



THERAPEUTIC HIGH INTENSITY FOCUSED ULTRASOUND FIELDS (HIFU): ACOUSTIC CHARACTERIZATION AND NONLINEAR MECHANISMS OF HEATING

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Abstract

Nonlinear acoustic waves have been widely employed in various areas of modern science and technology. Medical ultrasound, that includes both therapeutic and diagnostic techniques, is one of the most exciting examples. In therapy, high intensity focused ultrasound (HIFU) waves provides the ability to localize the deposition of acoustic energy noninvasively within the body, which can cause tissue necrosis (for tumor treatment) and stop bleeding (acoustic hemostasis). At HIFU intensity levels of 10000 - 30000 W/cm² the combined effects of nonlinearity and diffraction results in formation of shock waveforms and corresponding distortion of spatial distributions of various acoustic parameters, responsible for different therapeutic mechanisms. Super focusing effect occurs for the peak positive pressure and heat deposition, which makes acoustic measurements and modeling difficult. Formation of shock waves due to nonlinear propagation, violent ultrasound induced cavitation, and corresponding nonlinear enhancement of thermal and mechanical effects of ultrasound on tissue are strongly pronounced at the high intensity levels used in modern therapies. Heating may also result in formation of boiling vapor bubbles that grow much larger than the cavitation bubbles and alter lesion dynamics. In this paper nonlinear HIFU fields and the relevant role of nonlinear phenomena in HIFU induced bioeffects were investigated experimentally and numerically in a gel phantom. The KZK equation was employed for acoustic field characterization under experimental conditions. A fiber optic probe hydrophone, passive cavitation detection system, optical imaging were used to measure HIFU shock waveforms, cavitation thresholds, and boiling. Elevated static pressure was applied to suppress bubbles thus isolating the pure effect of acoustic nonlinearity in enhanced heating. Strongly distorted shock waves of up to 80 MPa peak positive and 15 MPa peak negative pressure were measured and modeled at focus in water and in the gel. It was observed that lesion distortion and migration was due to boiling detected in as little as 40 ms within the center of the lesion in agreement with nonlinear acoustic simulations. These data indicate that acoustic nonlinearity and the boiling play a significant role earlier in HIFU treatments than previously anticipated.

1. INTRODUCTION

Accurate characterization of HIFU fields is important for the prediction of thermal and mechanical bio-effects in tissue, as well as for the development of standards for medical Acoustic probes that withstand high pressure and measure the therapeutic systems. waveforms with high temporal and spatial resolution are thus required to capture shock fronts and highly localized spatial field structure. An experimentally validated numerical model can be an effective tool when direct measurements are not possible. If acoustic field is characterized, then the role of nonlinear mechanisms that significantly influence HIFU therapies can be better understood. The major nonlinear effects are nonlinear propagation and ultrasound-induced cavitation [1, 2]. Enhanced heating of the focal region may also result in boiling in tissue and formation of vapor bubbles that grow much larger than the cavitation bubbles. It is very important to distinguish between the forms of bubble activity in tissue and to reveal the role of nonlinear propagation effects in heating the tissue [3, 4]. Mechanical damage of tissue is typically attributed to ultrasound induced cavitation of micron-size bubbles. Much bigger millimeter size boiling bubbles occur, when the temperature exceeds the boiling level in tissue, significantly alter thermal lesion shape, and are the indicators of high temperature rise in the center of the lesion. Direct simultaneous registration of acoustic waveforms, cavitation, and boiling is not always possible in real tissues under realistic clinical conditions. Measurements in tissue-mimicking phantoms and correlation with modeling results are therefore an effective tool to better understand the contribution of these effects at various stages of lesion formation. In this work the nonlinear HIFU fields were measured and modeled and the effects of nonlinear propagation, cavitation, and boiling on lesion dynamics were investigated experimentally and numerically in a transparent, protein-containing, polyacrylamide gel phantom [5].

2. METHODS

2.1 Experiment

A 2-MHz transducer of 42-mm diameter and 44.5-mm radius of curvature was operated at different acoustic peak power of 30 - 300 W in a tone-burst mode. The measurements were performed in a transparent, degassed, protein containing acrylamide gel phantom [5]. Most of the acoustic properties of this phantom material have properties similar to tissue. The absorption is approximately 1/3 of the absorption in tissue, leading to more pronounced



Figure 1. Experimental arrangements to measure HIFU field in gel phantom and to study HIFU induced lesion formation.

