HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU) ABLATION USING THE FREQUENCY CHIRP EXCITATION: REDUCTION OF GRATING LOBE AND ENHANCEMENT OF LESION FORMATION AT THE FOCUS

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ABSTRACT

Phased array transducer has gained the more popularity in high-intensity focused ultrasound (HIFU) cancer/tumor ablation. However, the pre-focal heating due to the presence of grating lobe and the decreased intensity of shifted main lobe limit the steering abilities and safety of clinical HIFU applications. In order to solve this problem, a novel excitation strategy using the frequency chirp was proposed and evaluated both numerically and experimentally. First, a nonlinear acoustic propagation model using the established angular spectrum approach was used to simulate the propagation of HIFU burst through multi-layer media at different axial focus shifting distance and subsequently, the temperature elevation and lesion formation. The performances of downward and upward frequency sweeping in different frequency range and sweeping time were compared with that of conventional excitation at the constant frequency. It is found that downward frequency chirp excitation in a long time and large frequency range is preferable, and up to 40% reduction of pre-focal temperature elevations and 50% lesion enlargement at the focus were found in the gel phantom. Finally, the reduced temperature elevation in the pre-focal region, enhanced lesion production and bubble cavitation at the focus were further confirmed in the ex vivo porcine tissue samples. Altogether, the frequency chirp excitations are easy and effective approach to reducing the grating lobe and enhancing the ablation capability of HIFU at the focus, which may enhance the both efficacy and safety of clinical HIFU applications.

KEYWORDS: High-intensity focused ultrasound (HIFU), frequency chirp excitation, grating lobe, bubble cavitation, temperature elevation, lesion production

1. INTRODUCTION

High intensity focused ultrasound (HIFU) ablation on the soft-tissue sarcomas has been emerging as a novel therapeutic modality since this century.[1] Clinical treatment of a variety of targets has already achieved promising results. With this technique, sufficiently high ultrasound energy is brought into a tight focal region for fast temperature elevation over 60-65°C even within seconds, generating the well-controlled necrosis while leaving the other tissues unharmed. Because of the noninvasiveness, few complications, less in-hospital time, theoretically unlimited tissue tolerance for the recession and improved quality of life for the advanced cancer patients with metastasis, HIFU shows advantages over the open surgery and radio- or chemo-therapy.

Because the tumor size is much larger than the size of the HIFU-induced lesion, these small lesions need to be placed side by side with certain overlapping to cover the whole volume. The scanning of HIFU focus throughout the target can be achieved by either mechanical movement of the transducer or electronic beam steering using multi-element phased array. Mechanically translation is simple in the design and control, but slow. In contrast, phased array is able to yield a faster focus shifting and generate multiple foci, but with the high cost and complexity in the manufacture and control. In addition, the pre-focal heating was found after HIFU ablation due to the presence of the grating lobe. The grating lobe is dependent on the transducer design, driving ablation, and steering range.
To address this problem, several strategies have been implemented. The common way was to either optimize the scanning path or include a long enough delay between successive sonication so that the effect of beam overlapping could be minimized. A 30 s to 60 s delay between two successive sonication is essentially needed to reduce the pre-focal heating.[2] Use of aperiodic arrays with random and/or sparse arrays with unequal element sizes can also effectively suppress the grating lobe level.[3, 4] But the optimal design is time-consuming. Another type of methods for reducing grating lobes is to modulate the driving signals. Excitation using two waveforms with the equal amplitude but appropriate phase between them could increase the cavitation threshold pressure in the near-field by 20%.[5] Broadband signals (>10% fractional bandwidth) were applied to an annular array transducer.[6] The ratio of acoustic intensity between the on-axis grating lobe and the main lobe is inversely proportional to the bandwidth of the transmitted signal and to the number of array rings. However, significant distortion of the acoustic waveform was not accounted for.

