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# The effects of the size of a boiling bubble on lesion production in boiling histotripsy

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**Abstract**. Boiling histotripsy employs a number of millisecond-long High Intensity Focused Ultrasound (HIFU) pulses with high acoustic peak pressures at the HIFU focus to mechanically fractionate soft tissue. Studies have shown the mechanisms underpinning this tissue fractionation process; however, the question of how HIFU exposure conditions affect lesion formation still remains unclear. In the present work, a high-speed camera and a passive cavitation detection (PCD) system were used to investigate the dynamics of bubbles induced and the corresponding mechanical damage generated in optically transparent tissue-mimicking phantoms with two different boiling histotripsy exposure conditions (1. $P_+$ = 85.4 MPa, $P_-$ = – 15.6 MPa; 2. $P_+$ = 71.5 MPa, $P_-$ = – 13.4 MPa at focus). Our results clearly showed that there is a positive relationship between the size of a boiling bubble and the lesion dimension. At $P_+$ = 85.4 MPa and $P_-$ = – 15.6 MPa, a relatively larger boiling bubble was, for instance, produced at the focus in the gel phantom followed by the presence of a wider cavitation cluster progressing toward the HIFU transducer, resulting in the formation of a larger lesion compared to that with $P_+$ = 71.5 MPa and $P_-$ = – 13.4 MPa.

## 1. Introduction

Boiling histotripsy is a High Intensity Focused Ultrasound (HIFU) technique which uses shock wave heating and millisecond boiling to mechanically break down soft tissue without causing significant thermal damage [1]. The feasibility of using boiling histotripsy for the treatment of solid tumours has been demonstrated in animals [2-7]. These *ex-* and *in vivo* studies have clearly shown that a boiling histotripsy-induced lesion comprises complete fragmentation of soft tissue and is sharply demarcated between treated and untreated regions at a cellular level.

Mechanisms behind boiling histotripsy have been investigated both numerically and experimentally. Initially, a millisecond long shockwave with acoustic peak positive ($P_+$) and negative ($P_-$) pressures at the focus of $P_+ > 40$ MPa and $P_- < 10 – 15$ MPa can raise tissue temperature to 100°C, resulting in the creation of a boiling vapour bubble at the focus [8]. This is possible because enhanced tissue heating caused by shockwaves which contain tens of higher harmonics of the fundamental frequency can lead to a significant temperature rise. The size of a boiling bubble formed at the focus then expands to around a millimetre due to the asymmetry of the shape of a shockwave used in a boiling histotripsy exposure and water vapour that transports into the bubble [9, 10]. After the production and explosive growth of a boiling bubble, the shock scattering effect enables inertial cavitation clouds to be induced in front of the boiling bubble progressing toward the HIFU source [11]. Shear stresses produced around an oscillating boiling bubble together with violent bubble collapses involved in inertial cavitation can lead to the formation of a tadpole-shaped mechanically destructed lesion [11, 12], which is a typical lesion shape resulting from boiling histotripsy.

It is of paramount importance to control as well as to predict the size of a lesion at a given boiling histotripsy exposure condition. Whilst our previous study [11] has demonstrated the underpinning mechanisms of boiling histotripsy, particularly the interaction of a boiling vapour bubble with incoming incident shockwaves, the question of how exposure conditions affect the size of a lesion produced remains. To that end, in this study, a high-speed camera and a passive cavitation detection (PCD) system are used to investigate the dynamics of bubbles induced and the corresponding mechanical damage generated in optically transparent tissue-mimicking phantoms exposed to two different HIFU fields.

