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Optimization of Real-Time Acoustical and Mechanical Monitoring of High Intensity Focused Ultrasound (HIFU) treatment using Harmonic Motion Imaging for High Focused Ultrasound (HMIFU)

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Abstract— **Harmonic Motion Imaging (HMI) for Focused Ultrasound (HMIFU) is a recently developed high-intensity focused ultrasound (HIFU) treatment monitoring method with feasibilities demonstrated *in silica*, *in vitro* and *in vivo*. Its principle is based on emission of an Amplitude-modulated therapeutic ultrasound beam utilizing a therapeutic transducer to induce an oscillatory radiation force while tracking the focal tissue mechanical response during the HIFU treatment using a confocally-aligned diagnostic transducer. In order to translate towards the clinical implementation of HMIFU, a complete assessment study is required in order to investigate the optimal radiation force threshold for reliable monitoring the local tissue mechanical property changes, i.e., the estimation HMIFU displacement under thermal, acoustical, and mechanical effects within focal medium (i.e., boiling, cavitation, and nonlinearity) using biological specimen. In this study, HMIFU technique is applied on HIFU treatment monitoring on freshly excised *ex vivo* canine liver specimens. In order to perform the multi-characteristic assessment, the diagnostic transducer was operated as either a pulse-echo imager or Passive Cavitation Detector (PCD) to assess the acoustic and mechanical response, while a bare-wire thermocouple was used to monitor the focal temperature change. As the acoustic power of HIFU treatment was ranged from 2.3 to 11.4 W, robust HMI displacement was observed across the entire range. Moreover, an optimized range for high quality displacement monitoring was found to be between 3.6 to 5.2W, where displacement showed an increase followed by significant decrease, indicating a stiffening of focal medium due to thermal lesion formation, while the correlation coefficient was maintained above 0.95.**

I. INTRODUCTION

High intensity focused ultrasound (HIFU)[1] is a non-invasive, non-ionizing, extracorporeal method for thermal ablation of tumors with many applications. One of the biggest shortcomings of the first clinical applications of this technique is the optimization of treatment sequence. Currently, most of the HIFU treatment procedures can be categorized under two main sequences: 1) Short duration at higher acoustic energy and 2) Long duration at mild acoustic energy. The first approach stems from a set of previous studies which indicated that an effective cancerous cells are likely to be ablated at high energy[2,3], where tumor necrosis can be induced at an efficient rate but under strong presence of both acoustic and thermal effects such as cavitation, boiling, nonlinearity response and tissue pulverization or gelatification[4]. On the other hand, long duration at mild acoustic power, where thermal lesions are formed at a slow rate, is currently being applied to the existing clinical HIFU treatment monitoring techniques such as MRI-guided Focused Ultrasound Surgery (MRgFU) or B-mode guidance couples such treatment sequence since lesions can be formed under less influence of significant thermal and acoustical property changes.

Harmonic Motion Imaging for Focused Ultrasound (HMIFU) is a treatment monitoring technique using elasticity imaging that had been used *in silica*, *in vitro* and *in vivo*[5,6,7]. In HMIFU, the HIFU signal (carrier frequency typically in the MHz range) is modulated by a low-frequency waveform (in the tens of Hz range), generating an acoustic radiation force that induces an oscillatory motion at the focus. In turn, the change in this focal displacement is monitored throughout the HIFU treatment sequence as a qualitative assessment of the local elasticity and viscoelasticity. However, in order to prepare the translation of HMIFU to clinic, an optimization study is required to assess the quality of monitoring performance of HMIFU across a wide range of acoustic power based on simultaneously tracking thermal, acoustical, and mechanical change at the focal region. It is hypothesized that the outcome of this study will allow us to obtain a clear understanding of the simultaneously undertaking thermal and acoustic property changes, which in turn contributes to the establishment and optimization of clinically-translatable HMIFU sequences for reliable and efficient elasticity monitoring under existing clinical HIFU treatment sequences.

