Evidence of the formation of the shock scattering induced violent cavitation cluster during boiling histotripsy insonation: A numerical case study

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Abstract. Boiling histotripsy is a promising noninvasive ultrasonic technique that can be used to mechanically destroy solid tumours. In boiling histotripsy, the formations and dynamics of a boiling vapour bubble and cavitation clouds contribute towards mechanical tissue fractionation. Whilst a number of numerical and experimental studies have been performed to examine and understand the evolution of a boiling bubble at the HIFU focus in a viscoelastic medium, little is known about the subsequent generation of cavitation clouds that form in between the boiling bubble and the HIFU transducer during boiling histotripsy insonation. Previous experimental observations suggest that the shock scattering by a boiling bubble may play a significant role in producing cavitation clouds. The main objective of the present study is, therefore, to investigate the relationship between the shock scattering phenomenon and the occurrence of cavitation clouds through (a) performing a numerical simulation of nonlinear wave propagation with the presence of a bubble at the HIFU focus and (b) comparing with the previous high speed camera observations of a cavitation cluster formation. The size of a bubble (i.e., 95.7, 128.1 and 258 μm in diameter) as well as the HIFU exposure conditions (i.e., a driving frequency of 1.1 MHz, peak positive and negative pressures of 68.4 MPa and –13.9 MPa) used in the simulations were obtained from the previous boiling histotripsy experiments conducted with a tissue gel phantom. The numerical results presented in this study clearly demonstrate that the shock scattering is the main cause of the creation of a cavitation cluster in boiling histotripsy.

1. Introduction
Boiling histotripsy is a High-Intensity Focused Ultrasound (HIFU) technique that employs a number of milliseconds long HIFU pulses with strong peak positive ($P_+$) and negative ($P_-$) pressures at the HIFU focus to mechanically fractionate soft tissue without inducing significant thermal damage [1]. $P_+$ and $P_-$ used in boiling histotripsy are comparable to those in the shockwaves used in lithotripsy for kidney stone fragmentation. Two different types of bubble activities are typically observed in boiling histotripsy: a boiling vapour bubble and an inertial cavitation cluster [2]. Whilst numerous studies have been performed to investigate and understand the formation and dynamics of a boiling bubble in a viscoelastic medium under boiling histotripsy excitation both numerically and experimentally [2-5], not much is known about the subsequent formation of cavitation clouds.

A shockwave used in boiling histotripsy can drastically increase tissue temperature to boiling temperature (e.g., 100°C) within a few milliseconds. Boiling occurs in times much shorter than the
characteristic heat diffusion time scale so that thermal diffusion can be neglected (i.e., a shockwave induced fast heating) [6]. The interaction of this localised shockwave heating with the incoming incident acoustic waves can subsequently create a boiling vapour bubble at the HIFU focus [2, 7]. This bubble then grows to a millimetre in size due to the asymmetry of the shape of a shockwave that is used to excite a bubble and water vapour that transports into the bubble at high temperature [5, 8]. Shear forces generated around a boiling vapour bubble can mechanically tear off soft tissue at the HIFU focus [3], resulting in the production of the tail part of a tadpole shaped boiling histotripsy lesion. It has been reported that the margins of the tail are sharply demarcated with smooth boundaries [3].

Along with the generation of a boiling bubble at the HIFU focus, inertial cavitation clouds can subsequently be produced between the boiling bubble and the HIFU transducer, progressing towards the opposite direction to wave propagation (i.e., towards the HIFU source) [2]. Strong micro jetting and shockwaves resulting from inertial bubble collapse in this cluster enable the mechanical destruction of soft tissue, producing the head of a tadpole shaped boiling histotripsy lesion. In contrast to the cellular structure observed around the tail, pits with ragged boundaries between the treated and untreated regions have been clearly observed around the head in vivo [3]. It has been hypothesised that the formation of this violent cavitation cloud in boiling histotripsy is most likely as a result of the shock scattering effect [2, 3]. The shock scattering effect, which can lead to additional cavitation nucleation sites, likely appears because of the interaction between the reflected and inverted positive pressure phase from a bubble and the incoming incident rarefractional phase. This interference may generate a greater peak negative pressure field [9].

Previous high speed camera observations of bubble dynamics induced in a liver tissue phantom under a 1.1 MHz boiling histotripsy excitation with $P_0$ of 68.2 MPa and $P_r$ of $-14.7$ MPa show that a cavitation cluster started to form after the formation and growth of a single cavitating 285 μm-sized bubble at the HIFU focus [10]. This subsequent cavitation cluster event would likely be attributable to the constructive interaction of backscattered acoustic fields by the bubble with incoming incident shockwaves [2, 3]. To gain further insight into this observed phenomenon, in this study, a 2D numerical simulation of a 1.1 MHz nonlinear wave propagation with the presence of a bubble at the HIFU focus in a tissue phantom is performed. Numerical results of negative pressure fields produced around a bubble are also compared with the experimental results reported in [10].