## 2. Methods

### *2.1. HIFU experimental methods*

A schematic diagram of the experimental set up used in this study is depicted in figure 1. The HIFU experiments were conducted in a water bath filled with degassed and de-ionised water at 20ºC. A 2 MHz HIFU transducer (Sonic Concepts H106, Bothell, WA, USA) with an aperture size of 64 mm, a focal length of 62.6 mm and lateral and axial full width half maximum pressure dimensions of 1.05 mm and 6.67 mm respectively was used to perform boiling histotripsy. This HIFU source was experimentally characterised with a calibrated needle hydrophone (Precision Acoustics Ltd, Dorchester, UK) in our previous work [7]. A function generator (Agilent 33220A, Santa Clara, CA, USA) and a linear 55 dB power amplifier (ENI 1040L, Rochester, NY, USA) were employed to drive the transducer with the following pulsing protocol: a 10 ms-long HIFU pulse with either $P_{elect}$ = 200 W or 150 W electrical power supplied to the transducer. A power meter (Sonic Concepts 22A, Bothell, WA, USA) was connected between the HIFU source and the power amplifier to measure the level of electrical power $P_{elect}$. Acoustic peak pressure values at the focus with $P_{elect}$ = 200 W or 150 W and the corresponding temperature rises in an optically transparent tissue phantom were obtained by numerically solving the Khokhlov-Zaboloskaya-Kuznetsov (KZK) and the bioheat transfer (BHT) equations using the HIFU Simulator v1.2 [13]. From the simulations, the times to reach the boiling temperature of 100ºC were predicted to be 3.66 ms ($P_{elect}$ = 200 W, $P_+$ = 85.4 MPa, $P_-$ = – 15.6 MPa) and 6.97 ms ($P_{elect}$ = 150 W, $P_+$ = 71.5 MPa, $P_-$ = – 13.4 MPa). Figure 2 shows the calculated acoustic waveforms at the focus with the corresponding peak temperature in the phantom. The physical properties used in the KZK and the BHT simulations are provided in table 1.

During the experiments, the position of the HIFU source was fixed in the water bath whilst the tissue phantom was attached to a customised 3D positioning system. To minimise ultrasonic reflections, an acoustic absorber was placed on the opposite end of the water bath to the transducer. In addition, for recording purpose, a 10 MHz focused PCD transducer (Sonic Concepts Y107, Bothell, WA, USA) featuring of a wide bandwidth (10 kHz to 20 MHz) linked to an oscilloscope (LeCroy HDO 6054, Berkshire, UK) was employed to obtain acoustic emissions induced at the HIFU focus in the phantom during HIFU exposure. The recording was performed at a sampling frequency of 0.5 GHz.

