Variations of bubble cavitation and temperature elevation during lesion formation by high-intensity focused ultrasound

Yufeng Zhoua) and Xiaobin Wilson Gao
School of Mechanical and Aerospace Engineering, Nanyang Technological University, 50 Nanyang Avenue, Singapore, 639798

(Received 30 September 2012; revised 23 May 2013; accepted 23 May 2013)

High-intensity focused ultrasound (HIFU) is emerging as an effective therapeutic modality in both thermal ablations for solid tumor/cancer and soft-tissue fragmentation. Mechanical and thermal effects, which play an important role in the HIFU treatment simultaneously, are dependent on the operating parameters and may vary with the progress of therapy. Mechanical erosion in the shape of a “squid,” a “dumbbell” lesion with both mechanical and thermal lesions, or a “tadpole” lesion with mechanical erosion at the center and thermal necrosis on the boundary in the transparent gel phantom could be produced correspondingly with the pulse duration of 5–30 ms, which is much longer than histotripsy burst but shorter than the time for tissue boiling, and pulse repetition frequency (PRF) of 0.2–5 Hz. Meanwhile, variations of bubble cavitation (both inertial and stable cavitation) and temperature elevation in the focal region (i.e., $z = -2.5, 0, \text{ and } 2.5 \text{ mm}$) were measured by passive cavitation detection (PCD) and thermocouples during the therapeutic procedure, respectively. Stable cavitation increased with the pulse duration, PRF, and the number of pulses delivered. However, inertial cavitation was found to increase initially and then decrease with long pulse duration and high PRF. Temperature in the pre-focal region is always higher than those at the focal and post-focal position in all tests. Great variations of PCD signals and temperature elevation are due to the generation and persistence of large bubble, which is resistant to collapse and occurs with the increase of pulse duration and PRF. Similar lesion pattern and variations were also observed in ex vivo porcine kidneys. Hyperechoes in the B-mode ultrasound image were comparable to the shape and size of lesions in the dissected tissue. Thermal lesion volume increased with the increase of pulse duration and PRF, but mechanical erosion reached its maximum volume with the pulse duration of 20 ms and PRF of 1 Hz. Altogether, bubble cavitation and thermal field vary with the progress of HIFU treatment with different sonication parameters, which provide insights into the interaction of ultrasound burst with the induced bubbles for both soft tissue fractionation and enhancement in thermal accumulation. Appropriate synergy and monitoring of mechanical and thermal effects would broaden the HIFU application and enhance its efficiency as well as safety.

© 2013 Acoustical Society of America. [http://dx.doi.org/10.1121/1.4812895]

PACS number(s): 43.80.Gx, 43.80.Sh, 43.35.Ei, 43.25.Qp

Pages: 1683–1694

I. INTRODUCTION

High-intensity focused ultrasound (HIFU) is an emerging therapeutic modality for both benign and malignant tumors/cancers (Al-Bataineh et al., 2011; Zhou, 2011). In Asia and Europe, more than 100,000 patients have been involved with promising results. Application, investigation, and development of HIFU technology are becoming more and more attractive to physicians, patients, researchers, and medical device manufacturers since its first clinical trial in the 1990s. The major mechanism of HIFU is the thermal coagulation in the targeted volume due to the temperature elevation over 65 °C and consequent protein denature caused by the absorption of acoustic energy. Alternatively, due to the high acoustic intensity implemented in HIFU (>1000 W/cm²) the influence of bubble activities in the focal region is likewise of importance. Bubbles may form by the growth of tiny cavitation nuclei in blood or tissue under the negative pressure of the acoustic wave or from boiling of fluid at the high temperature. Bubbles are strong scatters of acoustic wave because of their much lower acoustic impedance compared to that of water and soft tissue. Therefore, they will shield the propagation of HIFU bursts and cause more energy to be absorbed proximally, resulting in lesion distortion from a symmetric cigar shape to an asymmetric tadpole one with its head moving toward the source (Watkin et al., 1996).

In comparison, the mechanical effects of high-intensity ultrasound wave (i.e., bubble cavitation, acoustic streaming, and radiation force) dominate the burst mode. Interaction of cavitation bubbles and ultrasound burst (i.e., 20 µs pulse duration at PRF of 1 kHz and rarefractional pressure of 18 MPa) would lead to mechanical fractionation of tissue structure, which is termed as histotripsy (Xu et al., 2007a; Xu et al., 2004; Xu et al., 2007b). The transducer used has similar geometry and acoustic specification as the HIFU type, but at a little lower frequency because of the proportionality between the cavitation threshold and ultrasonic frequency (Spomer, 1990). Both in the fluid-tissue interface and in bulk tissue, histotripsy mechanically fragments tissue to a liquefied

a)Author to whom correspondence should be addressed. Electronic mail: yfzhou@ntu.edu.sg
substance at the subcellular level with sharply demarcated boundaries (10–100 μm transition zone from all cells intact to those disrupted). Histotripsy provides a noninvasive option for tissue ablation and removal in vivo, such as perforation of the atrial septum in the treatment of congenital heart disease, owing to its technical advantages, such as well-controlled and precise lesion production, real-time monitoring energetic microbubble activities and lesion appearance as bright and dark spots on the B-mode ultrasound imaging, respectively.

