

Temperature Measurement Using Passive Harmonics during High Intensity Focused Ultrasound Exposures in Porcine Tissue

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It is important to deliver suitable thermal dose to target region during high intensity focused ultrasound therapy, and ultrasonic non-invasive temperature measurement is an easily accepted approach to monitor the temperature fields during the treatment process. Traditional method usually required another source for monitoring besides high intensity focused ultrasound source. This paper was based on passive scattering harmonics for high intensity focused ultrasound temperature measurement, and it could avoid the influence of treatment sources on temperature measurement. The purpose of this paper is to investigate the relationship between the nonlinear harmonic amplitude and temperature in porcine tissue (muscle and liver). The optical fiber hydrophone was used to receive passive scattering harmonics from high intensity focused ultrasound irradiation in porcine tissue, and the temperature of tissue in focal region was measured with a thermocouple needle at the same time. The relationship between harmonic amplitude and temperature was analyzed. Experimental results indicate that the values of amplitude for fundamental wave P_1 , the second harmonic P_2 , the third harmonic P_3 , the ratios of P_2/P_1 , P_3/P_1 , and P_3/P_2 decrease while temperature increases in the focal region of porcine tissue, and the slope of P_2/P_1 , P_3/P_1 , and P_3/P_2 have obvious decline at the beginning of temperature measurement, but their slope become flat as temperature increases, and the slope of P_2/P_1 , P_3/P_1 , and P_3/P_2 drop faster in porcine muscle than in liver. This study may potentially be used as a non-invasive method of temperature monitoring for ultrasonic thermal therapy in real-time.

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1. Introduction

High intensity focused ultrasound (HIFU) therapy is used to achieve therapeutic effect mainly by its thermal effect. Ultrasonic energy can be used to make the temperature of tumor cells elevated to 45°C or higher to inhibit tumor cells growth [1]. In order to safely and accurately kill the pathological tissue but do not damage normal tissue, it is necessary to monitor the process of treatment. In clinical treatment, the therapeutic dose of HIFU may be excessive and it may cause severe burn to skin and normal tissue, or it may lack effective monitoring in real-time, and this might affect tumor cells treatment. In order to guarantee the safety and reliability of HIFU therapy, the technology of temperature monitoring has become a hot topic in medical ultrasound engineering.

During the heat treatment process of cancer, the monitoring method can be achieved by temperature measurement, which includes non-invasive and invasive temperature measurement. The invasive temperature measurement inserts temperature sensors into the test site for direct measurement and it could cause damage to tissue. There are many methods of non-invasive temperature

measurement, such as MRI and ultrasound, etc. Temperature measurement with MRI is based on the shift of neutron resonance frequency [2, 3]. The advantage of this method is that the temperature distribution in the treatment area can be measured within a short time (5 s), and the dynamic temperature of the treatment area can also be obtained by continuous measurement at regular intervals. On the other hand, this method is too expensive and more complex. Ultrasound is penetrative and easily compatible with treatment equipment [4–6]. Temperature measurement with ultrasound included two different ways of ultrasonic signal and image, and their fundamental principles are all the relationship between the acoustical properties of biological tissue and temperature. From ultrasonic signal, temperature measurement is mainly based on ultrasonic sound speed, nonlinear parameter B/A , time shift of echo, frequency shift of echo, and scattering energy, etc. From ultrasonic image, temperature measurement is mainly based on image texture and image gray-scale [7]. All these ultrasonic methods mentioned above required a diagnostic ultrasound source for monitoring, and the method proposed in this paper is directly based on HIFU source and nonlinear characteristics of HIFU.