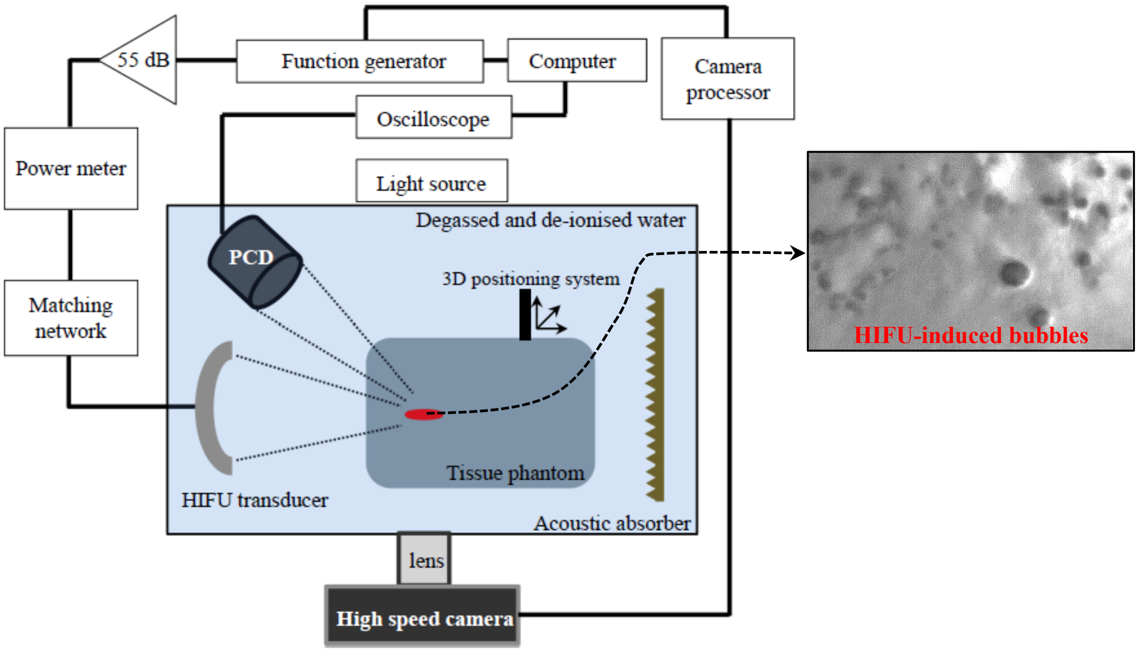


**Figure 1.** HIFU experimental set up used in the present study.

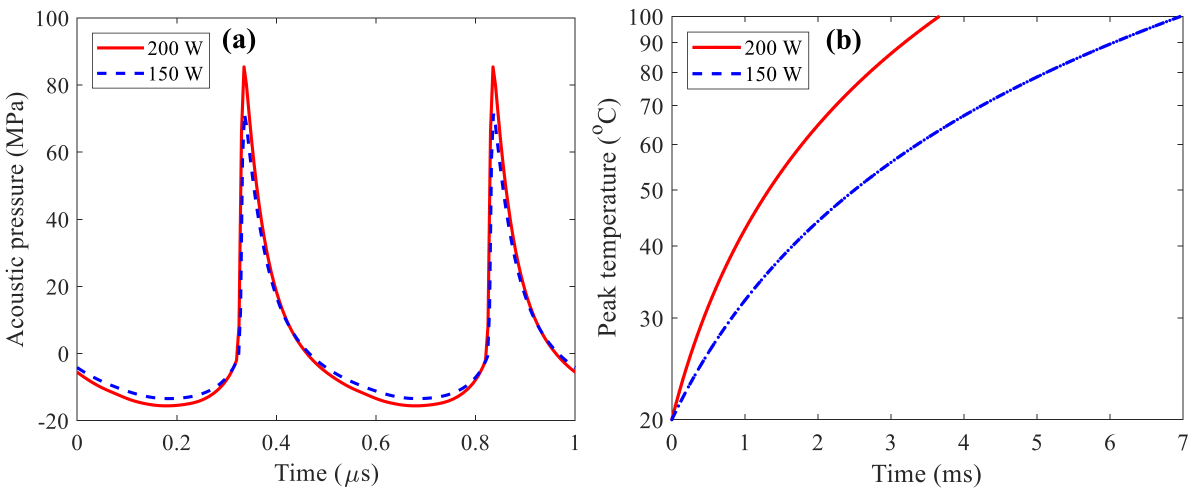


**Figure 2.** (a) Computed acoustic waveforms and (b) corresponding peak temperatures at the HIFU focus in the tissue phantom with $P_{elect}$ = 200 W (red solid lines, $P_+$ = 85.4 MPa, $P_-$ = – 15.6 MPa at focus) and 150 W (blue dashed lines, $P_+$ = 71.5 MPa, $P_-$ = – 13.4 MPa at focus). The times to reach boiling temperature of 100°C were respectively 3.66 ms and 6.97 ms.

**Table 1.** Physical properties of the tissue phantom used in the KZK and the BHT simulations. These parameters were obtained from [2].

| Properties | Value |
|---|---|
| Speed of sound | 1544 $ms^{-1}$ |
| Mass density | 1044 $kgm^{-3}$ |
| Absorption coefficient at 1 MHz | 15 $dBm^{-1}$ |
| Coefficient of nonlinearity | 4.0 |
| Specific heat capacity per unit volume | $5.3 \times 10^6$ $Jm^{-3o}C^{-1}$ |
| Thermal diffusivity | $1.3 \times 10^7$ $m^2s^{-1}$ |
| Ambient temperature | 20 $^oC$ |

In this work, an optically transparent tissue mimicking gel phantom (1.5 × 3 × 6 cm), which has similar acoustic and thermal properties to those of liver [2], was exposed to HIFU fields to examine (a) the dynamics of bubbles produced as well as (b) the level of mechanical damage induced at the HIFU focus. Prior to the experiments the phantom was kept at room temperature until its temperature reached 20$^o$C. A recipe for making this liver tissue phantom used, whose measured physical properties are shown in table 1, is well documented in [11]. The distance from the phantom surface to the centre of the HIFU transducer was 57.6 mm, whereby the HIFU focus was 5 mm below the surface of the phantom. A total of 23 tissue phantoms (i.e., 17 for $P_{elect}$ = 200 W and 6 for $P_{elect}$ = 150 W) was used in the present study.