Furthermore, nonlinear propagation of HIFU waves not only becomes distorted along the propagation path but also forms shock waves in tissue. As a result, the heating rate is significantly higher than that predicted for undistorted or weakly distorted ones, and boiling in tissue (e.g., temperature around 100 °C) could occur in milliseconds. Emulsified lesions without thermal denaturation were produced only when both initiation of boiling in milliseconds (i.e., the time-to-boil of 3 ms and pulse duration of 10 ms) and shock waves were present, but in a larger size (a few mm) than histotripsy (Canney et al., 2010; Khokhlova et al., 2011; Maxwell et al., 2012; Simon et al., 2012). This effective and reliable method resolves the problems of the inherent performance in the other tissue emulsification technologies stemming from the stochastic nature of cavitation. The lesion size can be predicted and controlled through the proper operation parameters (i.e., HIFU frequency and pulsing scheme).

In this study, a new tissue erosion method, whose pulse duration is much longer than histotripsy but shorter than the boiling time (∼103 ms), was proposed and tested in both gel phantom and ex vivo porcine kidney by utilizing both thermal and mechanical effects concurrently. Distinct types of lesions could be produced with varied pulse duration and PRF of HIFU bursts. With the increase of the pulse duration from 5 to 20 ms or PRF from 0.2 to 5 Hz, a mechanical erosion in the shape of a “squid” will evolve to a “dumbbell” lesion with both mechanical and thermal lesions and then to a “tadpole” lesion with mechanical erosion at the center and thermal necrosis on the boundary. The rapidly changing conditions during HIFU exposure have a notable impact on the bubble dynamics and subsequent heating enhancement and tissue damage (Coussios et al., 2007; Tu et al., 2006). Therefore, bubble cavitation and temperature in the focal region were measured throughout the HIFU exposure using the methods of passive cavitation detection (PCD) and thermocouples in order to understand the contributions of mechanical and thermal effects, respectively. Their dominance varied with the progress of HIFU ablation and sonication parameters. Both cavitation activities and temperature increased with the number of pulses delivered, and HIFU-induced microbubbles would enhance the contribution of thermal effects in lesion formation with the increase of pulse duration and PRF. However, at a long pulse duration (i.e., 30 ms) or high PRF (i.e., 5 Hz), HIFU-induced bubbles will coalesce into a large one, which is resistant to collapse and scatters acoustic energy toward the transducer for significant heat deposition, after a few bursts as shown by the decrease of inertial cavitation dose but an increase of stable cavitation one in the PCD spectrograms. The characteristics of peak-to-peak PCD signals and lesion volumes in ex vivo tissue with varied sonication parameters are similar to those in gel phantom. It is suggested that appropriately utilizing the mechanical and thermal effect of HIFU ablation would broaden its application and monitoring cavitation activities would provide a feedback in control of its effectiveness as well as safety.

II. MATERIALS AND METHODS

A. HIFU transducer

An annular focused HIFU transducer (H=102, outer diameter = 69.94 mm, inner diameter = 22.0 mm, F = 63.64 mm, Sonic Concepts, Woodinville, WA) working at its third harmonic frequency, 3.3 MHz, was used in this study (Fig. 1). The HIFU transducer was immersed in the degassed and deionized water (O2 < 4 mg/L, T = 25 °C, measured by DO700, Extech Instrument, Waltham, MA) of a Lucite tank (L × W × H = 70 cm × 50 cm × 30 cm) and driven by sinusoidal bursts produced by a function generator (AF3021B, Tektronics, Beaverton, OR) together with a 55 dB power amplifier (150 W, A150, ENI, Rochester, NY). An acoustic absorber was put on the opposite wall of the testing tank to prevent the ultrasound reflection. The HIFU transducer was attached to a three-axis positioning system (BiSlide, Velmex, Bloomfield, NY) to align its focus to the desired position (i.e., 2 cm from the sample surface). A LabView program (National Instruments, Austin, TX) was written to control the pulse delivery and translational motion.

