# Enhancement of Boiling Histotripsy by Steering the Focus Axially During the Pulse Delivery

Gilles P. L. Thomas<sup>®</sup>, Tatiana D. Khokhlova<sup>®</sup>, *Member, IEEE*, Oleg A. Sapozhnikov<sup>®</sup>, and Vera A. Khokhlova<sup>®</sup>

Abstract—Boiling histotripsy (BH) is a pulsed high-intensity focused ultrasound (HIFU) method relying on the generation of high-amplitude shocks at the focus, localized enhanced shock-wave heating, and bubble activity driven by shocks to induce tissue liquefaction. BH uses sequences of 1-20 ms long pulses with shock fronts of over 60 MPa amplitude, initiates boiling at the focus of the HIFU transducer within each pulse, and the remainder shocks of the pulse then interact with the boiling vapor cavities. One effect of this interaction is the creation of a prefocal bubble cloud due to reflection of shocks from the initially generated mm-sized cavities: the shocks are inverted when reflected from a pressure-release cavity wall resulting in sufficient negative pressure to reach intrinsic cavitation threshold in front of the cavity. Secondary clouds then form due to shock-wave scattering from the first one. Formation of such prefocal bubble clouds has been known as one of the mechanisms of tissue liquefaction in BH. Here, a methodology is proposed to enlarge the axial dimension of this bubble cloud by steering the HIFU focus toward the transducer after the initiation of boiling until the end of each BH pulse and thus to accelerate treatment. A BH system comprising a 1.5 MHz 256-element phased array connected to a Verasonics V1 system was used. Highspeed photography of BH sonications in transparent gels was performed to observe the extension of the bubble cloud resulting from shock reflections and scattering. Volumetric BH lesions were then generated in ex vivo tissue using the proposed approach. Results showed up to almost threefold increase of the tissue ablation rate with axial focus steering during the BH pulse delivery compared to standard BH.



Index Terms— Boiling histotripsy (BH), cavitation cloud, high-intensity focused ultrasound (HIFU).

Manuscript received 5 May 2023; accepted 9 June 2023. Date of publication 15 June 2023; date of current version 2 August 2023. This work was supported by the NIH under Grant R01EB007643, Grant R01GM122859, and Grant R01EB025187. (Corresponding author: Gilles P. L. Thomas.)

Gilles P. L. Thomas is with the Center for Industrial and Medical Ultrasound, Applied Physics Laboratory, University of Washington, Seattle, WA 69424 USA (e-mail: gillespierre.thomas@gmail.com).

Tatiana D. Khokhlova is with the Division of Gastroenterology, University of Washington School of Medicine, Seattle, WA 98105 USA.

Oleg A. Sapozhnikov and Vera A. Khokhlova are with the Center for Industrial and Medical Ultrasound, Applied Physics Laboratory, University of Washington, Seattle, WA 69424 USA, and also with the Physics Faculty, Moscow State University, 119991 Moscow, Russia.

This article has supplementary downloadable material available at https://doi.org/10.1109/TUFFC.2023.3286759, provided by the authors. Digital Object Identifier 10.1109/TUFFC.2023.3286759

#### I. INTRODUCTION

**B**OILING histotripsy (BH) is a high-intensity focused ultrasound (HIFU) method to generate mechanical disintegration of tissue via a combination of complex physical processes [1]. These processes include the generation of high-amplitude shocks at the focus due to nonlinear propagation effects yielding rapid initiation of localized boiling [2], [3], interaction of shock waves with a boiling cavity resulting in the generation of bubble clouds in front of the cavity [1], [4], [5], ejection and atomization of tissue debris into the cavity [6], and high-speed streaming in the liquefied tissue [7]. BH treatment can be readily monitored in real time using

1525-8955 © 2023 IEEE. Personal use is permitted, but republication/redistribution requires IEEE permission. See https://www.ieee.org/publications/rights/index.html for more information.

#### **Highlights**

- In this work the lesion created by boiling histotripsy is extended by steering the focus of the HIFU during the delivery
  of the pulse.
- Results show that the extension of the lesion increase the boiling histotripsy ablation rate up to almost threefold compared to standard boiling histotripsy.
- This work showed that it was possible to greatly increase the boiling histotripsy ablation rate for faster clinical treatment.

