Bubble Dynamics with the Progress of Histotripsy

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SUMMARY
Bubble cavitation plays an important role in the HIFU ablation as well as histotripsy. The characteristics of bubble cavitation were measured and found vary with the progress of histotripsy treatment. Ultrasound parameters (i.e., frequency and pulse duration) have a great effect on the bubble cavitation and the consequent lesion formation.

INTRODUCTION
High-intensity focused ultrasound (HIFU) is an emerging therapeutic modality for cancers and solid tumors, such as pancreatic, liver, kidney, prostate, breast and bone cancers and uterine fibroids [1]. In Asia and Europe, more than 100,000 patients were involved in the HIFU clinical treatment with promising results. Application, investigation and development of such a technology by physician, patients, researchers, and medical device manufacturers are becoming more and more attractive since its first clinical trial in 1990s. The mechanism of HIFU is the temperature elevation over 65 °C due to the absorption of acoustic energy, to denature the protein for necrosis production because of the absorption of acoustic energy by the tissue. However, the bubble cavitation is also of importance in the HIFU field. Bubbles may form from boiling of fluid in blood or tissue or by the growth of tiny cavitation nuclei within the body due to the negative pressure of the acoustic wave. Bubbles are strong scatterers of acoustic wave and, thus, significantly influence HIFU therapy. Bubbles scatter acoustic waves shielding tissue behind a bubble cluster from HIFU energy, causing more energy to be absorbed in the prefocal region before a bubble cluster than that occurring without bubbles, resulting in lesion distortion from a symmetric cigar shape to an asymmetric tadpole shape [2].

Recent investigation illustrated that interaction of acoustic cavitation bubbles and HIFU burst (20 µs duration 1 kHz pulse repetition rate, 18 MPa rarefractional pressure) would lead to mechanical fractionation of tissue structure, called histotripsy [3-4]. The transducer used has similar geometry and acoustic specification as the HIFU type. At a fluid-tissue interface, histotripsy results in localized tissue removal with sharp boundaries, which has vast clinical applications where tissue ablation and removal (i.e., perforation of the atrial septum in the treatment of congenital heart disease) are needed. In bulk tissue, histotripsy produces mechanical fragmentation of tissue resulting in a liquefied core with very sharply demarcated boundaries. Histology demonstrates treated tissue within the lesion is fragmented to a subcellular level surrounded by an almost imperceptibly narrow margin of cellular injury. Compared to non-invasive thermal therapy, histotripsy has some important advantages: (1) microbubbles produced at the US focus, shown as bright spots on US imaging; (2) energetic microbubble activities can be seen on imaging and provide real-time feedback; (3) the lesions appear darker on US imaging post-treatment; and (4) the lesions can be produced in a very controlled and precise manner.

Furthermore, nonlinear propagation and production of shocked focal waveforms in tissue by HIFU bursts induced boiling in milliseconds. Initiation of boiling could also cause tissue erosion, but in a larger size (a few mm) [5-6]. Both inertial cavitation and boiling were observed during HIFU exposures, but emulsification occurred only when shocks and boiling were present. Emulsified lesions without thermal denaturation were produced with shock amplitudes sufficient to induce boiling in less than 20 ms, duty factors of less than 0.02, and pulse lengths shorter than 30 ms. Higher duty factors or longer pulses produced varying degrees of thermal denaturation combined with mechanical emulsification. Meanwhile, this effective and reliable way to emulsify tissue could be monitored using B-mode ultrasound images.

Altogether, bubble cavitation plays an important role in the HIFU ablation of soft tissue, either thermally or mechanically in histotripsy. Although bubble cavitation or liquid boiling could be detected as fluctuation in the HIFU drive voltage and changes in the passive cavitation detection (PCD) signals, little study was carried out on the bubble dynamics with the progress of the histotripsy. In this study, the bubble cavitation was measured throughout the HIFU exposure using the methods of PCD, light transmission, and active cavitation detection (ACD, ultrasound B-mode imaging) in the gel phantom and ex vivo porcine kidney. Lesions formed in the gel phantom were captured by camera, simultaneously. It is found that the characteristics of bubble cavitation vary with the progress of histotripsy and depend on the ultrasound operation parameters (i.e., frequency and pulse duration). It is suggested that monitoring bubble cavitation activities would provide a
feedback in control the effectiveness and maybe safety of HIFU therapy.