B. Gel phantom

Polyacrylamide with 7% of bovine serum albumin (BSA) was used to prepare optically transparent gel phantoms, which have the acoustic impedance of 1.6 MRayls, the speed of sound of 1544 m/s, and the acoustic attenuation of

FIG. 1. (Color online) Schematic diagram of experimental setup that was used to monitor the HIFU-induced lesions and cavitation in transparent polyacrylamide gel phantom and ex vivo tissue.
0.15 dB/cm/MHz (Lafon et al., 2005). Temperature above 60°C—65°C would cause BSA to denature and become opaque for thermal lesion observation. The liquid mixture of gel constituents was degassed for about 1 h in a descant chamber (420100000, Scienceware, Pequannock, NJ) by a vacuum pump (VTE8, Thomas, Sheboygan, WI) at a pressure of 150 mbars, then poured into a mold for polymerization at room temperature within 1 min of adding N,N,N',N'-tetra-methyl-ethylene/diamine (TEMED, Sigma, Singapore).

C. Cavitation detection and lesion observation

A focused ultrasound probe (A319S, f = 15 MHz, D = 12.7 mm, F = 65 mm, Olympus-IMS, Waltham, MA) was aligned confocally and coaxially with HIFU transducer and worked as a PCD sensor (Nandlall et al., 2011). PCD signals of each burst were recorded by a digital oscilloscope (Wavesurfer MXs-B, LeCroy, Chestnut Ridge, NY) at a sampling frequency of 100 MHz and then transferred to a personal computer (PC) for data analysis. Variations of the peak-to-peak PCD values present the amplitudes of bubble cavitation during HIFU ablation (Everbach et al., 1997). Small-time Fourier transforms (STFT) were then performed on the collected PCD data in MATLAB (The Mathworks, N. Nortick, MA) for the corresponding spectrogram, F(t, f). A specific frequency window, 7.5–9 MHz, whose central value is the mean value of the second and third harmonic frequencies, was chosen to evaluate the amount of inertial cavitation-induced broadband noise during the HIFU exposure by calculating the temporal-average frequency-average amplitude

$$\tilde{F} = \frac{1}{T} \int_{f_2}^{f_1} \int_{0}^{T} F(t, f) df dt \cdot (f_2 - f_1),$$

where T is the pulse duration time, f_2 and f_1 are the upper and lower bounds of integral, respectively (Tu et al., 2006; Tung et al., 2010). Meanwhile, the amplitude of the fourth harmonic frequency (f_1 = 13.1 MHz and f_2 = 13.3 MHz) was used to represent the stable cavitation (Farny et al., 2009) as shown in Fig. 2.

A 100 W white-light bulb under the water tank provided the illumination source through the gel phantom for the photography. The progress of bubble formation and lesion growth in the BSA-embedded transparent gel phantom was recorded by a digital camcorder (Vixia HF M500, Canon, Tokyo, Japan) at a frame rate of 50 Hz and shutter speed of 1/2000 s. The photos were extracted from the videos (Movie Maker, Microsoft, Redmond, WA) and further processed in Photoshop (Adobe, San Jose, CA) for auto color and contrast correction.

D. Temperature measurement

To measure the thermal field in gel phantom during HIFU ablation, three thermocouples (T136-ICSS-020G-6, Omega Engineering Inc., Stamford, CT) with a diameter of 0.5 mm were inserted into the focal region (z = -2.5, 0, and 2.5 mm) through guided holes in a 2-cm thick Lucite plate under the guidance of the digital camcorder and connected to a data acquisition (DAQ) unit (NI-9214, National Instruments, Austin, TX). Sampling rate was 1000 Hz, and the data were then transferred to PC and processed in MATLAB. The viscous heating produced by the insonation would lead to a rapid temperature increase close to the thermocouple (Fry and Fry, 1954). The thermocouple measurement in the original a few pulses was compared to the theoretical simulation using the BioHeat equation (Zhou et al., 2011), and the discrepancy was fitted with an effective Gaussian radius (Morris et al., 2008). Then the artifact was minimized by removing the contribution of the viscous heat source throughout the whole measurement (Huang et al., 2004) as shown in Fig. 3(a). Owing to the large amount of data only the peak and ambient temperatures of each HIFU exposure were depicted for the variations of the thermal field [Fig. 3(b)].

E. Ex vivo study

In ex vivo experiment, fresh porcine kidney purchased from a local slaughterhouse (Primary Industries Pte Ltd,
Singapore) was immersed in phosphate-buffered saline (PBS) solution, degassed for at least 30 min, and used within 4 h of harvest for HIFU ablation. A convex array ultrasound image probe (G5-2/60 GPS, Ultrasonix, Vancouver, BC, Canada) was aligned perpendicular to the axis of the HIFU transducer in the testing tank, and the real-time B-mode images on a diagnosis system (SonicTouch, Ultrasonix) during the sonication were recorded. After the ablation, the tissue samples were frozen at $-4^\circ$C overnight, dissected in a thickness of 0.6 mm by a food slicer (Toledo001, Jian Machinery Ltd, China), and recorded photographically by a digital camera (PowerShot SX230 HS, Canon). Mechanical erosion and thermal coagulation in each slice were contoured and re-aligned in a program (3D Doctor, Able Software Corp., Lexington, MA), from which their volumes were reconstructed in three-dimensional space and calculated.