### *2.2. High speed camera set up used*

A high speed camera (FASTCAM-ultima APX, Photron, San Diego, CA, USA) operating at 15,000 frame per second (fps) with a 12 X Navitar lens (Navitar, Rochester, NY, USA) was employed in this study to optically capture bubble dynamics induced at the HIFU focus in the gel phantom with a shutter speed of 1/15,000 s and a pixel resolution of 1028$\times$128 (24 µm/pixel). The HIFU exposure and the image capturing process were in sync together *via* a camera processor (FASTCAM-ultima APX, Photron). After the experiments, captured images were post-processed in Photron FASTCAM Viewer (Photron) for size measurements of bubbles. This was done by counting the pixels representing the bubble. Each measurement was repeated over three times All experiments were backlit with an illuminating system (Solarc ELSV-60, General Electric Company, Fairfield, CT, USA).

## 3. Results

Figures 3 and 5 respectively show series of high speed camera images captured during a 10 ms-long HIFU pulse with $P_{elect}$ of 200 W ($P_+$ = 85.4 MPa, $P_-$ = – 15.6 MPa) and 150 W ($P_+$ = 71.5 MPa, $P_-$ = – 13.4 MPa). For the case of $P_{elect}$ of 200 W, a boiling bubble forms at the HIFU focus at 3.6 ms, followed by the cavitation clouds progressing toward the HIFU transducer at 5.2 ms. The generation of more boiling bubbles within localised heated region can be seen at $t$ = 5.7 ms. The corresponding PCD results plotted in figure 4 also indicate the presence of a boiling bubble which manifested as a significant increase in the PCD voltage with the sudden appearance of higher order multiple harmonic components of the fundamental frequency (2 MHz) in the spectrogram. These significant changes are likely to be due to the formation of a boiling bubble because of the reflection of an incident shocked wave from this large boiling bubble (i.e., acoustic impedance mismatch) [8]. In addition, broadband emissions appear in the spectrogram after 3.6 ms, which is an indication of the presence of cavitation clouds (i.e., inertial cavitation) during the course of boiling histotripsy exposure [11]. Similar experimental trends are also observed in the case of $P_{elect}$ of 150 W ($P_+$ = 71.5 MPa, $P_-$ = – 13.4 MPa), where a boiling bubble appears at the HIFU focus (7.1 ms) with the subsequent formation of cavitation clouds at 8 ms, as shown in figure 5. In both HIFU exposure conditions ($P_{elect}$ of 200 W and 150 W), the onset time of the boiling bubble closely matched the computed time to reach a boiling temperature of 100°C in the tissue phantom. This is summarised in table 2.