**EXPERIMENTAL SET UP**

The experiments were conducted at the Ultrasound Science and Application Research Laboratory at Nanyang Technological University in Singapore. An annular focused HIFU transducer (H-102, Outer Diameter = 69.94 mm, Inner Diameter = 22.0 mm, F = 62.64 mm, Sonic Concepts, Woodinville, WA) was used in this study (Fig. 1). The HIFU transducer, immersed in the degassed and deionized water ($O_2 < 4 \text{ mg/L}$, $T = 25 \degree\text{C}$) of a Lucite tank ($70 \times 50 \times 30$ cm, L×W×H), was driven by sinusoidal bursts produced by a function generator (AF3021B, Tektronics, Beaverton, OR) together with a 55 dB power amplifier (A150, ENI, Rochester, NY). The HIFU transducer was running either at its fundamental (1.1 MHz) or third harmonic (3.3 MHz) frequency. An acoustic tile was put in the opposite wall of the testing tank to prevent the ultrasound reflection.

A focused ultrasound probe (A319S, $f = 15$ MHz, $D = 12.7$ mm, $F = 65$ mm, Olympus-IMS, Waltham, MA) was aligned confocally with HIFU transducer and worked as passive cavitation detector (PCD). Peak-to-Peak values of PCD signals of each burst, which presents the amplitudes of bubble cavitation during that pulse exposure, were recorded by a digital oscilloscope (Wavesurfer MXs-B, LeCroy, Chestnut Ridge, NY) at the sampling frequency of 50 MHz and then transferred to a personal computer (PC) for data analysis. Variations of the peak-to-peak PCD values illustrate the different characteristics of bubble dynamics during the whole ablation.

The progress of the bubble formation and lesion growth in the bovine serum albumin (BSA) embedded transparent gel phantom was observed by light transmission method and high-speed camera. An expanded illumination light produced by a Helium-Neon laser (model 1507, $\lambda = 632.8$ nm, 1 mW, JDS-Uniphase, Manteca, CA) was transmitted through the gel phantom, and subsequently focused onto a fast photo-detector (PDA 36A-EC, Thorlabs, Newton, NJ). The laser beam size was about 15 mm. Meanwhile, the produced lesion in the BSA gel phantom was recorded by a camera, simultaneously.

In the ex vivo experiment, fresh porcine kidney purchased from local grocery store was immersed in PBS solution and degassed for at least 20 minutes before HIFU treatment. PCD and ACD signals were recorded during the exposure. Afterwards, the tissue samples were dissected. Erosion and lesion produced using our protocols were recorded photographically for comparison. Meanwhile, a linear array ultrasound image probe (12L5, Teracon, Burlington, MA) was aligned at the focal plane of HIFU transducer to show the B-mode images on a portable diagnosis system (T3000, Teracon) in real-time.

**RESULTS**

Representative PCD signals are shown in Fig. 2. It is clear that the cavitation dose is significantly different with the progress of ultrasound exposure even if the same ultrasound parameters are used.

![Figure 1: Schematic diagram of experimental setup.](image)

![Figure 2: PCD signals of (a) 1$^{st}$ and (b) 100$^{th}$ pulse with center frequency of 3.3 MHz and duration of 20 ms.](image)

Therefore, the trace of PCD signal would further our understanding of the bubble dynamics during the ultrasound exposure. For example, PCD and light transmission signals were monitored throughout a total delivery of 100 pulses with frequency of 3.3 MHz, pulse duration of 30 ms, and repetition rate of 1 Hz (Fig. 3). Light transmission signal decayed exponentially due to the generation of cavitation bubbles and lesions in the BSA gel phantom. In the first pulses, PCD signal increased quickly. However, there was great variation between 30-70 pulses. Afterwards, PCD decreased.
Photographic images illustrate the growth of lesions (Fig. 4). In the first a few pulses, the HIFU pulses generate multiple cavitation bubbles at its focal region. As a result, a large tadpole lesion formed quickly after only 10 pulses. Afterwards, although the lesion size increased gradually, its shape was almost the same. It is noticed that at the late stage of ultrasound exposure, a small tadpole lesion was formed distal to the transducer in comparison to that large one proximal to the acoustic source. The formation mechanism is under investigation.