nonlinear effects. Acoustic power was measured using a force balance method. Some experiments were performed in an overpressure chamber (Fig. 1, a) in which lesion development in the gel sample was monitored using a CCD and diagnostic camera а ultrasound system (ATL HDI-1000, Philips, Bothell, WA) [4]. Additional cavitation and acoustic measurements were performed with a high-speed camera (Imacon 200, DRS Imaging Systems, Cupertino, CA) (not shown in the photo) and a passive cavitation detection (PCD) system consisting of a 20 MHz focused transducer (Staveley Sensors Inc., East Hartford, CT), a 15 MHz high-pass filter (Allen Avionics Inc., Mineola, NY), a preamplifier (Panametrics-NDT Inc., Waltham, MA), and a Lecroy LT344 oscilloscope (Chestnut Ridge, NY). Following our earlier experiments in *ex-vivo* liver tissue, [6], elevated static pressure higher than the maximum negative acoustic pressure was applied to suppress bubbles and increase the boiling temperature, thus isolating the effect of acoustic nonlinearity. The overpressure experiments were performed at different peak acoustic powers and duty cycles, but with equal time-average power. Pressure waveforms were measured at high power level a gel phantom with a 100 μ m diameter FOPH 500 fiber optic hydrophone (Univ. of Stuttgart, Germany) (Fig. 1, b) [7, 8]. Experimental data were compared with the modeling results obtained using the KZK acoustic model [9].

2.2 Numerical Modeling

The HIFU field was modeled using the KZK - type nonlinear parabolic equation, generalized for the frequency dependent absorption properties of the propagation medium:

$$\frac{\partial}{\partial \tau} \left(\frac{\partial p}{\partial z} - \frac{\beta}{\rho_0 c_0^3} p \frac{\partial p}{\partial \tau} - L_{abs} \left(p \right) \right) = \frac{c_0}{2} \Delta_\perp p \,. \tag{1}$$

Here *p* is the acoustic pressure, *z* is the propagation coordinate along the axis of the beam, $\tau = t - z/c_0$ is the retarded time, c_0 is the sound speed, ρ_0 is the ambient density of medium, β is the coefficient of nonlinearity, $\Delta_{\perp} = \partial^2 / \partial r^2 + r^{-1} \partial / \partial r$ is the Laplacian with respect to the transverse coordinate *r*, L_{abs} is the linear operator that accounts for absorption and dispersion properties of the medium.

The propagation path for ultrasound was through a two-layer medium, first in water and then in the gel sample. For simulations in water, the thermoviscous absorption was included as

$$L_{abs} = \frac{b}{2c_0^3 \rho_0} \cdot \frac{\partial^2 p}{\partial \tau^2} , \qquad (2)$$

where b is the dissipative parameter of water. For simulations in gel, the operator L_{abs} accounted for the power law of ultrasound absorption measured in the gel [4]:

$$\alpha(f) = \alpha_0 \left(f/f_0 \right)^{\eta} \tag{3}$$

and variation of the sound speed with frequency calculated using the local dispersion relations as

$$\frac{c(f) - c_0}{c_0} = \frac{c_0 \alpha_0}{\pi^2 (\eta - 1) f_0} \begin{cases} \left((f/f_0)^{\eta - 1} - 1 \right), & \eta \neq 1\\ \ln(f/f_0), & \eta = 1 \end{cases}$$
(4)

Here α_0 is the absorption coefficient and $c_0 = c(f_0)$ is chosen as the ambient sound speed at the fundamental frequency f_0 . Equation (1) was solved numerically in the frequency-domain using a previously developed finite difference algorithm [9, 10]. The acoustic pressure waveform was represented as a Fourier series expansion; a set of nonlinear coupled differential equations for the amplitudes of harmonics was derived and integrated numerically using the method of fractional steps with an operator-splitting procedure. Simulations were performed with and without acoustic nonlinearity in order to predict the importance of nonlinear propagation effects for particular experimental conditions. Spatial distributions of the amplitudes and the intensities I_n of the harmonics nf_0 , and the total

intensity of the wave $I(z, r) = \sum_{n=1}^{\infty} I_n(z, r)$ were calculated. Acoustic waveforms were

reconstructed at various distances from the transducer. Heat deposition patterns due to the absorption of ultrasound

$$q_{v}(z,r) = 2\sum_{n=1}^{\infty} \alpha(nf_{0}) I_{n}(z,r)$$
(5)

were obtained for further simulations of the temperature rise in the gel.

The values of the physical constants used for the modeling were: $\rho_0 = 1000 \text{ kg/m}^3$, $c_0 = 1486 \text{ m/s}$, $\beta = 3.5$, $b = 4.33 \cdot 10^{-3} \text{ kg} \cdot \text{s}^{-1} \cdot \text{m}^{-1}$ for water; and $\rho_0 = 1044 \text{ kg/m}^3$, $c_0 = 1544 \text{ m/s}$, $\beta = 4.0$, $\alpha_0 = 1.6 \text{ m}^{-1}$ at 1 MHz, $\eta = 1$, for the gel [5]. No changes in the acoustic parameters of gel due to HIFU heating were considered in the simulations. The linear case was modeled by choosing $\beta = 0$.