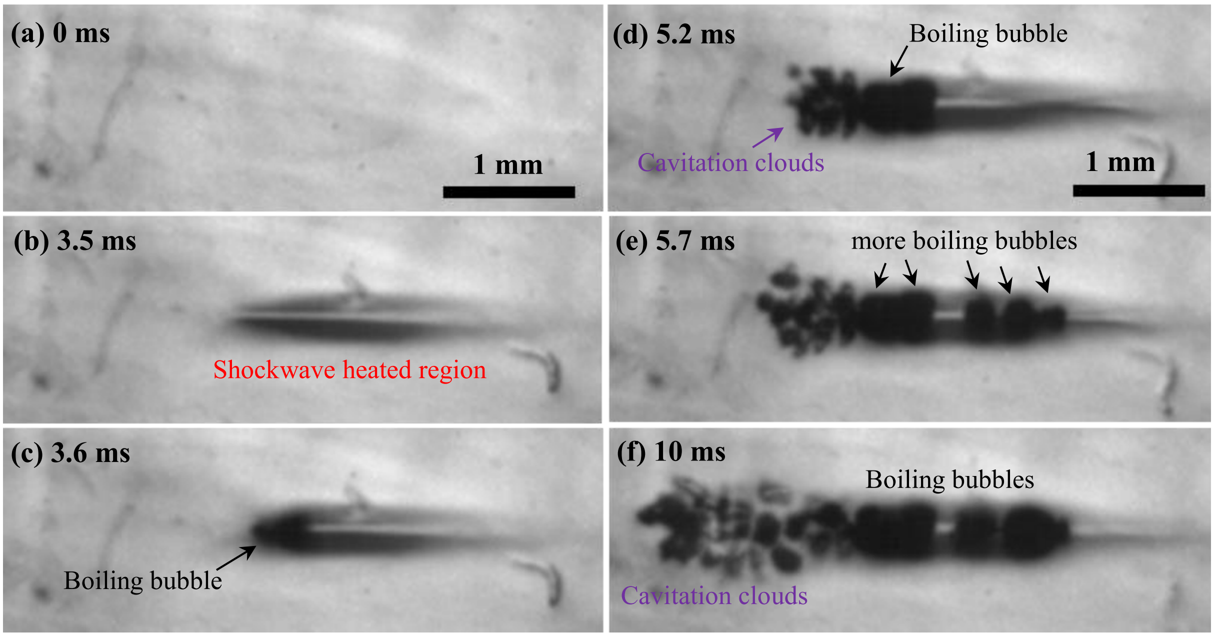


**Figure 3.** A sequence of high speed camera images (a)-(f) obtained in the tissue phantom during the 10 ms HIFU exposure with $P_{elect}$ of 200 W ($P_+ = 85.4$ MPa, $P_- = -15.6$ MPa). The HIFU beam propagates from left to right. The time at 0 ms indicates the start of the HIFU insonation. The corresponding PCD results are plotted in figure 4.

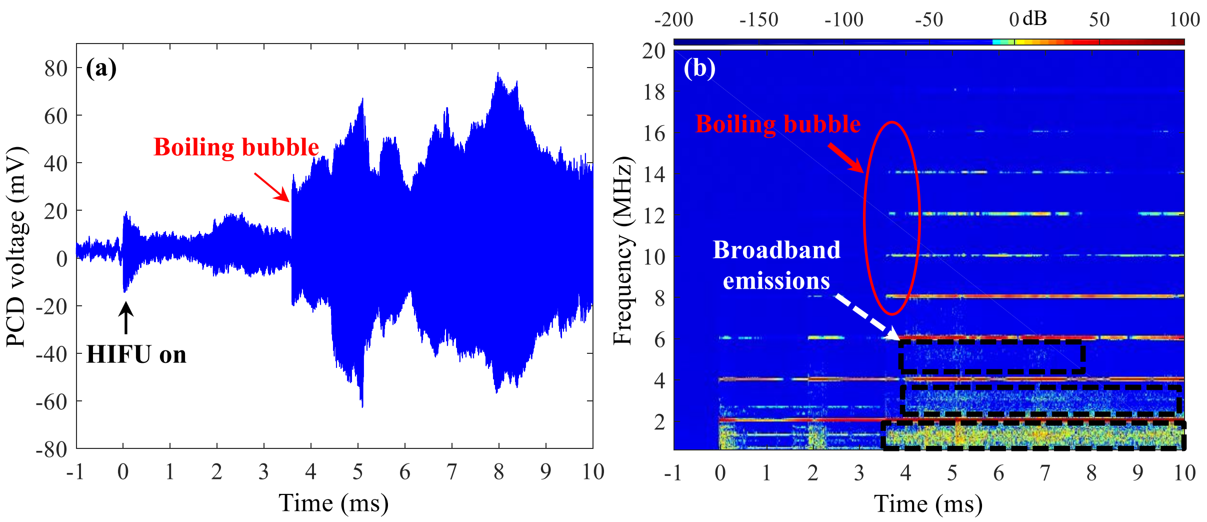


**Figure 4.** Acoustic emissions from the HIFU focus during the 10 ms HIFU pulse with $P_{elect} = 200$ W ($P_+ = 85.4$ MPa, $P_- = -15.6$ MPa). (a) The PCD voltage results. (b) The corresponding spectrogram of (a).