Besides the thermal effect, bubble cavitation induced by the HIFU pulses also has a significant effect on the tissue heating.[7] With the presence of bubbles, a great enhancement of converting the acoustic energy of HIFU burst to heat energy could be accomplished for the increased heating rate. The stable cavitation causes the high shear stress between the bubble and surrounding medium, and the inertial bubble collapse produces the broadband noise emission. Thus, it is desired to utilize bubbles and cavitation to enhance the efficiency of HIFU ablation. However, the realization of bubble-assisted HIFU is challenging due to the lack of bubble nucleation in the tissue. The peak rarefaction pressures required to initiate cavitation in vivo are high (7-10 MPa), making it difficult to localize, sustain, and confine cavitation activity. Ultrasound contrast agents (microbubbles) can provide cavitation nuclei, decrease the cavitation threshold, and repeatedly initiate cavitation at the same location.[8, 9] A strong correlation is found between enhanced heating and the inertial cavitation. Up to 12 fold larger necrosis could be achieved.[8] Another strategy is applying two or more frequencies during HIFU ablation. A high frequency (5 MHz) excitation was applied to a tissue-mimicking phantom to induce a rapid temperature rise followed by a low frequency (1 MHz) one to the same focal region to induce acoustic cavitation.[10] The cavitation enhancement was greater for high-frequency HIFU, which may be due to the temporary super-saturation of air in the initially air-saturated samples and the reduction of surface tension at an elevated temperature. Enhancement and quenching of HIFU cavitation activity were with short frequency sweeping range in negative and positive directions, respectively.[11] The frequency sweeping direction and rate govern the growth and coalescence of bubbles in the acoustic field.

2. MATERIALS AND METHODS

To simulate the HIFU ablation for the deep-seated tumor (e.g., liver), a 256-element phased array transducer (H-169, focal length of 200 mm, active diameter of 200 mm, a central opening of 64 mm, central frequency of 1 MHz, Sonic Concepts) was used. Circular elements with the diameter of 1 cm are regularly allocated on the concave surface. A multiple layer model modified from the human abdomen was used in the simulation (see Fig. 1), and the physical properties of all media are listed in Table 1. To include a pronounced nonlinear effect in the acoustic wave propagation, the acoustic pressure at the transducer surface was set as 300 kPa (3 W/cm²). The driving frequency of sinusoidal wave either linearly increases or decrease with the time. In this study, the frequency sweeping range was set as 0.2 MHz (from 0.9 MHz to 1.1 MHz) in a step size of 0.02 MHz, and the sweeping time was varied from 0.1 s to 2 s. The nonlinear wave propagation over incremental distance was simulated using the proposed angular spectrum approach (ASA) algorithm by first solving a half-step with the diffraction operator, then a full step with non-linearity and attenuation operator, and finally another half-step with the diffraction operator (Wang and Zhou 2016). The phases applied to the elements for the desired focus shifting were calculated by the Huygen’s principle. The Bio-Heat transfer equation (BHTE) was used to simulate the temperature elevation and lesion formation by HIFU (Pennes 1948). The BHTE was solved using the finite-difference time-domain (FDTD) method in a temporal step size of 0.01 s. The thermal dose, an equivalent exposure time at 43°C (CEM43), was used to characterize the ablation outcome (Sapareto and Dewey 1984). All the simulations ran in MATLAB (R2010b, Mathworks) on a PC (3.3 GHz Intel VR CoreTM i5-2500 CPU, 4 GB RAM) with Windows 7 32-bit operating system.

The optically transparent polyacrylamide gel with 7% of bovine serum albumin (BSA) which becomes denatured at the temperatures over 60-65°C and opaque was prepared to evaluate the HIFU-induced lesion. Briefly, the liquid
mixture of polyacrylamide, BAS, and the Tris-Buffer was degassed for about 1 h in a descant chamber (420100000, Scienceware) by a vacuum pump (VTE8, Thomas) at a pressure of 150 mbars, then the degassed mixture was poured into a custom mold (L×W×H = 6 cm×2.5 cm× 2.5 cm). The polymerization was then finalized by the addition of a 10% (w/v) ammonium persulfate solution (APS, Sigma-Aldrich) and N,N,N',N'-tetramethylethylene/diamine (TEMED, Sigma-Aldrich) in 5 min. Porcine muscles and kidneys were purchased from a commercial food market and then cut into the similar size as the mold. The surfaces were carefully peeled to provide a smooth water–tissue interface. All tissue samples were first immersed in the phosphate-buffered saline (PBS) and degassed for approximately 1 h before the experiments.

