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Radio Frequency Ultrasound Time Series Signal Analysis to Evaluate High-intensity Focused Ultrasound Lesion Formation Status in Tissue

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ABSTRACT

High-intensity focused ultrasound (HIFU) is a novel treatment modality used by scientists and clinicians in the recent decades. This modality has had a great and significant success as a noninvasive surgery technique applicable in tissue ablation therapy and cancer treatment. In this study, radio frequency (RF) ultrasound signals were acquired and registered in three stages of before, during, and after HIFU exposures. Different features of RF time series signals including the sum of amplitude spectrum in the four quarters of the frequency range, the slope, and intercept of the best-fit line to the entire power spectrum and the Shannon entropy were utilized to distinguish between the HIFU-induced thermal lesion and the normal tissue. We also examined the RF data, frame by frame to identify exposure effects on the formation and characteristics of a HIFU thermal lesion at different time steps throughout the treatment. The results obtained showed that the spectrum frequency quarters and the slope and intercept of the best fit line to the entire power spectrum both increased two times during the HIFU exposures. The Shannon entropy, however, decreased after the exposures. In conclusion, different characteristics of RF time series signal possess promising features that can be used to characterize ablated and nonablated tissues and to distinguish them from each other in a quasi-quantitative fashion.

Key words: *High intensity focused ultrasound, radio frequency signal, Shannon entropy, time series, tissue characterization, ultrasound*

INTRODUCTION

Cancer treatment with non-invasive or minimally-invasive techniques has been investigated by a number of researches. Implementation of ablation therapy techniques has led to permanent destruction of tumors.

High-intensity focused ultrasound (HIFU), has shown intrinsic potential to create well-delineated thermal lesions in tissue, making it an effective technique to treat cancer.[1] Ultrasound-guided HIFU has also been used to treat and monitor various consequent characteristics of normal and thermally-damaged tissues.[2] In this method, tissue destruction is caused by thermal coagulation that increases the tissue temperature rapidly and causes tissue necrosis in a short time. The rate and extent of temperature rise depend on the HIFU exposure parameters and the local properties of the target tissue. Different types of tissue and variation in HIFU exposure parameters may lead to potential variation in clinical outcomes.[2]

Therefore, accuracy and reliability of methods toward treatment real-time monitoring and control are among the major factors considered for defining a safe and efficient image-guided HIFU treatment strategy.[2]

Most of the previously published techniques have only considered target tissue's acoustic,[3] mechanical,[4] and statistical[1,5-7] parameters. A method was also introduced in 2011 for stiffness-dependent displacement

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estimation.[8] This method implements three types of displacement estimations: (i) Coarse displacement estimation, (ii) refining displacement estimation, and (iii) displacement mesh computation to finalize the evaluation. The method takes only about one-tenth of the computational time comparing to the earlier similar methods such as blind displacement estimation.[8] Furthermore, the acousto-optic imaging method was introduced, as an alternative approach, to monitor and register the formation of tissue thermal lesions.[9,10] On the other hand, using a different approach, the local minima of the harmonics of the passively monitored acoustic signal emitted from the tissue at the focal point of an HIFU beam was measured during exposure.[3] Mechanical methods were also introduced to address the problem based on the dynamic indentation, i.e. the spatial stiffness of tissue.[4] Accordingly, the dynamic indentation was used to quantify the material properties at radio frequency (RF) ablated regions locally, and the result of the spatial modulus distribution was further improved. Feed forward neural network based on multilayer perceptron was also used as a basis to introduce a novel HIFU lesion formation monitoring method.[6] The approach was performed *in vivo* on animal tissue samples. In this technique, backscattered RF ultrasound signals were used in real-time, before-HIFU (PRE-HIFU) and after-HIFU (POST-HIFU) exposures to distinguish ablated tissues. To detect thermal ablations caused by HIFU, the localized motion imaging was also proposed as a monitoring technique.[11] As a result, a localized mechanical response based on the changes in the stiffness caused by thermal coagulation was detected. The HIFU-induced thermal lesions were also effectively detected *in vitro* by Nakagami parametric imaging that was based on the distribution of ultrasound backscattered signals.[5]

The main objective of this study was to derive relevant features and statistical parameters to achieve an optimum precision method for the detection of lesions caused by HIFU treatment in soft tissues. The results revealed that four features extracted from the RF signals including: (i) The sums of amplitude spectrum in the four quarters of frequency range, (ii) the slope of the best fit line to the entire power spectrum, (iii) the intercept of the best fit line to the entire power spectrum, and (iv) the Shannon entropy can be used to develop a tissue characterization technique to detect thermal lesions and to differentiate them from normal tissue in a quasi-quantitative fashion. A block diagram of the procedure of this study has been shown in Figure 1.