F. Statistical analysis

At each testing condition, at least five data were collected. Analysis of variance (ANOVA) was performed in SPSS® Statistics (IBM Software, Somers, NY) to determine the statistical difference between the groups that was fixed at $p < 0.05$.

III. RESULTS

The acoustic pressures of the HIFU transducer with the peak-to-peak voltage of 1 V from the function generator were $p^+ = 46.8 \pm 1.3$ MPa and $p^- = -15.7 \pm 0.8$ MPa at the focus with $-6$ dB beam size of $0.5 \times 4$ mm measured by a fiber-optic probe hydrophone (FOPH-500, RP Acoustics, Leutenbach, Germany) (Zhou et al., 2006), and the acoustic power was $105.6 \pm 7.2$ W measured by a radiation force balance (RFB-2000, Onda Corp., Sunnyvale, CA). The boiling time of a single HIFU burst in the gel phantom was $81.4 \pm 17.2$ ms indicated as a significant increase in the measured PCD signals (Canney et al., 2010), which is close to the theoretical simulation result of temperature over $100^\circ$C at 103 ms. Sonication parameters in the gel phantom and ex vivo samples are listed in Table I.

A. Effect of the pulse duration

The progressive growth of a lesion produced in the transparent gel phantom was captured with a digital camcorder (Fig. 4). In the first HIFU pulse, the bubble nuclei will absorb the acoustical energy and then expand. Because of the acoustic reflection at the interface of phantom and air, dense bubble clouds were observed to form proximally toward the transducer (Maxwell et al., 2009). It is interesting

![Graph](image_url)

FIG. 3. (Color online) (a) Comparison of temperature measured by a thermocouple (solid line), simulated by a theoretical model (middle dashed line), viscous heating artifact fitted with an effective Gaussian radius (dashed-dotted line), and simulation result including the viscous heating artifact (short dashed line) in the focal region of a HIFU transducer with the pulse duration of 20 ms and a pulse repetition frequency of 1 Hz. A good agreement is found between the measurement and simulation results. The viscous heating artifact decays quickly after the termination of HIFU exposure and then its influence is minimized from the thermocouple measurement. (b) Envelopes of the temperature profile at $z = -2.5, 0,$ and 2.5 mm, respectively, during 200-burst HIFU exposure after artifact correction. Upper and lower lines of each plot are the peak and ambient temperature for each HIFU pulse exposure, respectively.

TABLE I. Summary of sonication parameters used in the experiments.

<table>
<thead>
<tr>
<th></th>
<th>Gel phantom</th>
<th>Ex vivo porcine kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRF (Hz)</td>
<td>Pulse (ms)</td>
<td>PRF (Hz)</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>0.2</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>5</td>
</tr>
</tbody>
</table>

*PRF: pulse repetition frequency*
to note that some bubbles appear distally (i.e., \( \sim 1 \) mm away from the lesion tip). They may be produced in the focal region initially and then pushed forward with the response to the acoustic radiation force \( \text{(Khokhlova et al., 2011)} \), and aggregation of these bubbles will occur in the succeeding exposure with a long lifetime. Details of this motion will be investigated in the future by using high-speed imaging. Interaction between 5-ms HIFU burst and these bubbles led to the formation of a “squid” lesion, which was predominantly mechanical erosion and quite flat (the thickness is less than 0.3 mm, much smaller than the projected lesion size). With the increase of the pulse duration time, bubbles produced in the focal region became large, and the acoustic scattering effects from bubbles were more significant because the acoustic intensity of the scattered wave is proportional to \( r^6 \), where \( r \) is the radius of a spherical source \( \text{(Cobbold, 2007)} \). A dumbbell lesion was induced by 10-ms bursts \( \text{[Fig. 4(c)]} \). Longer pulse duration led to the domination of thermal effect in the pre-focal region by the backscattering waves, the introduction of large boiling bubble \( \sim 3.5 \) mm in diameter at \( N = 10 \) in Fig. \text{4(d)}, and then formation of tadpole lesion moving toward the transducer although the forward motion of bubbles and mechanical erosion in the post-focal region still existed. Meanwhile, the high-speed jet emitting from the bubble along the ultrasound propagation direction was clearly illustrated, which was considered the mechanism of tissue fractionation \( \text{(Khokhlova et al., 2011; Xu et al., 2008)} \).