An annular HIFU transducer (H-102, Sonic Concepts) was used in the experiment. The sinusoidal signals produced by a function generator were amplified by a power amplifier before delivering to the matching unit and the HIFU transducer. Both the HIFU transducer and the phantom or tissue sample were immersed in the degassed and deionized water of a Lucite tank. A 0.5 mm diameter thermocouple (TJ36-ICSS-020G-6, Omega Engineering) was inserted into the sample to measure the temperature rise by a data acquisition (DAQ) unit (NI-9214, National Instruments). A LabView program (National Instruments) was written to control the HIFU pulse delivery, translational motion, and temperature data measurement. The lesion produced in the BSA polyacrylamide gel phantom was photographically recoded by a digital camera (PowerShot SX230 HS, Canon). Its area was determined quantitatively in image processing software (Photoshop, Adobe System). After 30-s HIFU exposure (PRF of 1 Hz, duty cycle of 90%, voltage of 0.3 V), the porcine samples were cut by a pathological slice in a thickness of about 1-2 mm, the maximum lesion found was recorded.

3. RESULTS

The distribution of maximum temperatures during a single HIFU burst exposure is shown in Fig. 1. It is found that frequency sweeping could significantly reduce the temperature rise induced by the grating lobe (~25%) and the temperature variation in the pre-focal region, but keep almost the same temperature rises at the main lobe (e.g., reduced by only about 1% using the frequency sweeping downward in 0.1 s). Frequency sweeping upward in 2 s and downward in 2 s, respectively, gives the highest and lowest temperature rise. With the increase of axial focus shifting distance, the maximum temperature at the main lobe and grating lobe gradually decreases and increases, respectively, because of the changes in the acoustic intensity.

![Fig. 1](image)

Fig. 1 The distribution of (a) maximum temperature at the grating lobe and (b) main lobe with the axial focus shifting distance of 2.5 cm during the HIFU exposure using the different frequency excitations.

The temperature rises in the BSA polyacrylamide gel phantom positioned at the pre-focal region during the 15-s HIFU exposure were measured by the thermocouple as shown in Fig. 2. Both the downward and upward frequency sweeping achieved lower temperature rises than that using the constant frequency excitation at the varied distances of 0.5 cm to 2.0 cm from the aperture of HIFU transducer. The corresponding reduction is from about 31% to 56%.
The lesions produced in the BSA polyacrylamide gel phantom by different excitation strategies are shown in Fig. 3. It’s clear that using both the downward and upward frequency chirp excitations could produce larger lesions than those using the constant frequency with the tadpole tails migrated towards the transducer by ~3 mm. As the frequency sweeping range decreased from 0.4 MHz to 0.2 MHz, the lesion area enlargement in the side view with the downward frequency sweeping gradually dropped in a similar way, from 50.0% to 35.1%. In comparison, the lesion enhancement using the upward frequency sweeping is slightly lower. The corresponding reduction is from 44.6% to 23.7%. However, with the increase of the sweeping time from 1 ms to 100 ms, the lesion size enlargement only drops slightly from 50.4% to 37.8% in the downward sweeping and from 44.6% to 37.4% in the upward sweeping, respectively. Overall, large frequency sweeping range in a short time is preferred for the lesion enlargement, and the frequency sweeping range has a great impact.

The lesions produced in the porcine kidney samples after 1 min-HIFU ablation are shown in Fig. 4, the frequency sweeping range and time was 0.4 MHz and 2 s, respectively. The lesion areas in the axial direction produced by the
downward and upward frequency chirp excitations were significantly larger than that by the constant frequency excitation (9.4±1.5 mm² and 9.0±1.0 mm² vs. 7.2±1.4 mm², p < 0.05). The porcine kidney samples were used in the ex vivo lesion comparison because of higher image contrast of tissue for easy boundary detection.

3. CONCLUSIONS

Pre-focal heating of HIFU focus shifting from a phased array design could be considerably reduced using the frequency chirp excitations but without compromising the thermal energy accumulation at the main lobe. Long time and downward chirp shows the best performance among all examined excitation strategies (upward frequency sweeping and single-frequency excitation). Gel phantom experiment further confirmed that the temperature rises in the pre-focal region by the frequency chirp excitations measured by a fine needle thermocouple were decreased by ~40%. With a proper selection of the frequency sweeping range and sweeping time, a 50% enlargement of lesion size at the focus could be achieved. In summary, a short sweeping time and large frequency sweeping range is preferred for the enhancement in bubble cavitation and HIFU-induced lesion at the focus.

REFERENCE