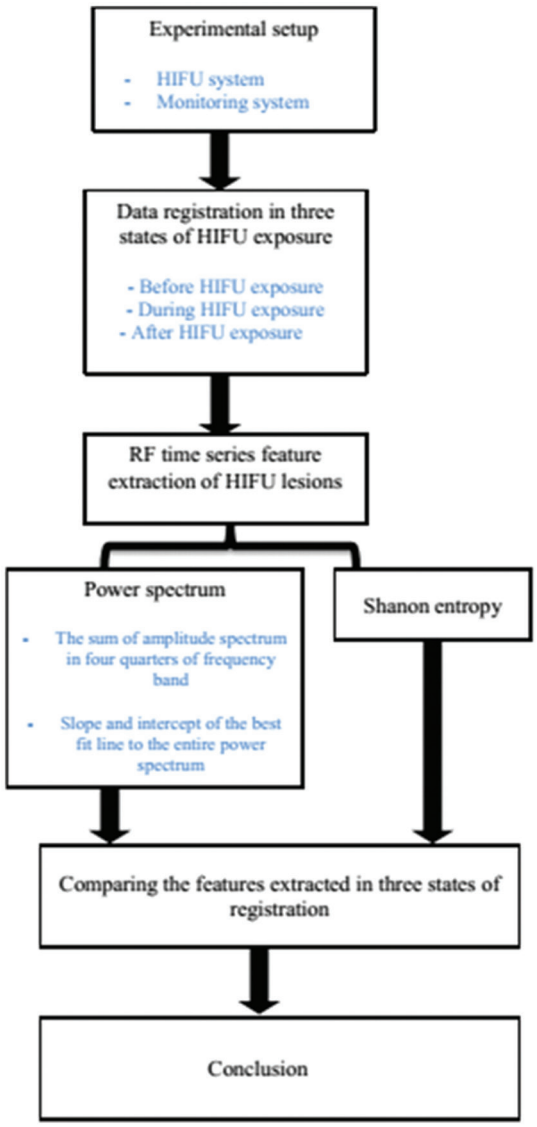

Figure 1: Block diagram of the study procedure

MATERIALS AND METHODS

Image-guided High-intensity Focused Ultrasound System

A clinical ultrasound scanner (Sonix RP®, Ultrasonix Medical Corp., Richmond, BC, Canada) was used in this study to acquire RF echo data and to monitor HIFU thermal lesion changes and growth in three stages of registration. Different modules of the system and their corresponding settings and specifications are shown in Table 1.[6] The schematic diagram of the HIFU transducer and embedded imaging probe is shown in Figure 2. The transducer had a 125 mm diameter aperture and a 100 mm geometric focal length. Tissues were placed on the common axis of both transducers, at a distance of 10 cm (equal to the focal length of both transducers) from both transducers (transmitter and the receiver).

Data Acquisition Timing Sequence

The HIFU exposures were applied to 5 different porcine muscle tissues, including 21 samples, *in vitro*. The PRE-HIFU data were initially saved and then HIFU exposures were applied for 40 s. During the exposures,

Table 1: Data registration properties

Module	Settings	Specification
HIFU module	Transducer	Imasonic S.A., Besançon, France
	Central frequency (MHz)	1
	F number	0.8
	Aperture diameter (nm)	125
	FWHM[a] lateral (nm)	1.7
	FWHM axial (nm)	6.8
Monitoring system	Ultrasound scanner	Sonix RP® clinical ultrasound scanner (Ultrasonix Medical Corp., Richmond, BC, Canada)
	Probe features	Convex array probe, which was coaxially mounted in the center of the therapy transducer
	Probe frequency (MHz)	4
HIFU exposure parameters	Function generator	AFG3101 arbitrary function generator (Tektronix, Inc., Beaverton, OR)
	Power amplifier	AG1012 RF power amplifier (T and C Power Conversions, Inc, Rochester, NY)
	Registration time during HIFU registration	40 s
	Electrical power (W)	70, 75, 80, 90,100
	Duty cycle (%)	77