Figure 2. Modeling and measurements with the FOPH500 of HIFU waveform (top) and spectrum (bottom) at the focus in the tissue-mimicking gel phantom for 114 W acoustic power.

3. RESULTS

Pressure waveforms were measured at the location of peak focal maximum pressure using a FOPH 500 fiber optic hydrophone casting in the gel phantom and oriented along the transducer focal axis (Fig. 1). Strongly asymmetric nonlinear waveforms of up to +80 MPa and -20 MPa peak pressures were obtained at the focus for the highest acoustic power of 300 W. Figure 2 shows the waveforms and spectra measured and modeled at a power level of 114 W. The calculation results agree very well with the FOPH measurement except the calculated peak positive pressure was higher, with a measured peak positive pressure of 37 MPa and a modeled peak positive pressure of 56 MPa. This discrepancy is attributed mainly to the limited bandwidths limitations of the FOPH [11].

After validation of the acoustic model in gel at very high intensities, spatial distributions of various acoustic parameters in the axial plane were studied numerically. As different parameters of the acoustic field are responsible for various physical mechanisms of the impact on tissue, it is important to consider the differences in spatial localization of these

acoustic quantities [10]. Figure 3 shows the spatial structure of the peak positive P+ and peak negative P- pressure, full intensity I and heat deposition H in the linear ($\beta = 0$, left) and nonlinear beam for 114 W acoustic power of the transducer. The patterns in Fig.3 are

presented in linear scale with eight equal levels changing from zero to the maximum value of the corresponding quantity. For the linear beam the distributions of pressure amplitude $P \pm$ and intensity *I* are presented only, because in this case the distributions of peak positive and negative pressure coincide, and the distributions of wave intensity and heat deposition are proportional to each other, i.e. also have identical spatial structure. As shown in the Figure 3, the focal area of peak positive pressure P+ and heat deposition in nonlinear field are significantly more localized in space as compared with the linear field. On the contrary, the



Figure 3. Spatial localization of peak positive P+ and negative P- pressure, full intensity, and heat deposition for linear ($\beta = 0$) and nonlinear (114 W acoustic power) HIFU beam in polyacrylamide gel. HIFU was applied from the bottom.

focal area of the peak negative pressure P- is noticeably displaced towards the source and is much less localized in space, especially in the direction across the beam. The negative phase of the waveform basically determines cavitation effect of high intensity focused ultrasound on biological tissue, while the thermal effect is mainly due to absorption of the energy wave on the The shock shocks. amplitude corresponds to the peak positive pressure. It is possible to expect, therefore, that in the powerful focused fields cavitational phenomena will be pronounces in essentially wider area in comparison with the thermal effects, and rapid localized overheating of up boiling tissue to temperatures is possible.

In order to avoid cavitation effect in the waveform measurements (Fig. 2), the HIFU source was operated in a tone-burst mode, typically with a 30-cycle burst and 5-Hz PRF. For longer exposures applied to create lesions in gel, cavitation was expected to occur. To ensure the presence of cavitation bubbles in the gel during HIFU therapeutic sessions, the cavitation threshold was measured in the gel. A 200 cycle burst was sent from the HIFU source at increasing power levels, and the resulting PCD traces were recorded. The onset of cavitation was evidenced by a dramatic change in signal level. Using this system, it was found that the cavitation threshold of the degassed, 7% BSA-polyacrylamide gel varied over a peak negative pressure of 2 - 6 MPa. In further experiments the lesions in gel were produced always above the cavitation threshold with peak negative pressure > 6 MPa at the focus.

Nonlinear effects in enhancement of lesion production were investigated by applying of lower and higher peak power of HIFU with corresponding duty cycle to maintain equal average acoustic power (Fig. 4). The lesions were induced in the gel with and without elevated static pressure so that cavitation and boiling were controlled by overpressure. Nonlinear acoustic propagation was controlled by increasing the peak pressure but decreasing the duration of the HIFU pulses. The modeled waveforms showed peak negative pressure of 70 bars (for 100% duty cycle (dc)) and 90 bars (for 50% dc), which was in both cases less than the static overpressure of 100 bars. Fully developed strong shocks were present in the waveform for higher peak pressure, and a distorted waveform but not yet containing shocks for lower peak pressure. Much larger lesions were obtained with higher peak pressures (Fig. 4, right column), so nonlinear effects were of evident importance. Lesion inception was delayed with overpressure; thus, cavitation of microbubbles contributed to the local increase of effective absorption coefficient in gel and thus to initial heating. However, the most dramatic acceleration of lesion inception time and growth was observed by comparing left to right in Fig. 4 where acoustic nonlinearity is enhanced. Without overpressure, boiling started almost immediate for higher peak acoustic pressure and the lesion grew asymmetrically toward the transducer. Boiling was detected much later with overpressure due to increase of boiling temperature, and, because bubble growth was suppressed, a symmetric lesion formed. It is concluded, therefore, that nonlinear heating due to absorption on the shocks results in rapid initiation of boiling in tissue phantom although microbubble cavitation may be also present.