II. MATERIALS AND METHODS

A. HIFU set up

A 4.755-MHz HIFU transducer (Riverside Research Institute, New York, U.S.A.) with a focal length of 9 cm was used on freshly excised canine livers (n=6). The carrier frequency was amplitude-modulated at 25 Hz in order to induce a 50 Hz oscillatory radiation force at the focus. A single-element pulse-echo transducer (Panametrics, Waltham, MA, U.S.A., f_{center} = 7.5 MHz, focal length= 60 mm) was positioned confocally with respect to the HIFU transducer at its targeted volume. To study the quality of monitoring, two different sets of HIFU sequences are used. One set will consist of lower power, long exposure time (240s) with acoustic intensities ranging from 1150 W.cm^{-2} to 4200 W.cm^{-2} (corresponding acoustic power range: 2 W to 5 W). The other will consist of very high power and short exposure time (30s) with acoustic intensities ranging from 5500 W.cm^{-2} to

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9050 W.cm^{-2} (corresponding acoustic power range: 7 W to 11 W).

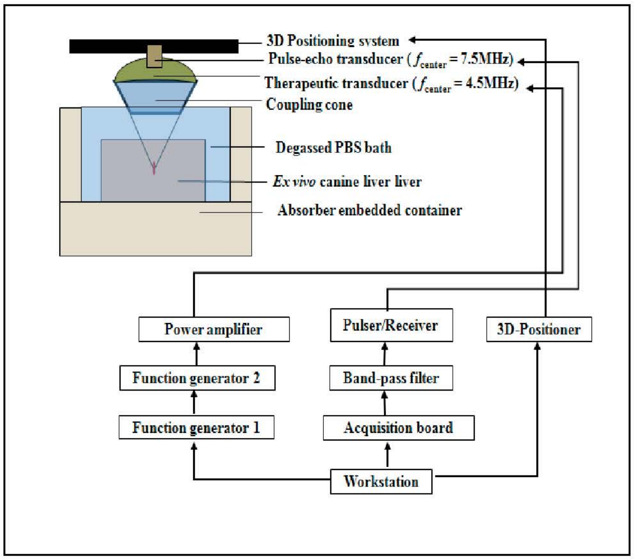


Figure 1. Schematic of the HMIFU set up

B. Displacement estimation

The RF signals received through the diagnostic transducer were acquired with a frame rate of 2000 Hz through a pulser (5800PR, Olympus NDT, NY, USA) and sampled at 80MHz from the pulse-echo transducer through a digitizer (Gage applied, Lockport, IL, USA) and used to estimate the displacement. An analog band-pass filter (Reactel, Inc., Gaithersburg, Maryland, USA, f_{c1} = 5.84 MHz and f_{c2} = 8.66 MHz, at -60dB) was used to filter out the spectrum of the HIFU beam and its harmonics prior to displacement estimation. A 1D normalized cross-correlation algorithm (window size of 3.85 mm and 90% overlap) was used to estimate the resulting axial displacement.

C. Temperature measurements

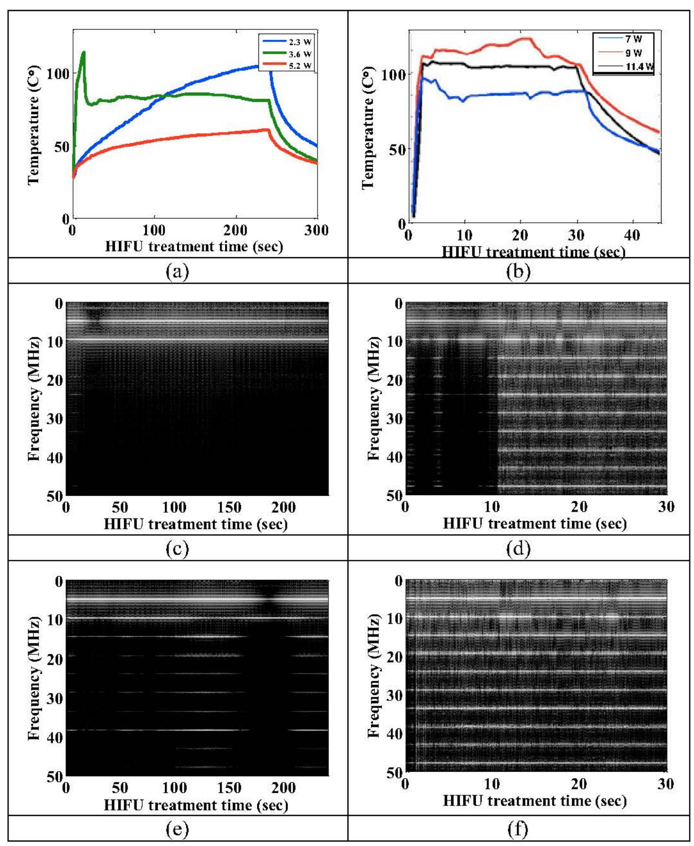
Focal temperature monitoring was performed by inserting a T-type bare wire thermocouple with diameter of 25 µm (Omega Inc., Stamford, CT) inside the tissue. The diameter of the thermocouple was chosen to be smaller than 1/10 of the carrier wavelength in order to minimize reflection and viscous heating artifacts[8]. These measurements were used to check for temperature spikes, signature of cavitation[6] and for boiling. One might note that due to the high frequency relatively to conventional HIFU, the temperature gradients are expected to be very strong. Therefore the thermocouple measurements depict a very local estimation of the temperature.