[a]Full Width at half maximum. HIFU – High intensity focused ultrasound

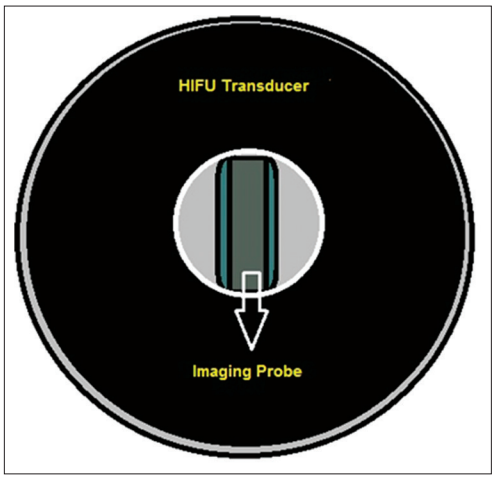

Figure 2: The schematic diagram of the imaging probe embedded with the high-intensity focused ultrasound transducer in a confocal arrangement

the during-HIFU (DUR-HIFU) data were acquired. At the last stage, 10 min after the HIFU exposure had been switched off, the POST-HIFU data were acquired. During the HIFU exposures, microbubbles are created in the lesion site. To remove this effect on the signal processing procedure, the data were acquired 10 min POST-HIFU exposures.

After the HIFU exposures, the bright hyperechoic region in the focal region of B-mode images began to gradually fade, and after 10 min of the exposures, it was hardly detectable and visible on the B-mode images. Hence, in this case, the data were acquired 10 min POST-HIFU exposures.

Feature Extraction

The characterization of the thermal lesions induced by HIFU exposures has been determined by extracting time series features from the RF signals.[1] Power Spectrum and Shannon entropy of every RF line were calculated.

Power Spectrum

The ultrasound RF time series was formulated as a function of the length of the signal and different characteristics of it were evaluated (Eq. 1)[1]

$$x_1(n);\ n = 1,\ldots,N \tag{1}$$

In the above equation, $N = 5200$ is the length of the time series. The mean value is obtained according to Eq. 2. The average value is then subtracted from the time series (Eq. 3).

$$\bar{x} = \frac{1}{N}\sum_{l=1}^{N} x_1(n) \tag{2}$$

$$\hat{x}_1(n) = x_1(n) - \bar{x} \tag{3}$$

A discrete Fourier transform is then applied to this time series, and its power spectrum $X_1(k)$ is obtained as given in (Eq. 4).

$$X_1(k) = \frac{1}{N}\sum_{l=1}^{N} \hat{x}_1(n)\, e^{-j2\pi kn/N} \tag{4}$$

The power spectrum is calculated over the length of the time series. The spectrum is normalized after dividing it by its maximum.[1]

Four different features, as defined by Eq. 5, were extracted for the RF time series signal based on the procedures defined by Imani *et al*.[12]

$$Feature(i) = \sum_{k=1+(i-1)N/8}^{N/8} \left|X_1(k)\right|, i = 1.\ldots.4 \tag{5}$$

Shannon Entropy

The Shannon entropy can be expressed based on the values of as the probability of existence of each feature in the time series given by Eq. 6:

$$H(A) = -\sum_{i=1}^{n} p_i \log_2 p_i \tag{6}$$

Shannon entropy defines the lower limit for compression; in other words, it can display the extent of information compression. Algorithmic complexity theory, also known as Kolmogorov complexity,[13] is dealing with this logic. According to mathematical infinity data sets, random data sets can be examined to find out the possible pattern involved. However, if the data sets are not random, it is still possible to identify the correlations and general pattern(s) of activities to formulate and present different data sets.[14]

Experiments

In this study, five porcine muscle tissue samples were used for HIFU ablations.[6] Applying HIFU exposures with electrical input powers of 70W, 75W, 80W, and 90W with the duty cycle of 77%, a total number of 19 lesions were induced.[6] The lesions were formed with various diameters in the range of 5–15 mm.

