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Sonoluminescence characterization of inertial cavitation inside a BSA phantom treated by pulsed HIFU

Hui Yin, Nan Chang, Shanshan Xu, Mingxi Wan *

The Key Laboratory of Biomedical Information Engineering of Ministry of Education, Department of Biomedical Engineering, School of Life Science and Technology, Xi'an Jiaotong University, PR China

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ABSTRACT

The aim of this study was to investigate the inertial cavitation inside a phantom treated by pulsed HIFU (pHIFU). Basic bovine serum albumin (BSA) phantoms without any inherent ultrasound contrast agents (UCAs) or phase-shift nano-emulsions (PSNEs) were used. During the treatment, sonoluminescence (SL) recordings were performed to characterize the spatial distribution of inertial cavitation adjacent to the focal region. High-speed photographs and thermal coagulations, comparing with the SL results, were also recorded and presented. A series of pulse parameters (pulse duration (PD) was between 1 and 23 cycles and pulse repetition frequency (PRF) was between 0.5 kHz and 100 kHz) were performed to make a systematic investigation under certain acoustic power (APW). Continuous HIFU (cHIFU) investigation was also performed to serve as control group. It was found that, when APW was 19.5 W, pHIFU with short PD was much easier to form SL adjacent to the focal region inside the phantom, while it was difficult for cHIFU to generate cavitation bubbles. With appropriate PD and PRF, the residual bubbles of the previous pulses could be stimulated by the incident pulses to oscillate in a higher level and even violently collapse, resulting to enhanced physical thermogenesis. The experimental results showed that the most violent inertial cavitation occurs when PD was set to 6 cycles (5 μs) and PRF to 10 kHz, while the highest level of thermal coagulation was observed when PD was set to 10 cycles. The cavitational and thermal characteristics were in good correspondence, exhibiting significant potentiality regarding to inject-free cavitation bubble enhanced thermal ablation under lower APW, compared to the conventional thermotherapy.

1. Introduction

As a non-invasive therapy, HIFU has developed several therapy techniques among which pulsed HIFU (pHIFU) induced histotripsy has made significant progress over the last decade [1,2]. Depending on pulse duration (PD) and acoustic pressure, numerous applications were put forward, such as microtripsy [3] or boiling histotripsy [4]. The mechanism of pHIFU with extremely short PD has been well examined by Xu et al. [5], where images of bubble clouds were acquired, generated by pHIFU with an ICCD camera. The PD of pHIFU source was ranging from 4 μs to 14 μs (3–10 cycles), the pulse repetition frequency (PRF) was relatively low, at 10 Hz, and the compressional intensity was higher than 10 kW/cm^2. Furthermore, Lin et al. [3] has recently reduced the PD to a single negative half cycle and the PRF to 1 Hz. These extreme parameter values managed to limit the unwanted thermal effect and ensure that the tissue disintegration was mechanical dependent. As the PD increases to the millisecond order of magnitude, which is a little longer than 'time-to-boil', the process of reaching boiling temperature, due to shock fronts of 40–80 MPa, is termed as the 'millisecond boiling' [6]. According to Canney et al. [4], the superheated process only takes place during time-to-boil, when high amplitude shocks develop in a small volume within the focal region of a HIFU beam and this superheated process lasts a few milliseconds. Following that, it is the interaction between shock waves and vapor cavity that generate atomization and an acoustic fountain from the tissue interface into the cavity. Based on the 'millisecond boiling' mechanism, another tissue fractionation treatment was developed. This treatment strategy was termed as 'boiling histotripsy', which still requires low duty cycle in order to reduce thermal accumulation, so that tissue is emulsified and mechanically removed.

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* Corresponding author at: The Key Laboratory of Biomedical Information Engineering of Ministry of Education, Department of Biomedical Engineering, School of Life Science and Technology, Xi'an Jiaotong University, Xi'an 710049, PR China.

E-mail address: mxwan@xjtu.edu.cn (M. Wan).

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However, both mechanical and thermal HIFU ablation techniques are now in development for noninvasive treatment of cancer [7]. Cavitation and heating are more synergistic than incompatible in some therapy strategies. Previous studies [8–10] have shown that injected ultrasound contrast agents (UCAs) or phase-shift nano-emulsions (PSNEs) could significantly enhance the heating effect and improve the speed of tumor coagulation. Based on these strategies, it is suggested that, if PD and PRF are appropriately adjusted, both cavitational and thermal characteristics will synergistically appear. So, it is essential to perform an overall examination on the pulse parameters in order to provide an advisable range of values. Also, cavitation may be considered as the stimulative of thermal coagulation, especially when the acoustic power (APW) is relatively low. Therefore, cavitation characterization is quite important.