Figure 4. Final lesions formed in gel under normal and elevated static pressure for higher (on the right) and lower (on the left) peak pressure of HIFU, 30 s exposure, equal time-average intensity of ultrasound source.

Further experiments were performed under normal static pressure conditions to determine how fast boiling can start due to absorption on the shocks. Strongly distorted shock waves were measured and simulated in the gel for 92 W acoustic power (Fig. 5, a,b). Experimental and modeled waveforms agree very well and show a strong fully developed shock of approximately $A_s = 35$ MPa amplitude. For comparison, simulations were also performed without account for the effects of nonlinear propagation (dashed curve in Fig. 5,b). The initial peak heating rate q_v was calculated for the linear ($q_v = \alpha p^2/c_0 \rho_0 = 500$ W/cm³) and the nonlinear waveform ($q_v = \varepsilon f A_s^3 / 6c_0^4 \rho_0^2 = 10000$ W/cm³) at the focus. The nonlinear prediction yields a 75°C temperature rise to above the boiling temperature in less than 40 ms whereas the linear prediction yields only 20°C rise. The extremely rapid boiling is the result of dramatic enhancement of heating due to absorption at the shocks. Boiling in gel in less than 40 ms was experimentally detected using PCD (Fig. 5, c and d) and high-speed camera [11]. The amplitude and spectral content of scattering was used to distinguish boiling from cavitation in the PCD signature. The initial signal level in Fig 5c is caviation signal and it is above baseline that occurs before HIFU is on, but the boiling signal is obvious at 40 ms.

These experiments indicate that short duration, high-amplitude HIFU pulses used to produce echogenicity for targeting therapy result from boiling not cavitation.



Figure 4. Acoustic pressure waveforms measured (a) and modeled (b) at the focus for 92 W acoustic power. Effective absorption at the shocks results in enhanced heat deposition and boiling start in 40 ms as detected by PCD (c and d).

6. CONCLUSIONS

The effect of nonlinear propagation and shock formation on the heating rates and initiation of boiling by HIFU was studied experimentally and theoretically in transparent protein containing tissue-mimicking gel phantom. HIFU transducer of 2 MHz frequency, 4 cm aperture, and 4.5 cm focal length operating at acoustic power level of 30 - 300 W was used in experiments.

Careful determination of the acoustic field in the phantom was attempted up to very high pressure levels. Nonlinear shock waveforms of -20 MPa peak negative and 80 MPa peak positive pressure were measured and modeled with a fiber optic hydrophone, and the results agreed very well, despite the bandwidth limitations of the hydrophone. For HIFU regimes with shocks it is critically important to accurately determine the high frequency components as they are the most readily absorbed and converted to heat in HIFU therapy. It was shown that in nonlinear beam the focal area of the peak positive pressure is much more localized and the focal area of peak negative pressure is much less localized in space as compared with the linear field. As the negative acoustic pressure basically determines cavitation effects in biological tissue while the thermal effect is mainly due to absorption of the wave energy on the shocks, it should be expected, that in HIFU fields cavitational phenomena would be pronounced in essentially wider area closer to transducer than the thermal localized overheating effects and boiling.

The relative roles of acoustic nonlinearity and cavitation in enhanced heating by HIFU, corresponding temperature rise up to boiling, and qualitative changes in lesion growth from symmetric cigar to tadpole shape was evaluated experimentally and numerically in gel. The experiments were performed for ultrasound peak negative pressures above the cavitation

threshold. The experimental results indicated that both nonlinear propagation and cavitation mechanisms accelerate lesion production with acoustic nonlinearity responsible for the greater effect.

It was observed that asymmetric lesion distortion and migration toward the transducer was due to boiling that was visible in the gel and distinguished from cavitation as a big change in PCD signals. No lesion distortion was observed in the absence of boiling. The presence of shocks in acoustic waveform resulted in rapid localized heating and initiation of boiling at the focus detected in gel in as little as 40 ms within the center of the lesion. This observation was in agreement with nonlinear acoustic simulations and clinical observations in recent *in vivo* experiments [13]. Evidence indicated that the dramatic increase of heat deposition leading to boiling in less than 40 ms was due to absorption at the shocks in the nonlinear acoustic wave. This effect can be utilized for targeting the treatment with B-mode imaging and should be taken into account when planning the treatment, as the appearance of boiling bubbles results in effective scattering of ultrasound and therefore in lesion displacement and distortion. These data indicate that acoustic nonlinearity and the boiling play a significant role earlier in HIFU treatments than previously anticipated.

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