Several lesions were created in porcine tissue samples by HIFU exposures[6] as shown in Figure 3. Which corresponds to tissue sample #2, lesion #4.

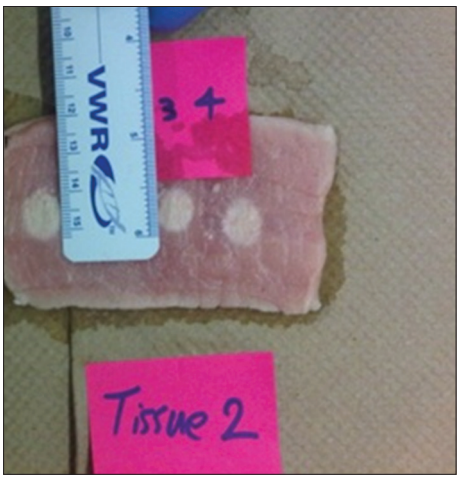

Figure 3: Tissue samples showing the length of the high-intensity focused ultrasound lesions (tissue #2, lesion #4)

RESULTS

In this study, the HIFU thermal lesion formation was recorded as a function of time and the changes occurring in lesions during the treatment time, including three stages of registration, was tracked. Consequently, the RF signals and B-mode images were obtained and used for further analysis [Figure 4].

We calculated the sum of the power spectrum in four quarters of frequency bands. The slope and intercept of the best fit line to the entire power spectrum were extracted from the RF time series signals related to the lesions. These features showed an increase of almost two folds in the value DUR-HIFU over PRE-HIFU in comparison to POST-HIFU over PRE-HIFU [Figures 5 and 6]. The ratios were normalized by PRE-HIFU values, to track the changes and increase the resolution. In Figures 5 and 6, columns 1–4 refer to the four quarters of frequency bands and columns 5 and 6 are the slopes and the intercept of the best-fit line to the entire power spectrum, respectively.

The increase in the power spectrum features is related to the effect of HIFU exposures in the tissue. These observations have already been made by other researchers who have indicated the increase is caused by backscatter coefficient in a frequency dependent manner and remarked that the change in the average size of the scatterers is the