The ultrasound wave with finite amplitude is gradually distorted in the propagation process, which can produce high order harmonics and they can be detected in the frequency spectrum of signal. According to the simulation

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of sound pressure and transmission distance with transducer, ultrasonic distortion and harmonics generation depend on B/A parameter, attenuation coefficient, and acoustic speed in media [8, 9]. Because these three parameters are relatively easy to be influenced by temperature, so harmonics are correlated with temperature. In a numerical simulation study, van Dongen and Verweij [10] found that ultrasonic amplitude in glycerol was related to temperature. They proved that temperature can be measured by amplitude ratio between fundamental wave and second harmonic. In this paper, the scattering harmonics came from HIFU irradiation in porcine muscle and liver, and they were passively received by a fiber hydrophone. A thermocouple needle was used to monitor focal region temperature of porcine muscle and liver.

2. Materials and methods

2.1. Experimental setup

The experimental porcine tissue (muscle and liver) were fresh, and large blood vessels and meridians were avoided. The tissue was cut to a size of around $6\text{ cm} \times 7\text{ cm} \times 4\text{ cm}$. The povidone and 95% alcohol were mixed with 1:4 proportion to scavenge oxygen in water, then mixing them and water with 1:20 proportion and pour them into the water tank, waiting for about one hour before experiment. The porcine tissue was mounted on a sample holder and immersed in water under HIFU source (PRO2008, Shenzhen, CN). Acoustic rubber was placed at the bottom of water tank to absorb ultrasound, and the position of transducer can be shifted by computer controlled 3D mobile platform. In the experiment, the HIFU source was self-focusing transducer with concave spherical surface, and it had a circular hole at the top that allowed the fiber probe of hydrophone (FOPH2000, Leutenbach, DE) and type-B mode ultrasound probe to pass through. The center frequency of self-focusing transducer was 1.39 MHz and the geometric focal length was 13 cm, the aperture of transducer was 11 cm and the diameter of circular hole was 4.7 cm, and the source pressure of transducer was 0.23 MPa. The input electric power of transducer can be adjusted during experiment.

All exposures were accomplished using quasi-continuous HIFU wave and its pulse length was 10 ms. The average temporal power of transducer can be measured by radiation force balance method as follows [11]:

$$P = 2Fc / (\cos \alpha_1 + \cos \alpha_2), \quad (1)$$

where P was the average temporal power, F was the radiation force, c was the acoustic speed in propagating medium, α_1 was half of the internal hole aperture angle of the self-focusing transducer, and α_2 was half of the outer aperture angle of the self-focusing transducer.

The spatially peak acoustic intensity I_{SP} was calculated by the equation [12]:

$$I_{SP} = 1.56 \frac{P}{D^2}, \quad (2)$$

where D was the focal beam width of transducer. The average temporal power of transducer was 290 W, the ellipsoidal -6 dB focal beam width of this transducer was 1.6 mm.

The scattering acoustic signal was received by hydrophone, then the signal was amplified by broadband amplifier and sent into digital oscilloscope (Tektronix MDO3032, USA) for observation, and signal was also stored and processed in computer. The thermocouple (DT-3891G, Shenzhen, CN) needle was placed in the focal region of porcine tissue during HIFU irradiation and the temperature was measured in real-time. The intensity and time of HIFU irradiation can be controlled by computer. The detection device of harmonics was shown in Fig. 1. The experiments were repeated 6 times at each temperature.

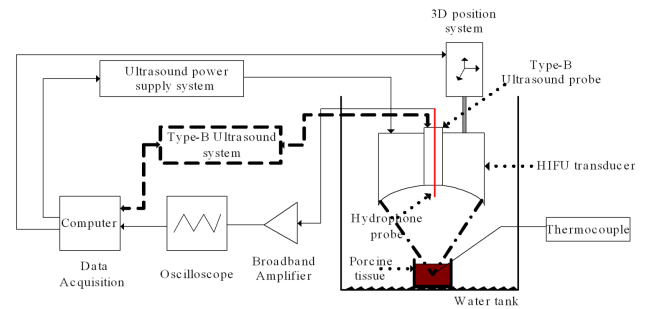


Fig. 1. Passive detection device of scattering harmonics.