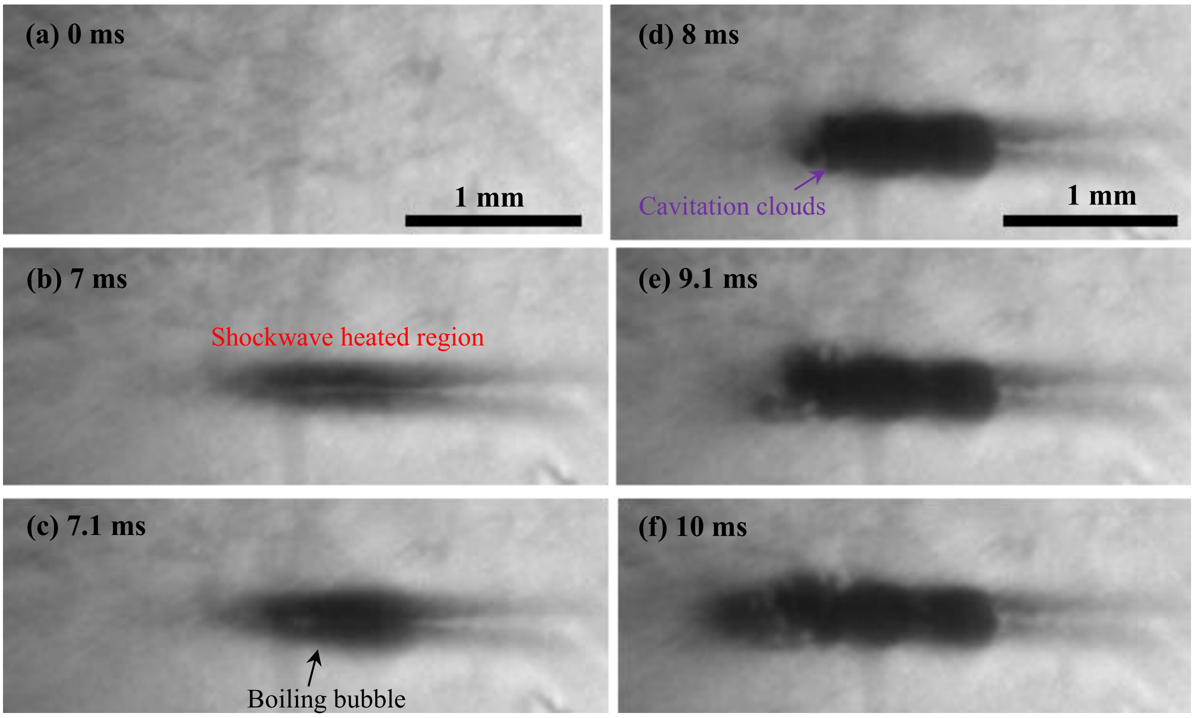


**Figure 5.** High speed camera images (a)-(f) obtained in the tissue phantom during the 10 ms HIFU exposure with $P_{elect}$ of 150 W ($P_+$ = 71.5 MPa, $P_-$ = – 13.4 MPa). The HIFU beam propagates from left to right. The time at 0 ms indicates the start of the HIFU insonation. The corresponding PCD results are plotted in figure 6.