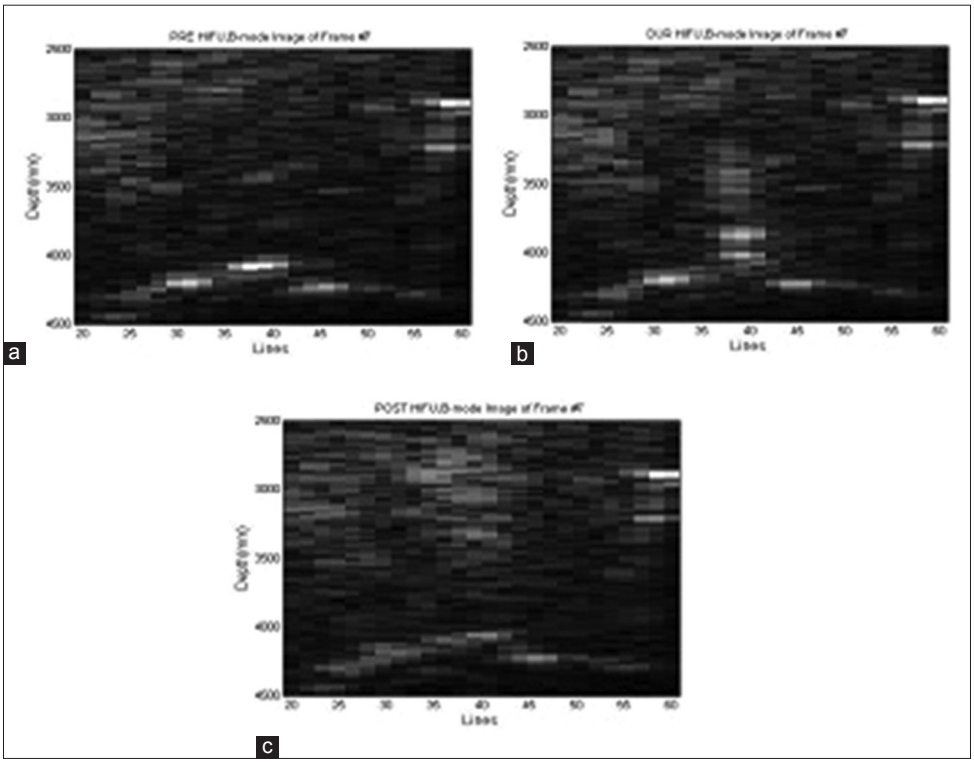

Figure 4: Selected region in the reproduced B-mode images of lesions induced by High-intensity focused ultrasound exposures. The shown area correspond to (a) PRE-HIFU, (b) DUR-HIFU, (c) POST-HIFU exposure stages in lesion #4 of tissue #2. PRE-HIFU – Pre-high-intensity focused ultrasound; POST-HIFU – Post-high-intensity focused ultrasound; DUR-HIFU – During-high-intensity focused ultrasound

main reason for this increase.[6,15] The increase in the power spectrum features showed that during the HIFU exposures different power spectrum characteristics of the exposed tissue were affected. This estimation was made at different HIFU electric powers of 75W and 90W [Figures 5 and 6], respectively.

Increasing in output power causes a significant effect on the lesion characteristics so that the higher the power, the larger was the effects as shown in Figures 7 and 8. The results of Shannon entropy feature extraction with electric powers of 75W and 100W shown in Figures 7 and 8, relatively. As it is shown, the values of DUR-HIFU over PRE-HIFU with 75W electrical power were 1.0 and the rate of POST-HIFU over PRE-HIFU exposures was 0.5, whereas the value of DUR-HIFU over PRE-HIFU with 90W electrical power was 1.9 and the rate of POST-HIFU over PRE-HIFU exposures was 0.8.

The entropy values were decreased POST-HIFU exposures. There were much fewer disorders in the lesions caused by the HIFU exposures in this stage of registration. The decrease in the entropy was manifested in the tissue coagulation area. These results indicate that the amount of Shannon entropy increases DUR-HIFU exposures.

Time Domain Estimation

In this work, the Shannon entropy analysis was conducted in different time instances. In other words, the changes of this feature were monitored throughout the experiments at

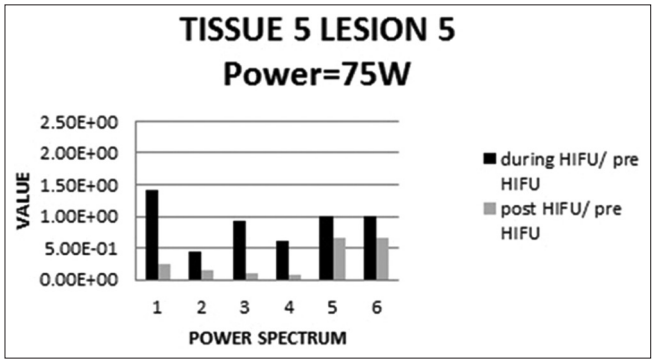

Figure 5: The ratio of POST-HIFU and DUR-HIFU to PRE-HIFU against power spectrum in tissue #5, lesion #1 exposed to 75W electrical power. The black and gray color columns refer to DUR-HIFU/PRE-HIFU and POST-HIFU/PRE-HIFU exposure registration, respectively. Columns 1–4 refer to the four quarters of frequency bands and columns 5 and 6 are the slope and the intercept of the best fit line to the entire power spectrum, respectively. PRE-HIFU – Pre-high - focused ultrasound; POST-HIFU – Post-high intensity focused ultrasound; DUR-HIFU – During-high-intensity focused ultrasound