D. Backscattered emissions analysis

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[9]. The backscattered spectrum signal recorded from a passive recording transducer has been commonly used to characterize bubble activity. While harmonics encompass potential bubble non-linear oscillations along the ultrasonic excitation and non-linear response of the medium, ultra-harmonics are only caused by bubbles and thus are the signature of stable cavitation[8]. The broadband signal increase caused by bubbles bursting and collapsing will be detected if strong inertial cavitation or boiling occurs. Backscattered emissions measurements depict a global indication of bubble activity because the pulse-echo focal region is larger than the HIFU focus.

III. RESULTS

Fig. 2 depicts typical results comparing the two sequence types under both set of treatment protocols. First, thermocouple measurements exhibited strong boiling behavior at power above 3.6 W. Before boiling, no sudden temperature rise were detected. As shown in the backscattered spectrograms, the frequency content of the backscattered signal did not present any ultraharmonics. This might be explained by the relatively high frequency used in this study. Therefore, it can be deduced that the combination of high absorption with high cavitation threshold causes boiling to be the driving force for this mechanism. Consequentinally, the detection of a strong broadband noise on the spectograms would be the indication when boiling is generated.



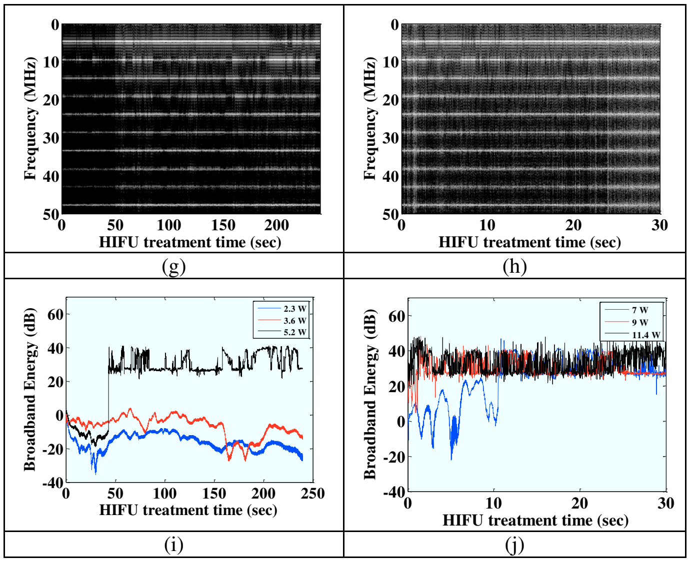


Fig 2. Aggregate thermocouple and backscattered spetrum analyses results. Left column (a,c,e,g,i) correspond to the thermocouple (a), spectrogram(c-g), and broadband energy (i) of HIFU treatment cases with lower power at 2.3 W_{ac} (c), 3.6W_{ac} (e), 5.2W_{ac} (g) for 240 seconds, respectively. Right column (b,d,f,h,j) correspond to the thermocouple (b), spectrogram(d-h), and broadband energy (j) of HIFU treatment cases with lower power at 7 W_{ac} (c), 9 W_{ac} (e), 11.4 W_{ac} (g) for 30 seconds, respectively.

In addition, from the thermocouple and broadband energy increase measurements, we can define the onset of boiling and the duration of generated boiling mechanisms. These results are summarized in Table 1.