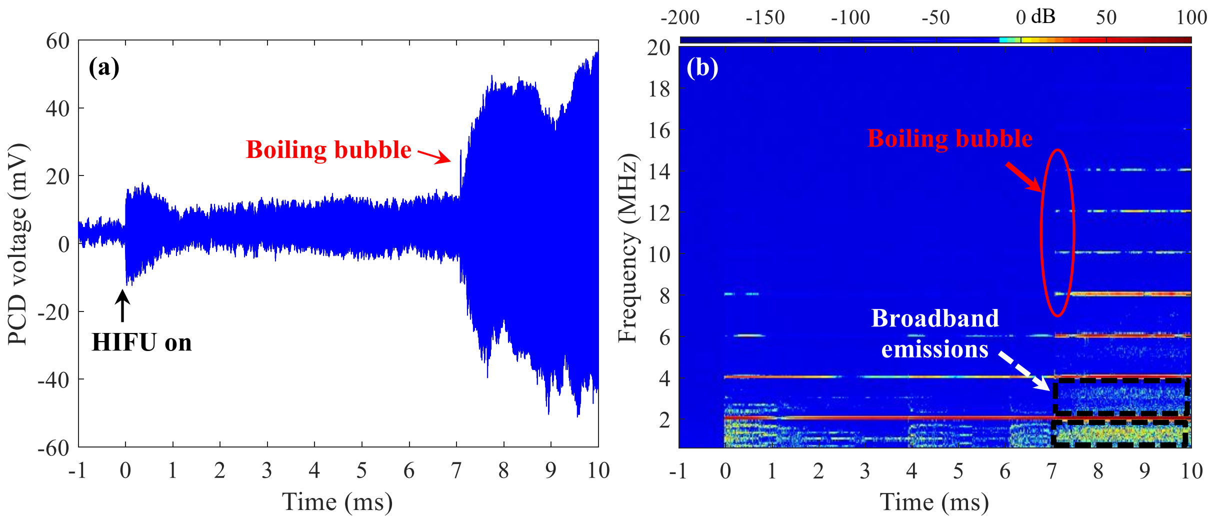


**Figure 6.** Acoustic signals emitted from the HIFU focus in the phantom during the 10 ms HIFU pulse with $P_{elect}$ = 150 W ($P_+$ = 71.5 MPa, $P_-$ = – 13.4 MPa). (a) The PCD voltage results. (b) The corresponding spectrogram.

**Table 2.** A comparison of the experimentally measured onset time of a boiling bubble and the temperature simulation of the time to reach 100ºC.

| Electrical power supplied to the HIFU transducer (W) | Simulated *in situ* acoustic peak pressures at focus (MPa) | Number of tissue phantom used | PCD measurements of the onset time of the boiling bubble | Temperature simulation of the time to reach 100ºC | Differences between the experiment and the simulation |
|---|---|---|---|---|---|
| 200 | $P_+ = 85.4$<br>$P_- = -15.6$ | 17 | *3.78 ± 0.67 ms | 3.66 ms | 0.12 ms |
| 150 | $P_+ = 71.5$<br>$P_- = -13.4$ | 6 | *7.32 ± 0.81 ms | 6.97 ms | 0.35 ms |

*mean ± standard deviation (SD) with *n* of 23 tissue phantoms

In our previous study, we hypothesised that the change of the dimension of a boiling histotripsy-induced lesion is primarily dependent on the extent of a localised heated region and the pressure amplitude of backscattered HIFU fields [11]. Although the effects of the formation and dynamic behaviour of a boiling bubble on acoustic and temperature fields were not accounted for in the simulations performed in this work, the numerical and experimental results shown in figure 7 can possibly support our hypothesis. In the case of $P_{\text{elect}}$ of 200 W ($P_+ = 85.4$ MPa, $P_- = -15.6$ MPa) exposure condition, a larger region is heated over a 10 ms of exposure time (see figures 7(a) and (b)), resulting in the formation of a larger boiling bubble within the heated volume (see figure 7(c)) compared to those with 150 W ($P_+ = 71.5$ MPa, $P_- = -13.4$ MPa). This larger boiling bubble with a larger surface area can then lead to the generation of a wider backscattered acoustic field, thereby creating a wider cavitation cluster toward the HIFU source (see figure 7(d)). As a result the size of a lesion produced with higher acoustic peak pressures is larger than that with lower acoustic pressures at a given sonication time (see figures 7(e) and (f)). In addition, the onset time of a boiling bubble with respect to a HIFU pulse length is also of importance for lesion production in boiling histotripsy, because the process of a mechanical tissue fractionation starts after the formation of a boiling bubble at the focus.