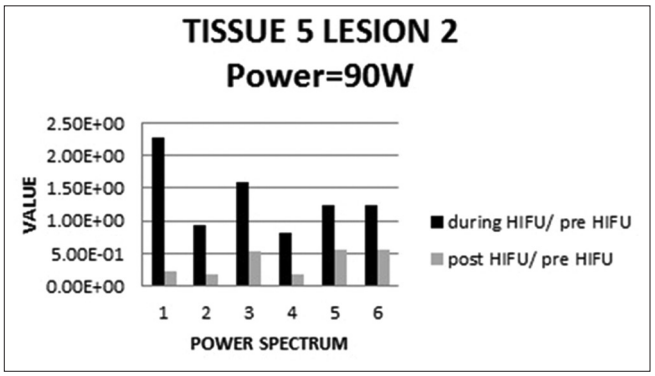

Figure 6: The ratio of POST-HIFU and DUR-HIFU to PRE-HIFU against power spectrum in tissue #5, lesion #2 exposed to 90W electrical power. The dark and light color columns refer to DUR-HIFU/PRE-HIFU and POST-HIFU/PRE-HIFU exposure registration, respectively. Columns 1–4 refer to the four quarters of frequency bands, and columns 5 and 6 are the slopes and the intercept of the best fit line to the entire power spectrum, respectively. PRE-HIFU – Pre-high-intensity focused ultrasound; POST-HIFU – Post-high-intensity focused ultrasound; DUR-HIFU – During-high-intensity focused ultrasound

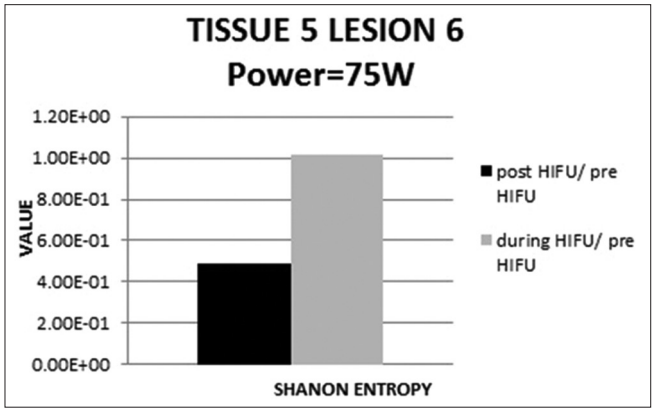

Figure 7: The ratios of POST-HIFU/PRE-HIFU and DUR-HIFU/PRE-HIFU against the corresponding Shannon Entropy at the lesion site (tissue #5, lesion #6) exposed to 75W electrical power. The black and gray color columns refer to DUR-HIFU/PRE-HIFU and POST-HIFU/PRE-HIFU exposure registration, respectively. PRE-HIFU – Pre-high-intensity focused ultrasound; POST-HIFU – Post-high-intensity focused ultrasound; DUR-HIFU – During-high-intensity focused ultrasound

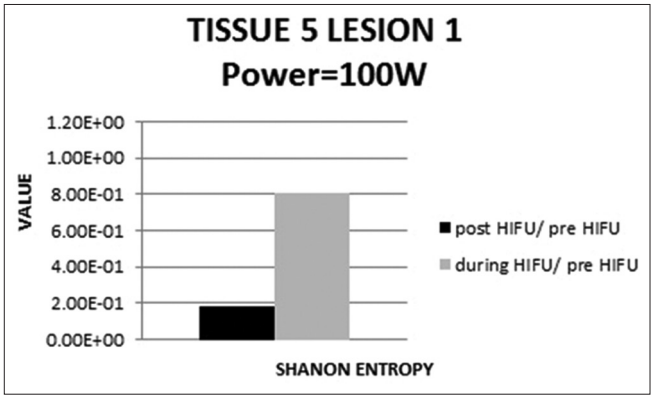

Figure 8: The ratios of Shannon entropy POST-HIFU/PRE-HIFU and DUR-HIFU/PRE-HIFU against in tissue #5 at the lesion #1 site exposed to an electrical power of 100W. The black and gray color columns refer to DUR-HIFU/PRE-HIFU and POST-HIFU/PRE-HIFU exposure registration, respectively. PRE-HIFU – Pre-high-intensity focused ultrasound; POST-HIFU – Post-high-intensity focused ultrasound; DUR-HIFU – During-high-intensity focused ultrasound

three stages of RF data registration defined as PRE-HIFU, DUR-HIFU and POST-HIFU exposures. The resulting data set was analyzed and evaluated at different HIFU electric powers (70W-100W) [Figures 5-8].

The first point (yellow point) of the diagram represents the mean of 9 RF frames that were registered PRE-HIFU exposures. The next 9 points obtained from the analysis of 9 frames registered during the HIFU exposures, and the last point (red point) indicates the mean of 9 RF frames that were registered POST-HIFU exposures. The results show a jump at the first stage of the exposure [Figure 9].