Meanwhile, PCD signals from cavitation bubbles produced in the focal region throughout the HIFU exposure were recorded using the confocal and coaxial ultrasound transducer. It is found that with the increase of the HIFU pulse duration from 10 to 30 ms there are significant differences between the peak-to-peak PCD signals \( \text{[Fig. 5(a)]} \). When the pulse duration is smaller than 20 ms, PCD signal increased with the progress of the sonication despite higher
variation in longer bursts. At the pulse duration of 30 ms, PCD signals reached the maximum after about 60 bursts. Afterward, a reduction in the bubble activity was found, even less than those produced by 20-ms burst. Thus, there is no statistical difference between the maximum or average PCD signals for 20-, 25-, and 30-ms bursts (0.44 ± 0.11 vs 0.46 ± 0.08 vs 0.49 ± 0.07 V and 0.24 ± 0.05 vs 0.23 ± 0.03 V, respectively, \( p > 0.05 \), Fig. 5(b)).

Because of the large amount of data, PCD signals of every 25 pulses were transferred from the digital oscilloscope to the PC for STFT analysis to quantify both stable cavitation (SC) and inertial cavitation (IC) in Fig. 2. SC, nonlinear bubble oscillation and acoustic scattering signals from bubbles, are represented by the appearance of the fundamental and harmonics (up to the seventh one due to the bandwidth of PCD transducer) of the driving burst (Lauterborn, 1976). Appearance of higher-order harmonics and increase of spectrum amplitude may indicate the larger bubble. Meanwhile, IC is shown as the white noise between harmonics (Frohly et al., 2000). SC and IC doses were quantized for easy comparison in Fig. 6. For the first burst, the cavitation doses increased with the pulse duration (i.e., SC from \(-18.0 ± 0.5\) dB to \(-14.6 ± 1.9\) dB and IC from \(-24.8 ± 0.1\) dB to \(-22.5 ± 0.5\) dB with the pulse duration increasing from 5 to 30 ms). SC increased with the progress of HIFU exposure for the pulse duration no more than 20 ms (i.e., SC increased from \(-16.6 ± 1.2\) dB to \(-4.3 ± 1.1\) dB for 20-ms burst). In comparison, SC dose reached its saturation quickly only after 50 pulses (i.e., 0.18 ± 2.4 dB) and began to decrease at the end of exposure for the pulse duration of 30 ms [Fig. 6(a)]. Such a peak distribution is more noteworthy in the detected IC dose [Fig. 6(b)], whose value reached the maximum (i.e., \(-18.5 ± 1.0\) dB) around the 50th pulse and then decayed quickly. Therefore, although SC signals were still strong (i.e., \(-1.4 ± 2.7\) dB) at the end of the sonication, IC became considerably less (i.e., \(-24.2 ± 0.7\) dB). SC strength is usually higher than that of IC because IC has a much broader bandwidth (Frohly et al., 2000).

The sum of simulated temperature elevation by HIFU burst and viscous heating artifact in an effective Gaussian diameter matched with the thermocouple measurement of the first 4 pulses quite closely [Fig. 3(a)], so the artifact could be minimized assuming its consistency throughout the exposure. The temperature rose rapidly for about 15 °C in the 20-ms HIFU exposure and then decayed exponentially. Because of the long thermal diffusion compared to the pulse interval time, the ambient temperature increased exponentially with the progress of HIFU exposure. The temperature in the pre-

FIG. 5. (Color online) (a) Representative peak-to-peak PCD signals with the progress of HIFU exposure in the gel phantom, and (b) comparison of the maximum and average peak-to-peak PCD signals in gel phantom (solid line) and \textit{ex vivo} porcine kidney (dashed line) during the 200-burst exposure with varied pulse duration up to 30 ms and a pulse repetition frequency of 1 Hz. Similar characteristics of PCD signals are found between the gel phantom and \textit{ex vivo} studies. ANOVA is used to determine the statistical difference (\( p < 0.05 \), \( n > 5 \)).

FIG. 6. (Color online) (a) Stable and (b) inertial bubble cavitation dose with the progress of HIFU exposure in the gel phantom with varied pulse duration from 5 to 30 ms and a pulse repetition frequency of 1 Hz. Stable cavitation dose is usually higher than that of inertial cavitation.
focal region \((z = -2.5 \text{ mm})\) is always higher than that at the focus \((z = 0 \text{ mm})\) and in the post-focal region \((z = 2.5 \text{ mm})\) from the first pulse \([63.2 \degree C \text{ vs } 52.4 \degree C \text{ and } 40.5 \degree C]\) respectively, in Fig. 3(b)] due to the thermal enhancement by the acoustic scattering from the bubbles (Chen et al., 2003; ter Haar, 1995). Although temperature rise was quite consistent throughout the whole exposure (i.e., \(\Delta T = 33 \degree C - 40 \degree C\) at \(z = -2.5 \text{ mm}\)), large variation occurred at the end of sonication (i.e., the smallest \(\Delta T\) of 23.2 \degree C around the 175th burst at \(z = -2.5 \text{ mm}\)), which correlates well with the significant changes in the peak-to-peak PCD signals [Fig. 5(a)].