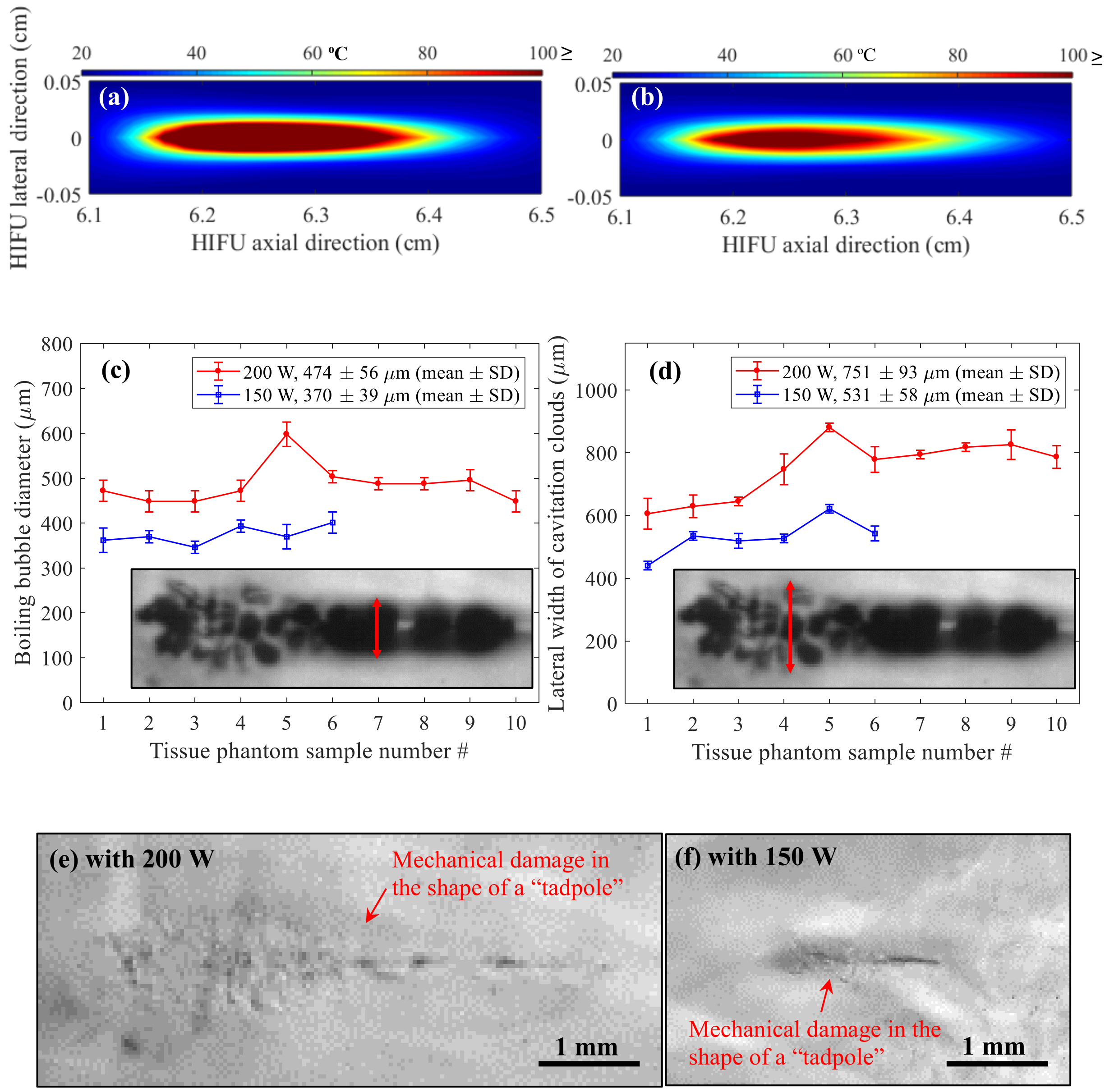


**Figure 7.** Computed contour plots of heated regions in the tissue phantom (a) with $P_{elect}$ of 200 W ($P_+$ = 85.4 MPa, $P_-$ = – 15.6 MPa) and (b) 150 W ($P_+$ = 71.5 MPa, $P_-$ = – 13.4 MPa) over a 10 ms exposure period. The lateral widths of the heated regions above 100°C are 220 μm and 110 μm for 200 W and 150 W, respectively. (c) Size measurement of a boiling bubble at the end of the HIFU pulse (mean ± standard deviation SD). (d) Width along the lateral direction of cavitation clouds at the end of the HIFU exposure. Each measurement was repeated three times. The inset images in (c) and (d) respectively show examples of the measurements of the maximum boiling bubble formed in the heated region and of the lateral width of cavitation clouds induced (24 μm/pixel). (e) and (f) are images showing the shape of a tadpole-like mechanical damages induced at the HIFU focus in the tissue phantom 80 ms after the end of the 10 ms HIFU exposure.

## 4. Conclusions

In this work, the effects of the size of a boiling bubble formed at the HIFU focus on lesion production in boiling histotripsy were investigated both experimentally and numerically. The results presented clearly demonstrated a positive relationship between the size of a boiling bubble and the degree of mechanical damage induced. In order to predict the lesion size at a given HIFU exposure condition, an accurate and reliable numerical model capable of dealing with scattering by localised heterogeneities (i.e. the presence of a boiling bubble at the HIFU focus) for simulating acoustic and temperature fields, would be required, which warrants further investigation in the near future.

## Acknowledgements

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