2.2. Data processing

The scattering harmonics were analyzed and processed with Matlab programming. Firstly, the noise in ultrasonic signal was filtered out by sym8 wavelet with 4 layer decomposition, then we used signal processing box FDATool to design bandpass filter and made harmonics pass through. Because of the rapid attenuation of high order harmonic amplitude, the designed filter and data analysis were no more than third-order harmonics. Furthermore, fast Fourier transform (FFT) transform was performed for the scattering signals with the Hanning window. P_1 , P_2 , and P_3 are corresponding to fundamental wave, second harmonic, and third harmonic respectively, which came from HIFU irradiation in porcine tissue. Harmonic amplitude was acquired by calculating frequency spectrum of ultrasonic pulse with the Fourier transform. Both harmonic amplitude and the ratios of harmonic amplitude (P_2/P_1 , P_3/P_1 , and P_3/P_2) with temperature variation in focal region of porcine tissue were analyzed.

3. Results

From Figs. 2 and 3, it can be found that the harmonic amplitude of P_1 , P_2 , and P_3 decrease while temperature increases in porcine muscle and liver, and the amplitude of high order harmonic is smaller than low order harmonic at certain temperature.

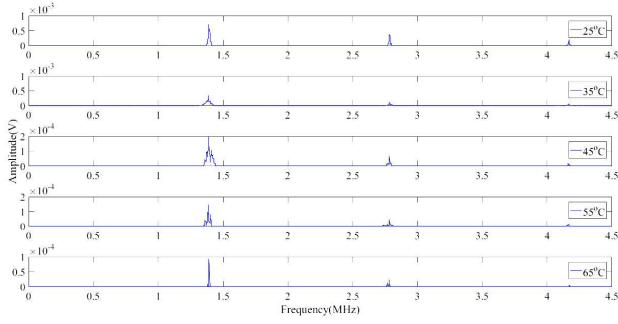


Fig. 2. Amplitude spectrum for the scattering HIFU signal in focal region of porcine muscle at 25 °C-65 °C.

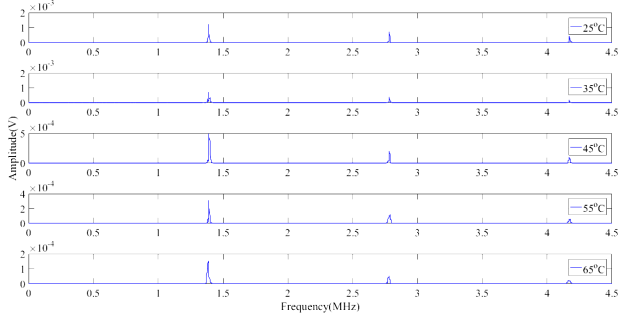


Fig. 3. Amplitude spectrum for the scattering HIFU signal in focal region of porcine liver at 25 °C-65 °C.