Although three thermocouples are close to each other \((\Delta z = 2.5 \text{ mm})\), the measured temperatures are significantly different with varied pulse duration from 5 to 30 ms \([p < 0.05 \text{ in Fig. 7(a)}]\). Over 100 \degree C could be reached with the appearance of the thermal necrosis in tadpole shape (Fig. 4) if the pulse duration is longer than 15 ms. Temperatures generally increased with the pulse duration despite a slight decrease at \(z = 0\) and 2.5 mm for 30-ms HIFU burst. When the pulse duration is short, the temperature elevation of each HIFU burst exposure was quite consistent (i.e., \(\Delta T = 14.7 - 29.1 \degree C\) at \(z = -2.5 \text{ mm for 5-ms burst}\), shown as the small discrepancy between the first and third quartile in the box plot [Fig. 7(b)]. With the increase of the pulse duration, the variation became significant (i.e., \(\Delta T = 9.1 - 82.3 \degree C\) at \(z = -2.5 \text{ mm for 30-ms burst}\) with the average moving to the fifth percentile, which may be due to the great attenuation of large bubble(s) on the HIFU propagation for much lower temperature rise. These suggest that bubble cavitation have a great impact on the thermal field in HIFU ablation.

**B. Effect of pulse repetition frequency**

Varying PRF could also adjust the role of mechanical and thermal effect on HIFU ablation (Fig. 8). At low PRF of 0.2 Hz, bubbles may have sufficient time for dissolution because no persisting bubbles were found between bursts. Bubbles distal to the lesion were also found after five pulses. The lesion pattern (”squid” type) is similar to that produced using the pulse duration of 5 ms and PRF of 1 Hz [Fig. 4(a)], but larger in size \((3.1 \text{ mm } \times \text{ 8.9 mm vs } 1.6 \text{ mm } \times 5.6 \text{ mm})\). As expected, with the increase of PRF, thermal effect induced by bubble scattering became significant and led to the growth of a “tadpole” lesion (i.e., 4.4 mm \(\times 10 \text{ mm}\) at PRF of 5 Hz) toward the transducer source and decrease of the mechanical erosion in the distal (Fig. 8).

Measured PCD signals at varied PRF [Fig. 9(a)] illustrate similar characteristics as those with a varied pulse duration [Fig. 5(a)]. When PRF is 0.2 Hz, the peak-to-peak PCD signals increased slowly with the sonication progress. If PRF is higher than 1 Hz, the maximum PCD signal could be reached in the first 50–60 bursts and then followed by a decrease with notable variations. Both the maximum and average PCD signals increased with varied PRF from 0.2 to 1 Hz, but decreased slightly at higher PRF with no statistical difference \([p > 0.05, \text{ Fig. 9(b)}]\). SC dose increased with the sonication progress and PRF (i.e., from \(-16.9 \pm 0.7 \text{ dB to } -3.3 \pm 1.9 \text{ dB}\) in the first 25 pulses at PRF of 5 Hz in Fig. 10). In contrast, IC dose increased almost monotonically with the number of HIFU pulses delivered at low PRF (i.e., 0.2 Hz). With the increase of PRF, the variation had a peak distribution with the summit moving toward the beginning and narrow width. At PRF of 5 Hz, IC dose increased slightly from \(-23.5 \pm 0.4 \text{ dB at } N = 1 \text{ to } -22.5 \pm 0.7 \text{ dB at } N = 25\) and then decreased greatly (i.e., \(-24.7 \pm 0.4 \text{ dB at } N = 200\)), which suggests that HIFU-induced bubbles at high PRF may coalesce into a large one for strong acoustic scattering and be resistant to collapse.