DISCUSSION

In similar studies conducted by other research groups, extraction of RF time series features had been demonstrated in 12 *ex vivo* chicken breast and 2 *in situ* bovine liver tissue samples based on PRE- and POST-HIFU exposure treatments.[1,12] In this study, 6 *ex vivo* porcine tissue samples were analyzed in three PRE-HIFU, DUR-HIFU, and POST-HIFU exposure stages. The approach presented in this work is different from the previously published ones[1] because, here, the main focus is on the estimation of the changes occurring DUR-HIFU exposure. This approach made it possible to monitor certain type of parameters DUR-HIFU lesion formation process. The study was conducted on 21 lesions obtained from 5 different tissue samples. The HIFU input electric powers of 10W to 100W were applied to reach optimum estimations. To perform the analysis, three registration stages whose RF signals contained 9 frames were considered.

The effects of HIFU exposures, with different electric powers, were monitored throughout the HIFU exposure and evaluated using the power spectrum in four quarters of frequency bands. The slope and intercept of the best fit line to the entire power spectrum of the DUR-HIFU increased by about two folds in comparison to POST-HIFU exposures. This parameter is mainly associated to the tissue microstructure. It is known that the average size of the scatterers changes DUR-HIFU and POST-HIFU exposure.[6] These phenomena cause a significant increase in the power spectrum features due to the HIFU exposures.

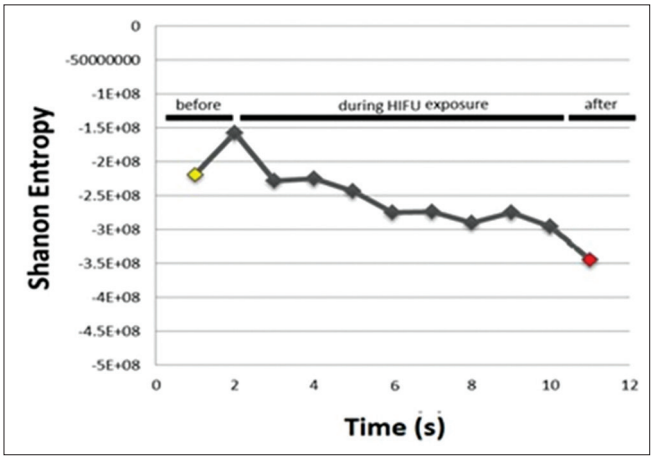

Figure 9: Time domain Shannon entropy changes at three stages (before, during, and after) of high-intensity focused ultrasound exposures with electric power of 80W in the tissue #1 at the site of lesion #4

As expected, increasing power causes a significant effect on the thermal lesions. The values of electric power showed a direct effect on the lesion characteristics, the higher the power, the larger was the effects [Figures 5 and 6]. The range of changes in feature 1, in Figure 5, with 75W electric powers is 1.4, whereas applying an electric power of 90W in the same feature in Figure 6; the resulting change is measured as 2.3. These changes in the physical properties of the tissues as a function of the electric power DUR-HIFU exposures led to variation in the power spectrum features of the RF time series. The frequency dependence of backscatter coefficients, which is one of the ultrasonic tissue characterization parameters, is related to tissue microstructure. As it has been studied in various works,[6,15] the acoustic scattering properties is mainly related to the tissue structure and the distribution size of the scatterers.

Figures 5 and 6 are representing two different lesions, which have been formed by two different electric powers, 75W and 90W, respectively. The rate of POST-HIFU/PRE-HIFU in column 3 is greater than those in columns 1, 2, and 4 in Figure 6, whereas the rate of change in column 1 is greater than those in columns 2, 3, and 4 in Figure 5. As it has been mentioned previously, these four columns represent the sum of amplitude spectrum in four quarters of the frequency band. This different behavior of the frequency quarters may be caused by the tissue microstructure, and the effect of the scatters on the frequency bands. The main purpose is to investigate the changes of power spectrum features as the electric power is increased and to obtain the difference between the three states of registration.