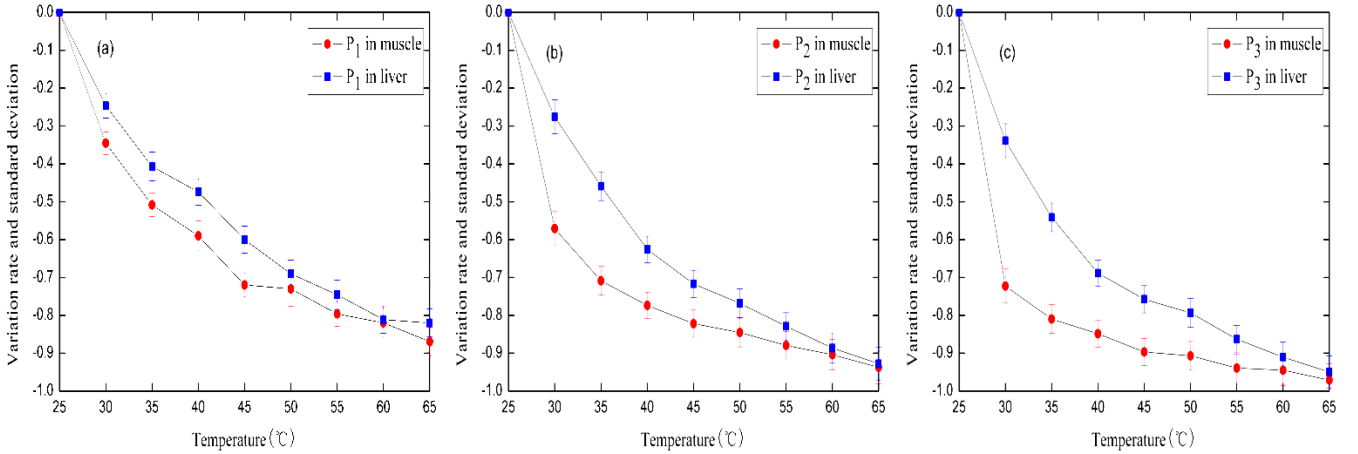


Fig. 4. Variation rate and standard deviation of harmonic amplitude at different temperature comparing to 25 °C in porcine muscle and liver. (a) P_1 , (b) P_2 , (c) P_3 .

From Figs. 2 to 5, it can be seen that harmonic amplitude decreases gradually while temperature increases in the focal region of porcine muscle and liver under the frequency of 1.39 MHz, this is mainly correlated with nonlinearity and absorption of ultrasound. The Gol'dberg number is expressed as $\Gamma = N/A$ [16] (N is related with nonlinearity and it is defined as $N = 2\pi f p_0 f b e \beta$, f is the center frequency of transducer and p_0 is the source pressure of transducer. A is related with absorption and it is defined as $A = \rho c^3 \alpha$), which defines the balance between

Figure 4 shows the variation rate and standard deviation of harmonic amplitude (P_1 , P_2 , and P_3) at different temperature in porcine muscle and liver. The variation rate is actually a relative value comparing to 25 °C, which can be decided with the variation divided by the amplitude at 25 °C. It can be found that the descending gradient of harmonic amplitude is bigger in porcine muscle than in liver, because the attenuation in muscle is greater than in liver [13, 14]. With the increase of temperature, the difference of variation rate of harmonic amplitude decrease in porcine muscle and liver. Keck and Beyer [15] confirmed that the amplitude of n -order harmonic was proportional to $[\beta/(\alpha\rho c^3)]^{n-1}$ ($\beta\alpha$ and ρ denote nonlinear coefficient, attenuation coefficient, and density, respectively) during the propagation of finite amplitude wave in attenuation medium. The ultrasonic parameters which correlated with temperature are more prominent to the amplitude of high order harmonics, and the acoustic damping of high order harmonics is faster, so its amplitude is relatively low. Figure 5 shows the ratio (P_2/P_1 , P_3/P_1 , and P_3/P_2) and standard deviation of various harmonic amplitude at different temperature in porcine muscle and liver, and the slope of P_2/P_1 , P_3/P_1 , and P_3/P_2 have obvious decline at the beginning of temperature measurement, but their slope becomes flat as temperature increases, and the slope of P_2/P_1 , P_3/P_1 , and P_3/P_2 drop faster in porcine muscle than in liver.