The thermal field in HIFU ablation at the varied PRF showed distinct characteristics as that with the varied pulse duration (Fig. 11). The maximum temperature increased with PRF in the focal and post-focal region (i.e., from \(66.1 \pm 3.9 \degree C\) at PRF of 0.2 Hz to \(96.9 \pm 3.0 \degree C\) at PRF of 5 Hz at \(z = 0 \text{ mm}\)), which is due to rapid increase of the ambient temperature in the short interval time (high PRF). In contrast, the corresponding value at \(z = -2.5 \text{ mm}\) decreased slightly from \(111.5 \pm 4.3 \degree C\) to \(102.7 \pm 4.8 \degree C\). In addition, there is large variation in the temperature elevations during the sonication (i.e., high temperature rise initially but more low ones at the end) with the increase of PRF in the whole focal region [Fig. 11(b)]. At PRF of 5 Hz, although the

**FIG. 7.** (Color online) (a) The maximum temperatures and (b) the box plot of temperature elevations of each burst at \(z = -2.5, 0, \text{ and } 2.5 \text{ mm}\), respectively, by 200-burst HIFU exposure with varied pulse duration from 5 ms to 30 ms and a pulse repetition frequency of 1 Hz in the gel phantom \((n > 5)\). Whiskers are 1.5 interquartile ranges. The lower and upper outliner shows the 5th and 95th percentile of the data, respectively. Great variations are indicated as the significant difference between high and low measurements.
temperature elevation at $z = -2.5\, \text{mm}$ had similar average value as that of the focus (14.0 ± 9.9 vs 12.4 ± 5.4°C), the variation range was much larger (6.6–91.2 vs 4.8–37.3°C).

C. Ex vivo study

Characteristics of peak-to-peak PCD signals measured in porcine kidney with varied pulse duration [Fig. 5(b)] and PRF [Fig. 9(b)] are similar to those in the gel phantom although the amplitude is a little lower due to the acoustic attenuation in tissue. Hyper-echoes were observed immediately on the sonography after the delivery of the first pulse with pulse duration of 20 ms and PRF of 1 Hz and then grew into a tadpole shape with very high echogeneity at the center, which may be mechanical erosion and thermal necrosis induced by HIFU pulses, respectively ($N = 200$, Fig. 12). Although the active cavitation detection (ACD) may be less sensitive to the presence of bubbles than PCD (Madanshetty et al., 1991; Roy et al., 1990), the shape and size of hyper-echo (7.1 mm × 10.1 mm) measured by the sonography caliper were close to the lesion found in the tissue [6.5 mm × 9.3 mm in Fig. 13(a)]. A 3D lesion was reconstructed from the tissue slices, and mechanical erosion and thermal necrosis were presented by the inner and outside meshes, respectively; characteristics of lesion production in the tissue are similar to those in the gel phantom [Fig. 13(b)]. When PRF is 1 Hz, the thermal lesion volume increased from 2.0 ± 0.8 mm$^3$ at the pulse duration of 10 ms to 139.1 ± 17.6 mm$^3$ for 30-ms burst. However, the largest mechanical lesion occurred at the pulse duration of 20 ms (i.e., 11.3 ± 3.8 mm$^3$). Similarities in the trend of lesion production were found by varying PRF. Thermal lesion increased from 1.1 ± 0.9 mm$^3$ at PRF of 0.2 Hz to 409.5 ± 84.9 mm$^3$ at PRF of 5 Hz. Although the projected

---

**FIG. 8.** (Color online) Progressive lesion production by a HIFU burst in a transparent 7% BSA gel phantom with the pulse duration of 20 ms and a pulse repetition frequency of (a) 0.2 Hz, (b) 0.5 Hz, (c) 2 Hz, and (d) 5 Hz. The values at the top of the frames are the number of bursts delivered. Characteristics of lesions are similar to those produced by changing the pulse duration in Fig. 4 that with the increase of PRF thermal effect will play an important role in the prefocal region and change the lesion to “tadpole” shape. Arrow and arrowhead present the bubbles in the distal end of the lesion and scattered bubbles around the lesion, respectively. Ultrasound propagates from the bottom to the top. The scale is 2 mm.
area of a “squid” lesion is big, its volume is usually small because of the thin thickness.

IV. DISCUSSION

High-intensity short-duration focused ultrasound bursts were used in the tissue emulsification and ablation. In this study, bubble cavitation, thermal field, and the consequent lesion formation were monitored during the HIFU exposure at the frequency of 3.3 MHz and electrical output power of 150 W using PCD, thermocouple, and the digital camcorder, respectively. It is found that lesion would vary from a mechanical erosion in the shape of a “squid” to a “dumbbell” lesion with both mechanical and thermal lesions, and then to a “tadpole” lesion with mechanical erosion at the center and thermal necrosis on the boundary in the phantom by changing the pulse duration from 5 to 30 ms and PRF from 0.2 to 5 Hz. The similarities are found for the maximum and average PCD signals between in the gel phantom and ex vivo studies.