2. Numerical methods

In the present study, a 1.1 MHz nonlinear HIFU field around a scatterer (i.e., a bubble) was simulated using the open source k-Wave v1.2 MATLAB toolbox. The experimental validation of k-Wave, which numerically solves the generalised Westervelt equation that accounts for heterogeneities in the ambient mass density, material nonlinearity (up to second-order) and power law absorption and dispersion [11], has been previously carried out for nonlinear wave propagation in a homogeneous medium as well as in a heterogeneous medium with simple geometric scatterers. In addition, k-Wave has been previously employed in a number of studies for simulating nonlinear wave propagation through multiple tissue layers such as skin, muscle, blood vessels and ribs [12].

Figure 1 shows a schematic diagram of the 2D geometrical model used in the k-Wave simulations performed in this study. The same HIFU transducer model (#H102, Sonic Concepts, Bothell, USA) used in [10] was considered here (i.e., a 1.1 MHz single element bowl-shaped HIFU transducer with an aperture size of 64 mm and a radius of curvature of 63.2 mm). In the k-Wave model, 1.1 MHz acoustic waves travelled through a layer of water followed by a liver tissue phantom layer. A bubble was modelled as a non-translational 2D infinite cylinder whose acoustic properties are equal to those of vapour. For simplicity, this bubble was located at the HIFU focus (i.e., 63.2 mm in the axial direction) and the potential effects of acoustic emissions emitted during bubble oscillations under HIFU excitation on wave propagation were not accounted for (i.e., resonant oscillations of a free bubble were not modelled here). The total grid size of $2^{14} \times 2^{14}$ points, a computational domain size of 73.4 mm $\times$ 73.4 mm including a perfectly matched layer on each side of the domain, 300 points per wavelength and a CFL number of 0.05 with a temporal step of 0.15 ns and a grid spacing of 4.49 μm in both the axial and
lateral directions were employed in the simulations. All k-Wave simulations were conducted on a desktop PC with 3.6 GHz CPU (i9-9900K), 64 GB of RAM and NVIDIA GeForce RTX 8000 (48 GB) GPU. Each simulation took around 100 hours to complete. The physical properties of water, liver tissue phantom and a bubble used in the k-Wave simulations are tabulated in Table 1. For comparing the experimental results reported in [10], the pressure amplitude of a 1.1-MHz input sinusoidal signal used in the simulations gradually increased until the simulated peak positive and negative pressure values at the HIFU focus in the absence of a bubble were similar to those used in [10] (i.e., within a difference of 10%). The size of a bubble employed in the simulations was also varied as 95.7, 128.1 and 285 μm, which were obtained from [10].

![Diagram of the geometrical model used in the k-Wave simulations conducted in the present study.](image)

**Figure 1.** A schematic diagram of the geometrical model used in the k-Wave simulations conducted in the present study.

**Table 1.** Physical properties used in the simulations [13]

|                          | Water      | Liver tissue phantom | Vapour bubble | Units     |
|--------------------------|------------|----------------------|---------------|-----------|
| Speed of sound           | 1482       | 1544                 | 477.5         | m s⁻¹     |
| Density                  | 1000       | 1044                 | 0.598         | kg m⁻³    |
| Attenuation coefficient  | 0.217      | 15                   | 164*          | dB m⁻¹ MHz⁻¹|
| Nonlinear parameter (B/A)| 5          | 6                    | 0.4*          | -         |
| Power law exponent (y)   | 2          | 0.93                 | 2*            | -         |

*obtained for air; *assumed to equal to water.

3. Results
Simulated 2D spatial distributions of 1.1 MHz nonlinear acoustic fields and 1D nonlinear waveforms at a given distance (i.e., at 61.33 mm, 62.03 mm, 62.97 mm and 64.37 mm) in the HIFU axial direction in the absence of a bubble are plotted in Figure 2. A nonlinear waveform with \( P_+ \) of 68.4 MPa and \( P_- \) of –13.9 MPa can be obtained from the k-Wave simulations with the input parameters used in the present study. The differences between the simulated peak positive and negative pressure values and those employed in [10] were, respectively, 0.2 MPa (i.e., a difference of 0.29%) and –0.8 MPa (i.e., a difference of 5.44%). As can be seen, the wave asymmetry is greatest at the HIFU focus where nonlinear effects are the strongest (Figure 2e).

Figure 3 shows the simulated nonlinear acoustic fields generated around a 285 μm-sized bubble at the HIFU focus in the tissue phantom with the same input parameters used to obtain Figure 2. The bubble size was obtained from [10]. It is observed that stronger peak positive (Figure 3a) and negative (Figure
3b) pressure fields are generated between the bubble and the HIFU transducer, compared to those predicted without the bubble at the HIFU focus. The highest peak positive ($P_+ = 83.04$ MPa) and negative pressure ($P_- = -29.9$ MPa) magnitudes occur at 63.05 mm and 63.02 mm in the axial direction (i.e., in front of the bubble towards the HIFU source), respectively. This increase in the peak pressure magnitude is likely to be due to the constructive interference of the backscattered wave by the bubble with the incoming incident acoustic waves (Figure 3e) [13].