In order to characterize cavitation, ultra-high speed photography (HSP) is commonly considered as one of the paramount methods, whose temporal resolution can reach down to the nanosecond scale of magnitude [11–15]. Also, passive cavitation imaging (PCI) has been developed by Salgaonkar et al. [16], in order to monitor cavitation bubbles with ultrasound arrays. Also, Gyöngy et al. [17] have monitored the spatial distribution of cavitation during HIFU treatment inside agar gel. However, active bubbles were not specifically presented, therefore, sonoluminescence (SL) and sonochemiluninescence (SCL) recordings were put forward [18]. Previous research work has employed SL/SCL recordings to map the cavitation during continuous HIFU (cHIFU) treatment in free field [19], an artificially constructed standing-wave field [20], a large phantom vessel [21] and a bioreactor [22]. The propagation media employed were all liquids. However, because of the different viscoelasticity, cavitation activities inside a tissue mimicking ultrasound phantom are quite different from those in liquids. Furthermore, the SL characteristics induced by pHIFU, especially inside a phantom without any inherent bubbles, have been rarely reported up to date. In this work, a series of pulse parameters (PD was between 1 and 23 cycles, PRF was between 0.5 kHz and 100 kHz) were systematically examined. SL recordings were employed to specifically characterize inertial cavitation inside a bovine serum albumin (BSA) phantom during pHIFU treatment. High speed photographs were also recorded to show bubble activity and the development of thermal coagulations.

2. Materials and methods

2.1. System configuration

The schematic illustration of the experimental arrangement is presented in Fig. 1(a). Water, circularly processed by a degasser pump, was filled in a water tank (~50 cm × 28 cm × 28 cm) as the ultrasonic propagation medium. The HIFU transducer was a single element, spherically focused piezoceramic crystal (Imasonic, Besancon, France), whose active diameter and geometrical focal length were 156 mm and 120 mm, respectively. It has a working frequency of 1.2 MHz, and is mounted on the side of the tank. The HIFU transducer was driven by a double channel arbitrary wave generator (AWG420, Tektronix) amplified by a linear radiofrequency amplifier (AG1017, T&G Power Conversion, Inc., Rochester, NY). The diagram of the adjustable pulse parameters is presented in Fig. 1(b). The APW and average spatial intensities, at the focal region, were calculated and presented elsewhere [19]. The phantom held by a skeleton, termed as a phantom-skeleton complex, was positioned by a 3D controller and is presented in Fig. 1(c). It had four uncovered sides, positioned vertically for ultrasound exposure, which effectively reduced the unwanted obstruction and reflection. As the vertical width of the HIFU beam at the focus was 1.2 mm, the complex was positioned either upwards or downwards by 4 mm, in order to avoid overlapping of each HIFU exposure.

The SL adjacent to the focal region were captured through a quartz window by an EMCCD camera (iXon3 897, Andor Technology PLC, Northern Ireland, UK), triggered by channel II of the wave generator. Its image resolution was 512 × 512 pixels. A Nikon lens (50 mm, *f*/1.4D) was connected with the EMCCD camera. A light-proof box was employed to cover the whole system in order to increase the contrast of SL images. Additionally, bubble activities were also captured by a high-speed framing camera (MotionPro Y3-S1, IDT, Inc., USA). In order to capture the details of the bubbles, a Nikon macro-lens (105 mm, *f*/2.8D) was employed. During the HSP experiments, an accent light was placed on the opposite side of the high-speed camera, across the phantom. As a result, the high-speed photographs had bright contrasted background, while bubbles and thermal lesions were dark contrasted. An acoustic absorber (the tested acoustic absorptive was 0.538) was attached on the opposite side of the HIFU transducer to reduce the reflected signals.

A preliminary experiment was performed to discover the range of pulse parameters, under which SL could be observed, meaning that the inertial cavitation should be violent enough to be able to be captured. Based on this premise, it was attempted to lower the acoustic power (APW) in order to reduce the energy-loss in the pre-focal region. Also, regarding security and efficiency, low APW will be required for possible future applications, thus, the APW was fixed at a constant value of 19.5 W. With this APW, a fiber-optic probe hydrophone (FOPH) was used to measure the acoustic output pressure at the focus point of HIFU in the free field. The measured positive and negative pressure values were 6.5 MPa and 4 MPa, respectively. The exposure time of EMCCD was set to 10 s, during which the generated photons within the whole visual field were captured and presented in SL images.

2.2. Materials

The treated phantom is optically transparent and is composed of polyacrylamide hydrogel and BSA. The ingredients used and proportions required are listed in Table 1. Ammonium persulphate (APS, Sigma) solution and N-N-N′-N′-tetramethylethylene/diamine (TEMED, Sigma) are the catalysts for condensation polymerization of acrylamide. Before they were instilled, the mixture solution was degassed in a vacuum chamber for 30 min and was then poured into the mold with caution. Following the instilling of APS and TEMED, the solution was solidified within 5–10 min, at 4 centigrade. Finally, the phantom-skeleton complex were cautiously pulled out of the housing and kept submerged in degassed water, at room temperature. The phantom was an elastic hydrous gel, containing 95% (v/v) water, rather than a firm solid. The density of this phantom was 1.005 ± 0.001 g/cm^3. The ultrasound propagation speed and attenuation coefficient were 1516.3 ± 3.0 (m/s) and 0.2 ± 0.01 (dB/cm), respectively, at 1 MHz [23]. The viscoelastic properties of this type of phantom have been studied by Kumar et al. [24]. According to that study, the storage modulus of this phantom was in the range of 2–8 kp and the loss modulus in the range of 0.4–0.9 kp. The polyacrylamide and BSA were long fibers that provided a structure to the gel, but within interstices between polymer molecules, there existed dissociative liquids. These liquids acted as the required environment for cavitation nucleation, which was similar to interstitial fluids in soft tissues.

3. Results and discussion

As described above, the SL images were cumulative results of time, covering the whole treatment time of 10 s, providing spatial