The occurring time of tissue boiling depends on the acoustic pressure in the focal region of the HIFU transducer and the tissue absorption. At the low acoustic pressure exposure, it varies from a few hundreds of milliseconds to several seconds. As a result, a vaporized core will appear in the center of a pre-existing thermally necrotic volume (Khokhlova et al., 2009). Although similar lesions were produced with the pulse duration of 30 ms and PRF of 1 Hz in our study, the mechanism is different. The lesion produced in the original...
10 bursts is mechanical erosion. Afterward, the increase of ambient temperature due to the thermal diffusion (Zhou et al., 2011) and significant acoustic scattering from bubbles lead to the gradual dominance of the thermal effect, production of boiling bubbles, and formation of opaque BSA necrosis. In the previous studies, high power output (i.e., 300 W) could produce a boiling bubble within milliseconds using a single-element air-backed transducer at a frequency of 2.158 Hz (Canney et al., 2010; Khokhlova et al., 2011). When the interval time between bursts was sufficiently long for thermal diffusion, no thermal denaturation but purely mechanical erosion could be observed. Increasing duty cycles or pulse duration would lead to the production of a thick white paste with different thermal denaturation (Khokhlova et al., 2011), which was not found in this study because of the different time-to-boil (3 ms vs 103 ms) and limited operation parameters. Altogether, varying the sonication parameters would produce different types of lesions.

Several phenomena are involved in the HIFU ablation, such as energy absorption, temperature elevation for necrosis formation, bubble cavitation, liquid boiling, acoustic scattering from bubbles, acoustic microstreaming, and atomization, which are usually categorized as mechanical and thermal effects and work synergistically instead of independently in the sonication. Introduction of commercially available ultrasound contrast agent would enhance the thermal accumulation due to the intense acoustic backscattering at the interface of microbubbles. However, the lesion will shift in the proximal direction and change the shape. For example, 0.001% of Definity® by volume in gel phantom produced a lesion 12 times larger with an acceptable shift toward the source in the HIFU ablation (Tung et al., 2006). Also, 2 ml intravenous injects of SonoVue into a rabbit would result in the threefold increase of coagulated volumes in the liver with more severe cell ultrastructure disorder and more interrupted cell nuclear membranes after 2 s of HIFU exposure at the acoustic power of 600 W (Luo et al., 2007). Furthermore, low pulse duration and high PRF of HIFU burst (histotripsy) could cause noninvasive tissue erosion because of the interaction of bubbles and ultrasound burst, which is a purely mechanical effect. Making use of the significant heat increase rate by a shock wave in nonlinear acoustics could produce tissue boiling in milliseconds for large tissue erosion without thermal coagulation (Canney et al., 2010; Khokhlova et al., 2011). Therefore, it suggests that appropriately utilizing both thermal and mechanical effects would enhance the efficiency.
of HIFU therapy in diverse applications. As indicated in this study, the dominant mechanism varies with the advance of ablation using the same pulse duration and PRF. An adaptive method is in need to dynamically adjust the sonication parameters based on the real-time feedback in order to achieve the desired outcome.

In tissue removal by either a conventional scalpel or recent radio-frequency (RF) or ultrasound method, the hemorrhage caused by the rupture of vessels or capillaries is the most critical safety issue in clinics, which may be fatal in the case of hemostatic defects. For example, dissection of the liver parenchyma using the standard techniques may cause a death rate ranging from 4% to 20%, considerable blood loss, and other serious complications, such as liver failure, hemotoma, infections, and bile leakage (Schmidbauer et al., 2002; Tranberg et al., 1986). Although histotripsy has already been proven effective in the noninvasive removal of canine prostate, the degree of hemorrhage in the treatment was not reported (Hall et al., 2009). Meanwhile, HIFU has also been applied in hemostasis in a variety of organs (i.e., liver and spleen) by activating the platelet by bubble cavitation and temperature elevation (Vaezy et al., 1997). A new type of lesion with tissue fragmentation at the center and thermal coagulation on the boundary was produced in this study. The ratio of the inner and outer radius of the lesion depends on the sonication parameters. Therefore, combination of tissue erosion and thermal necrosis concurrently may be a solution in dissecting the hypervascular tissue. This hypothesis will be evaluated in the future animal experiment.

In summary, HIFU bursts with pulse duration longer than that of histotripsy but shorter than the time-to-boil could produce various types of lesions, from a mechanical erosion in the shape of a “squid” to a “dumbbell” lesion with both mechanical and thermal lesion and then to a “tadpole” lesion with mechanical erosion at the center and thermal necrosis on the boundary, at different sonication parameters (i.e., pulse duration and PRF). Bubble activities and thermal elevation change with the progress of HIFU exposure and sonication parameters because of the varied dominant mechanisms (mechanical and thermal effects). Monitoring bubble activities in real-time not only enhances our understanding of bubble 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 (M4080184.050).