**Figure 2.** Simulated 1.1 MHz nonlinear acoustic fields without a bubble at the HIFU focus with $P_+$ of 68.4 MPa and $P_-$ of $-13.9$ MPa. The simulated 2D spatial distributions of (a) positive $|p_+|$ and (b) negative $|p_-|$ pressure fields. Images (c, d, e and f) are, respectively, show the computed 1D waveforms at 61.33
mm, 62.03 mm, 62.97 mm and 64.37 mm in the HIFU axial direction. The simulations were conducted over $t = 60 \mu s$. The HIFU beam propagates from left to right.

Figure 3. Simulated 1.1 MHz nonlinear acoustic fields with a 285 $\mu$m-sized vapour bubble at the HIFU focus. The simulated 2D spatial distributions of (a) positive $p_+$ and (b) negative $|p_-|$ pressure fields. Figures (c, d, e and f) are, respectively, represent the computed 1D waveforms at 61.33 mm, 62.03 mm, 62.97 mm and 64.37 mm in the HIFU axial direction. The simulations were conducted over $t = 60 \mu s$. The HIFU beam propagates from left to right.

Moreover, 2D negative pressure fields in the presence of a bubble with different size are simulated and plotted alongside with a number of high speed camera images obtained from [10]. This comparison is shown in Figure 4. Briefly, in [10], bubble dynamics induced at the HIFU focus in an optically
transparent liver tissue phantom, particularly the formation of cavitation clouds, were captured using a high speed camera operating at 15,000 frames per second with a pixel resolution of 1024 × 128 (116 μm/pixel). From the high speed images shown in Figure 4, it can be clearly noticed that cavitation clouds appear when a bubble grows to 285 μm (~1/5th of the wavelength at 1.1 MHz) (Figure 4d) from 95.7 μm (~1/15th of the wavelength, Figures 4b and c). Numerical results shown in Figures 4(e) to (h) indicate the relationship between the magnitude of negative pressure fields produced and the size of a bubble $D_{\text{bubble}}$. The simulated peak negative pressure value is $-13.9$, $-22.4$, $-23.3$ and $-29.9$ MPa at $D_{\text{bubble}} = 0$ (Figure 4e), $D_{\text{bubble}} = 95.7$ (Figure 4f), 128.1 (Figure 4g) and 285 μm (Figure 4h), respectively. Interestingly, the latter pressure value of $-29.9$ MPa is above the cavitation cloud’s intrinsic threshold of $-28$ MPa, which is the reported threshold for negative pressure at which cavitation clouds are almost certain to occur in soft tissue [14, 15]. Furthermore, the spatial distribution of the cavitation clouds observed in Figure 4(d) closely matches that of the simulated 2D negative pressure fields plotted in Figure 4(h).

The numerical results depicted in Figures 2 to 4 together with the previous boiling histotripsy studies [2-5, 13] can (a) support the hypothesis of the formation of cavitation clouds in boiling histotripsy as a result of the shock scattering, and also (b) suggest that this bubble cluster formation is a threshold event which is mainly dependent upon the negative pressure magnitude of backscattered fields as well as the size of a bubble produced at the HIFU focus. Though there is a qualitative agreement between the experimental results and the numerical simulations performed in the present study, a larger number of points per wavelength and a smaller CFL number would be required in order to fully capture a steep shock wave front for a better agreement as well as to predict the shape of a boiling histotripsy lesion under a given HIFU exposure condition, which warrants further investigation in the future, with a numerical scheme better suited to this problem than k-Wave.

![Figure 4](image-url)  
**Figure 4.** A direct comparison between the numerical simulations and the experimental results. Upper images (a) to (d) represent the high speed camera results showing the bubble dynamics induced in a liver tissue phantom, whereas (e) to (h) show the simulated 2D spatial distributions of negative $|p|$ pressure fields for a given bubble size: 0, 95.7, 128.1 and 285 μm in diameter. The 1.1 MHz HIFU beam with $P_+$ of 68.4 MPa and $P_-^{*}$ of $-13.9$ propagates from left to right. High speed images (a to d) were reproduced with permission from [10].

### 4. Conclusions

The numerical study of a 1.1 MHz nonlinear wave propagation with the presence of a bubble was carried out to examine the shock scattering effect and compare with the experimental observations of cavitation clouds formation in boiling histotripsy. The results presented clearly indicate that the shock scattering by a bubble is the main cause of the generation of a violent bubble cluster during boiling histotripsy.
exposure. Furthermore, the backscattered peak negative pressure magnitude and the size of a boiling vapour bubble can significantly affect the degree of the shock scattering effect.

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