HIFU sequence	Thermocouple	Backscattered
2.3 W_{ac} (240s)	> 240s	>240s
3.6 W_{ac} (240s)	212s	>240s
5.2 W_{ac} (240s)	16s	50s
7.0 W_{ac} (30s)	Instantaneous	12s
9.0 W_{ac} (30s)	Instantaneous	1s
11.4 W_{ac} (30s)	Instantaneous	Instantaneous

Table 1. Summary of the onset of boiling (thermocouple) and generalized boiling (backscattered) times.

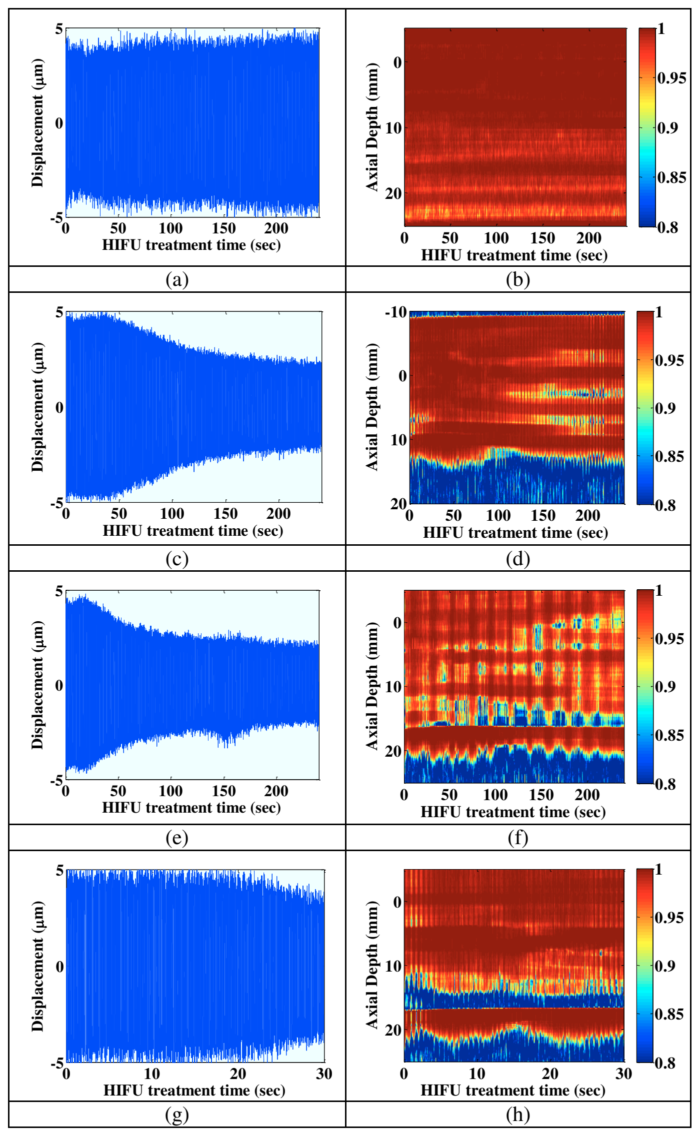
Given the underlying mechanical effects occuring during HMIFU treatment, we can now assess the quality of the displacement estimation. In figure 3, the correlation coefficient and incremental displacement were calculated and its variation during sonication are presented for different acoustic parameters. We observed consistent displacement decrease of -4.62±0.83 μm, indicating a gradual increase in tissue stiffening (i.e., thermal lesion formation), which were consistent with previous literature finding[6,10]. For the treatment cases with boiling detected, all had reversal increase of 14.62±2.83 μm, which comes from a simultaneous change in both acoustic absorption and mechanical stiffness, but when the which in turn contributed to an ehnaced radition force at the focal region. Another detailed study regarding monitoring of HIFU treatment under boiling can be found in a separate manuscript[11].

These typical results show than despite the presence of strong boiling effects HMIFU monitoring remained feasible.

It is noteworthy that, at very strong acoustic intensities, the combination of significant acoustic absorption increase (leading to an increase in the radiation force) and the local disruption of the tissue structure might lead to an increase of the focal peak to peak incremental displacements. Nevertheless, either the displacement increases or decreases during treatment, a good contrast ratio C was reliably observed. Contrast, C, was defined using Michelson's optics definition:

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

The displacement increase during treatment typically occurredin conjunction with sudden decorrelation as the RF signals became distorted due to boiling activity. Nonetheless, even after these extremely noisy events, displacement estimation was achievable given the transient nature of boiling. Full statistical analysis results are summarized in figure 4.