nonlinearity and absorption process, the effect of nonlinearity is more obvious than absorption as $\Gamma > 1$, but the effect of absorption is more obvious than nonlinearity as $\Gamma < 1$. As the temperature increases in porcine muscle and liver, the increase of attenuation coefficient which decreases the generation of harmonics and the increase of ultrasonic nonlinearity enhances the number of wave distortion [17–19]. The values of physical constants used for porcine tissue are as follows: $\rho_m = 1060 \text{ kg m}^{-3}$, $c_m = 1550 \text{ m s}^{-1}$, $\alpha_m = 6.1 \text{ Np m}^{-1}$, $\beta_m = 4.55$

for muscle and $\rho_l = 1050 \text{ kg m}^{-3}$, $c_l = 1596 \text{ m s}^{-1}$, $\alpha_l = 4.5 \text{ Np m}^{-1}$, $\beta_l = 6.0$ for liver at 37°C [9, 20–22]. For 1.39 MHz ultrasound, the Gol'dberg number is about 0.26 and 0.43 for porcine muscle and liver at 37°C , respectively. It means that the absorption effect is more obvious in porcine muscle than in liver at 35°C ,

and we can find that the harmonic amplitude is smaller in porcine muscle than in liver at 35°C in Figs. 2 and 3. As a result, combining the effect of nonlinearity and absorption with temperature, the harmonic amplitude decreases while temperature increases.

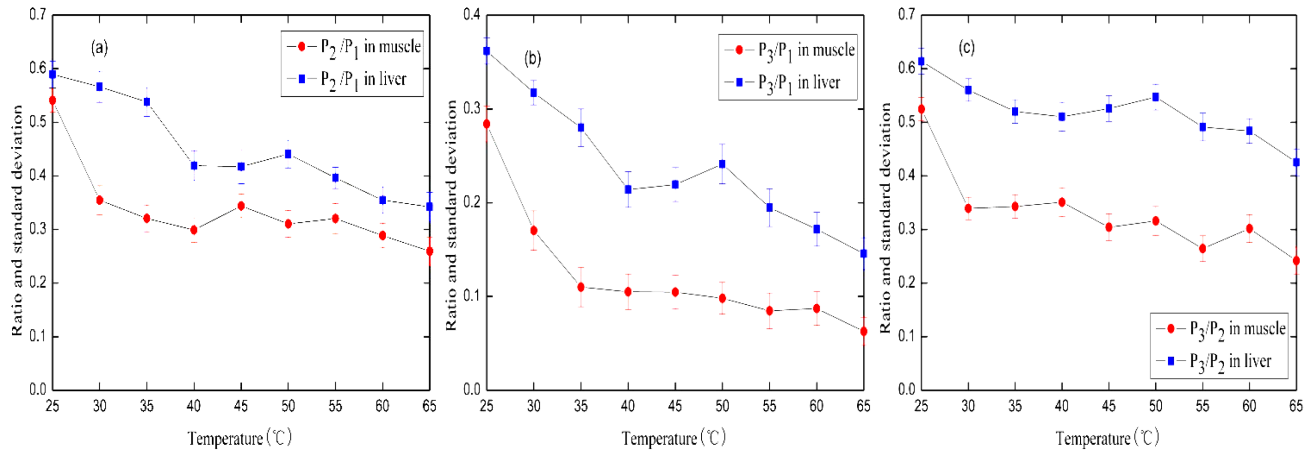


Fig. 5. Ratio and standard deviation of various harmonic amplitude at different temperature in porcine muscle and liver. (a) P_2/P_1 , (b) P_3/P_1 , (c) P_3/P_2 .

4. Discussion and conclusions

In this paper, the relationship between scattering harmonics and temperature in the focal region of porcine muscle and liver was studied. Following conclusions can be obtained through our research:

1. The nonlinear harmonics generated in porcine muscle and liver are correlated with the change of temperature, and the temperature has certain effect on harmonic amplitude.
2. As temperature increases in the focal region of porcine muscle and liver, the difference of variation rate of harmonic amplitude decreases in porcine muscle and liver.
3. The slope of P_2/P_1 , P_3/P_1 , and P_3/P_2 have obvious decline at the beginning of temperature measurement, but their slope become flat as temperature increases. The slope of P_2/P_1 , P_3/P_1 , and P_3/P_2 drop faster in porcine muscle than in liver.
4. The amplitude variation of P_1 , P_2 , and P_3 associated with temperature is correlated with the affection of nonlinearity and absorption.