Another estimation method that was found to be feasible is based on the effects of the increase of electric power of the HIFU exposures on the targeted tissue. As it was mentioned earlier in this paper, with the increase of the electrical power, the amplitude of the power spectrum features increases. It is noted that at an electric power of 75W, the rate of DUR-HIFU over PRE-HIFU exposures is about 0.4–1.4, whereas the rate of POST-HIFU over PRE-HIFU exposures is 0.1–0.6. However, for the electric power of 90W, these ratios were increased to about 0.8–2.3 and 0.3–0.6, relatively. This shows a significant increase in the power spectrum features that was caused by increasing the input electric power. This indicates that by applying higher electric power, the lesion corresponds to higher power spectrum amplitude of the RF signal.

In this study, the Shannon entropy was extracted from the RF signals. The results showed that the rate of DUR-HIFU

over PRE-HIFU entropy was much higher than the rate of POST-HIFU over PRE-HIFU. This increment during the HIFU ablation was most probably caused by the air bubbles and cavitation. These air bubbles are mainly produced during the exposure and increase the irregularity and randomness in the tissue ablation process. The Shannon entropy obtained with 75W electric powers in DUR-HIFU over PRE-HIFU stage was one, whereas for POST-HIFU over PRE-HIFU a value of 0.5 was obtained. The corresponding values at the electric power of 100W were 0.8 and 1.9, respectively. These results show that for different electric powers, the Shannon entropy gives similar results with greater values during the HIFU exposures.

The Shannon entropy parameter was estimated in the time domain to monitor the formation of the HIFU thermal lesion in different stages of registration with the RF frames. The results showed a sudden increase in the value of Shannon entropy at the beginning of the exposure that referred to as the transition stage occurring from the first stage (PRE-HIFU exposures) to the second stage of registration (DUR-HIFU exposures). The increase was most probably caused by the effect of cavitation in the focal zone that eventually led to the formation of a lesion. In other words, the formation of air bubbles caused an increase in the irregularity in the tissue ablation process. At the subsequent stages of exposure, a descending trend in the level of Shannon entropy was observed that represents a resulting decline in the irregularity of the lesion. This trend indicated that throughout the ablation process, due to the formation of the thermal lesion in tissue, the tissue becomes stiffer and less disordered in structure.

According to the entropy definition, it was expected that POST-HIFU exposures, entropy values decrease. Based on the general definition of entropy, which refers to the degree of disorder, and with application of HIFU exposures, irregularities in the tissue lesions are reduced. The tissue coagulation area has typically a more uniform structure, and this phenomenon could potentially be linked to the amount of entropy decrease.

During the HIFU exposures, the entropy increased mainly due to bubbles formation in the focal zone in tissue. However, POST-HIFU exposures the entropy decreased which was an indication of the status in which the scatterers disorder is reduced, and the texture of the tissue becomes more uniform. As it has been mentioned in other works,[16,17] the tissue stiffness during ablation initially decreases and then increases above a certain temperature threshold. In another work,[6] it has been declared that the tissue vibration of the lesion site was decreased POST-HIFU ablations. This could be another reason for the increase in the Shannon entropy that was observed during the HIFU ablation in our study.

The sudden increase in the Shannon entropy represents the cavitation process that occurs in the initial steps of lesion formation. The gas bubbles produced by cavitation increase the amount of disorder and raise the corresponding entropy level in the related stage of registration. The increase was identified at the transition states from PRE-HIFU exposures to DUR-HIFU exposures. Further HIFU exposure caused a roughly linear decline in the level of Shannon entropy by about 20% [Figure 9]. This event might be interpreted as the decline of the tissue structural irregularity due to creation of a more uniform lesion in the tissue.

Consequently, taking the approach of the current study, it was possible to identify the tissue structural irregularities by means of the entropy parameter. Application of HIFU for tissue coagulation purposes normally leads to a hardening process at the lesion formation stage. These changes lead to a decrease in the irregularities of the tissue. Based on these facts, a reduction in the entropy values was expected after the HIFU exposure that was clearly observed as a result of the current study.

CONCLUSION

In conclusion, the promising result of this study paves the path to establish a new monitoring technique to control the extent of thermal lesion formation during the HIFU exposure. The approach proposed in this study requires further development before it can be used for *in vivo* clinical procedures in which real-time monitoring of HIFU lesion creation in the presence of various artifacts such as tissue inhomogeneity and motion exhibits additional challenges to overcome.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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