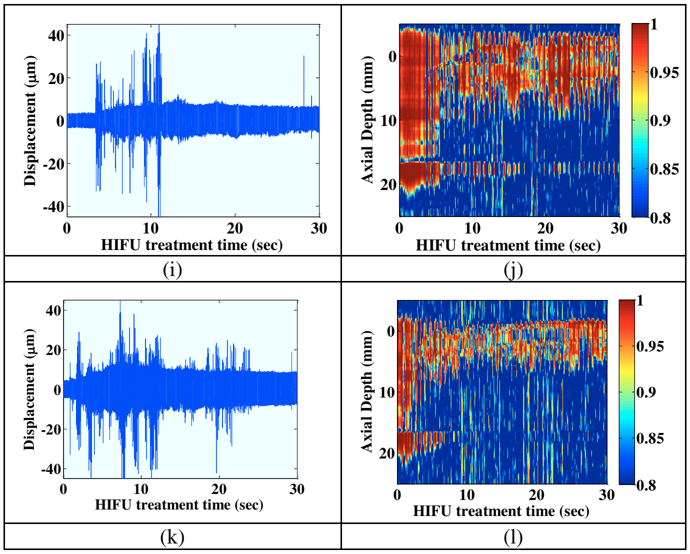


Fig 3. Performance assessment of HMIFU monitoring. The left column shows the estimated displacement while the right column shows the corresponding correlation coefficient. The corresponding HIFU treatment are 2.4W_{ac} (a,b), 3.6 W_{ac} (c,d),5.2W_{ac} (e,f) for 240 seconds, and 7 $_{Wac}$ (g,h), 9 W_{ac} (i,j), and 11.4 W_{ac} (k,l) for 30 seconds. One can note that when the boiling becomes too strong the displacement may increase during treatment due to a combination of severe acoustic abosrption increase and local tissue ruptures

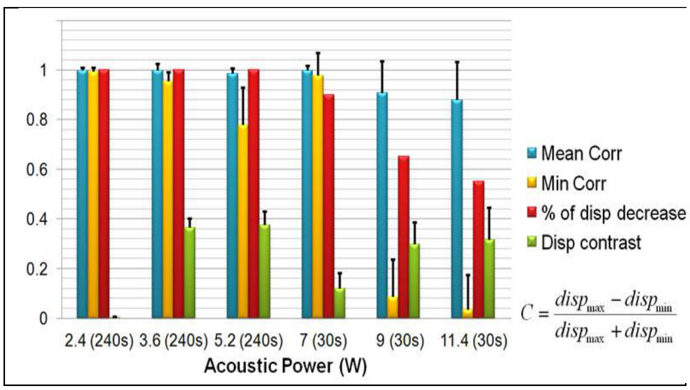


Fig 4. Statistical analysis of the samples studied. Average correlation during sonication, minimum correlation value reached during sonication, percentage of post-treatment displacement decrease and displacement contrast are displayed.

IV. DISCUSSION

For high acoustic intensities (above 4000 W.cm^{-2}), boiling at the focus was almost immediately reached. Evidences of mechanical effects on the tissues were also confirmed with presence of tissue scar and tear on gross pathology analysis. The thermocouple was used to determine the onset of boiling while generalized boiling was detected as high broadband noise on the backscattered measurements. However, despite it being noisier than without HIFU, HMI displacement estimation was accurately performed throughout boiling. Reducing the acoustic power to a more moderate range (1000 – 4000 W.cm-2) while increasing the exposure time led to negligible mechanical effects (temperatures below 80°C) and higher displacement estimation quality as the corresponding displacement estimations were strongly correlated (correlation coefficient strictly above 0.95 with reduced mechanical effects).

V. CONCLUSION

This study explored the robustness of HMIFU monitoring under strong mechanical effects such as inertial cavitation and boiling as well as the performance of high-frequency HIFU treatment. HMIFU was found capable of estimating displacement and monitoring ablation during cavitation and boiling. Operating at higher frequencies increased the tissue absorption while lowering the cavitation threshold. Optimal power and exposure time windows for HMIFU were identified in order to further improve displacement estimation and thereby monitoring performance toward its clinical implementation.

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