoring displacement for HIFU treatment with boiling (red) and slow denaturation. (d) Displacement contrast between maximum to minimum displacement monitored during the treatment window for HIFU treatment with boiling (red) and slow denaturation.

Table 1

Summary of HIFU treatment case categories by HIFU treatment type and HIFU monitoring type.

HIFU treatment type	Slow denaturation HIFU cases	Boiling HIFU cases	Total cases
HIFU monitoring type			
HMIFU monitoring only	34	9	43
PCD monitoring only (NO HMIFU monitoring)	21	6	27
Total cases	55	15	70

Table 2

Comparative summary of HMIFU monitoring parameters throughout the entire treatment window under HIFU treatment sequences slow denaturation and boiling. Note that the average values include all of the cases in each regime with respective treatment durations and treatment power level. All statistical representations shown are in the format of $\bar{\mu}$ (mean value) $\pm \sigma$ (one standard deviation).

Monitoring Parameter	in HMI displacement before and after (%)	Phase shift (φ) (°)	Mean correlation Coefficient	Min correlation Coefficient	Displacement contrast
HIFU Treatment Case					
Slow denaturation HIFU cases (n =34)	-36.7 $\pm$ 15 (n =34)	12.9 $\pm$ 2.0 (n =34)	0.97 $\pm$ 0.08 (n =34)	0.81 $\pm$ 0.14 (n =34)	0.34 $\pm$ 0.18 (n =34)
Boiling HIFU cases (n = 9)	197.4 $\pm$ 315.3 (n = 9)	7.0 $\pm$ 16.3 (n = 9)	0.81 $\pm$ 0.19 (n = 9)	0.26 $\pm$ 0.4 (n = 9)	0.46 $\pm$ 0.37 (n = 9)