Furthermore, ultrasound parameter is found to affect the bubble cavitation significantly (Fig. 5). At 3.3 MHz, the maximum PCD signal of 10 ms, 20 ms, and 30 ms pulses are 74 mV, 132 mV, and 266 mV, respectively. For 10 ms pulse, although the PCD signal increased gradually, the variation was quite small. However, the variation became significant after about 70 pulses with duration of 20 ms, which is much later than those with duration of 30 ms. In comparison, the characteristics of bubble cavitation using the fundamental frequency of HIFU transducer at the same energy power are different. First, the bubble cavitation decreased in the initial pulses. Second, after the initial cavitation, the PCD signal was small for a time until the other activities. The starting time decreased with the increment of pulse duration. 44th, 76th, and 88th pulse became such a great variation for the HIFU burst with duration of 80 ms, 100 ms, and 120 ms, respectively. Last, the maximum PCD signal is lower than that at 3.3 MHz. It is well known that the bubble cavitation threshold is lower and the focal width is larger at low frequency. The tadpole lesion and large PCD signal at 3.3 MHz suggests that there may be large bubble at the focus for the consequent strong cavitation activities.
Figure 5: Comparison of peak-to-peak PCD signals at varying pulse duration at (a) 3.3 MHz and (b) 1.1 MHz.

Histotripsy lesions in the porcine kidney are shown in Fig. 6. When the pulse duration was 10 ms, only mechanical erosion was found. When the duration increased to 20 ms, some thermal necrosis showed up on the boundary of the tissue erosion. However, if the HIFU duration was 30 ms, the thermal lesion became larger while the mechanical erosion shrank.

Figure 6: Histotripsy lesions produced in porcine kidney.

The measured PCD signals are shown in Fig. 7. Their characteristics are similar to those in the BSA gel phantom. For 30 ms burst, the cavitation increased in the first 30 pulses. Afterwards, there is significant variation. The corresponding B-mode ultrasound images are shown in Fig. 8. Hyper-echoes were observed immediately after the delivery of the first pulse, and then grew with the increment of the number of pulses. Finally, the shape of hyper-echo is in good agreement with the lesion in the gel phantom.

Figure 7: Peak-to-peak PCD signal measured in ex vivo experiments at 3.3 MHz.

Figure 8. B-mode ultrasound images of (a) 1st, (b) 5th, (c) 50th, and, (d) 100th pulses with frequency of 3.3 MHz and duration of 30 ms.
DISCUSSION

In this study, bubble cavitation was monitored throughout the HIFU exposure. Several phenomena may be involved, such as stable cavitation, inertia cavitation, liquid boiling, acoustic scattering, and atomization. Although the cavitation was found to vary with the progress of ultrasound delivery, the underlying mechanisms are not understood completely. Several phenomena work synergistically instead of independently, which will be investigated in the next step.

A new type of lesion (thermal lesion on the boundary and soft tissue emulsification in the core) was formed using HIFU pulses, which may be developed due to both thermal and mechanical effects of HIFU. In the tissue emulsification produced by HIFU shock waves and millisecond boiling, such a lesion also appears. However, in our study the boiling time in the gel phantom at 3.3 MHz was measured to be about 120 ms. In the clinical application of tissue removal, the blood bleeding is a big concern. In comparison to histotripsy technology developed at University of Michigan [3-4], the duration of our work is much longer although the pressure output at the focus is lower (~ 45 MPa). So the erosion area is quite large, a few millimeters after 100 exposures. The interaction of the HIFU-induced cavitation bubbles with the subsequent ultrasound burst would lead to the atomization effect at the interface of gas and soft tissue and result in emulsification of soft tissue in the core. At the same time, the bubble produced by HIFU also scatters acoustic waves with the consequently enhanced temperature elevation for hemostasis of potential blood bleeding.

In the tissue removal by either conventional scalpel or recent RF or histotripsy method, the hemorrhage caused by the rupture of small vessel or capillaries is the most important safety issue in the clinics. Although histotripsy has already been proved effective in the noninvasive removal of canine prostate, the degree of hemorrhage in the treatment was not reported [7]. Meanwhile, HIFU has also applied in hemostasis in a variety of organs (i.e., liver, spleen) by activating the platelet using bubble cavitation and temperature elevation [8]. Therefore, combination of HIFU-induced hemostasis and histotripsy may meet the clinical requirement. This hypothesis will be evaluated in the animal experiment in the near future.

CONCLUSION

Bubble activities of HIFU exposure vary with the progress of HIFU exposure. Different ultrasound parameters (i.e., frequency and pulse duration) would lead to the changes of bubble cavitation and the consequent lesions produced. Combining both thermal and mechanical effects of HIFU could produce a new type of lesion, which may have potential in the clinical removal of soft tissue. Monitoring bubble activities in real time not only enhances our understanding of cavitation in the acoustical field but also provides feedback information to control the efficiency and efficacy of HIFU therapy.

ACKNOWLEDGMENTS

This research was supported by Startup Grant of Nanyang Technological University, Singapore.

REFERENCES