On the basis of this study, further testing on *in vivo* or perfused tissue is required to verify the relationship between harmonic amplitude and temperature. We used the change of harmonic amplitude to measure temperature, which does not need another source and could reduce damage to normal tissue caused by excessive thermal dose. This study shows us a potential approach to monitor the process of HIFU treatment.

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References

- [1] J. Huang, R.G. Holt, R.O. Cleveland, R.A. Roy, *J. Acoust. Soc. Am.* **116**, 2451 (2004).
- [2] V. Rieke, P.K. Butts, *J. Magn. Reson. Imag.* **27**, 376 (2008).
- [3] N.M. Hijnen, E. Heijman, M.O. Köhler, M. Ylihautila, G.J. Ehnholm, A.W. Simonetti, H. Grull, *Int. J. Hyperther.* **28**, 141 (2012).
- [4] P. Rangraz, H. Behnam, P. Sobhebidari, J. Tavakkoli, *Ultrasound Med. Biol.* **40**, 2841 (2014).
- [5] N.P. Brodin, A. Partanen, P. Asp, C.A. Branch, C. Guha, W.A. Tomé, *Med. Phys.* **43**, 1167 (2016).
- [6] D. Melodelima, V. Barrere, *J. Acoust. Soc. Am.* **137**, 2399 (2016).
- [7] C. Yang, H. Zhu, S. Wu, Y. Bai, H. Gao, *J. Ultrasound Med.* **29**, 1787 (2010).
- [8] S.Y. Shalhoub, A.A. Badr, *J. Acoust. Soc. Am.* **20**, 1028 (2006).
- [9] Z. Zhang, T. Chen, D. Zhang, *Chin. Phys. Lett.* **30**, 024302 (2013).
- [10] K.W. Van Dongen, M.D. Verweij, *Int. J. Hyperther.* **27**, 612 (2011).
- [11] W. Shou, X. Huang, S. Duan, R. Xia, Z. Shi, X. Geng, F. Li, *Ultrasonics* **44**, e17 (2006).
- [12] M. He, Z. Zhong, X. Li, X. Gong, Z. Wang, F. Li, *Ultrason. Sonochem.* **36**, 36 (2017).

- [13] J.C. Bamber, *Ultrasonic Properties of Tissues*, IOP Pub., Bristol 1998.
- [14] C.A. Damianou, N.T. Sanghvi, F.J. Fry, R. Maassmoreno, *J. Acoust. Soc. Am.* **102**, 628 (1997).
- [15] W. Keck, R.T. Beyer, *Phys. Fluids* **3**, 346 (1960).
- [16] F.A. Duck, *Ultrasound Med. Biol.* **28**, 1 (2002).
- [17] S. Zhang, M. Wan, H. Zhong, C. Xu, Z. Liao, H. Liu, S. Wang, *Ultrasound Med. Biol.* **35**, 1828 (2009).
- [18] J.C. Min, S.R. Guntur, J.M. Lee, G.P. Dong, I.L.L. Kang, A. Coleman, *Ultrasound Med. Biol.* **37**, 2000 (2011).
- [19] V. Zderic, A. Keshavarzi, M.A. Andrew, S. Vaezy, R.W. Martin, *Ultrasound Med. Biol.* **30**, 61 (2004).
- [20] T. Koch, S. Lakshmanan, S. Brand, M. Wicke, K. Raum, D. Mörlein, *Meat Sci.* **88**, 67 (2011).
- [21] I.M. Hallaj, R.O. Cleveland, K. Hynynen, *J. Acoust. Soc. Am.* **109**, 2245 (2001).
- [22] A. Payne, R. Merrill, E. Minalga, U. Vyas, B.J. De, N. Todd, R. Hadley, E. Dumont, L. Neumayer, D. Christensen, R. Roemer, D. Parker, *Med. Phys.* **39**, 1552 (2012).