B-mode [1], [5] and Doppler ultrasound [7] as the presence of BH-generated bubbles yields the appearance of a hyperechoic region at the focus during sonications and mechanical destruction of tissue removes tissue scatters, producing a hypoechoic cavity after the treatment is completed. BH lesions have sharp margins between the disintegrated and intact tissues, while causing negligible thermal effect on the surrounding tissues [8], [9], [10], [11], [12]. The treatments can be safely delivered transcutaneously and partially transcostally, allowing noninvasive ablation of targets in the liver and kidneys [10], treatments of abscesses [11], liquefaction of hematomas [12], ablation of prostate tissue [13], [14], noninvasive liquid biopsies [15], and tissue decellularization [9], [16].

The method uses sequences of millisecond-long-from 1 to 20 ms-focused pulses with shocks, delivered at a low duty cycle of 1%–2% [1], [17]. Periodic shocks of each pulse with shock amplitudes over 60 MPa heat the tissue at the focus up to the boiling point in a few milliseconds [3], resulting in the creation of mm-sized vapor cavities before the end of the pulse. Most BH exposures utilize acoustic output levels close to the one at which fully developed shocks form in the pressure waveform at the focus, i.e., when its amplitude coincides with peak positive pressure [18]. The remaining shocks of the pulse then interact with the boiling vapor cavities, resulting in a tadpole-shaped lesion [1], [12]. BH differs from shock-scattering cavitation histotripsy, in which the pulses usually are of lower frequency, higher amplitude, and are only a few-around 5-20-cycles long, also delivered at similar duty cycle [19], [20]. Generation of bubble clouds in this case relies on scattering and inversion of the shock fronts of each wave cycle off the surface of cavitation bubbles from the previous wave cycle (shock-wave scattering mechanism) [4]. However, this method requires preexisting bubbles to be present at the focus to initiate the shock scattering process. Those bubbles have probability to appear depending on the peak negative pressure of the waveform [21], number of cycles [22], frequency [23], temperature [24], and mechanical properties of the medium [23], [25]. Bubble clouds can be also reliably generated without shocks if the peak negative pressure at the focus is very high, exceeding the intrinsic cavitation threshold of about -28 MPa (microtripsy) [21], [26]. A combination of intrinsic threshold histotripsy and shock-scattering phenomenon has been used to elongate the size of the bubble cloud with short monopolar pulses [27].

In BH, the shock-scattering mechanism also plays an important role and contributes to the lesion creation [1], [5].

Generation of the bubble cloud starts when the first boiling cavity forms in the focal region of the BH beam. The shocks are inverted when reflected from a pressure-release cavity wall resulting in negative pressures sufficient to reach intrinsic cavitation threshold and generating a bubble cloud in front of the cavity. This cloud then serves as a pressure-release region and extends toward the transducer due to shock-wave scattering from the bubbles. Diffraction of the incoming cycles of the BH pulse at the existing vapor cavity combined with the refraction within prefocal bubble cloud may generate additional vapor bubbles behind the initial one, i.e., distally to the focus [1], [2], [28].

While having several potential clinical advantages, the volumetric ablation speed of BH treatments is lower than the characteristic ablation rates of the thermal therapies. For example, the ablation rate in thermal treatments of uterine fibroids using a MR-HIFU system (Sonalleve Philips Health-care, Vantaa, Finland) was about 60 cc/h [29], whereas for BH treatments in ex vivo bovine liver tissue using the same system and standard 10 ms pulses with 1% duty cycle, the volumetric mechanical ablation rate was 2.4 cc/h [9]. BH studies using other systems reported an ablation rate of 1.9 cc/h for the in vivo treatment of porcine liver tissue [10], and up to 36 cc/h for ex vivo hematoma treatments [12].

The axial size of the bubble cloud resulting from shock scattering in a standard BH treatment is limited by the prefocal point where the sum of the incident and reflected pressures is not sufficient to exceed the intrinsic cavitation threshold [5]. This bubble cloud is thought to be responsible for the proximal part of the BH lesions, i.e., the "head" of their tadpole shape. The size of the BH lesion is thus limited in a similar manner. As such, the idea in this work was to extend the axial dimension of this bubble cloud by moving the focus axially toward the BH transducer within the duration of each BH pulse after vapor bubbles were created, thus generating an elongated bubble cloud through shockscattering mechanism. The feasibility of this approach was first demonstrated in optically transparent tissue-mimicking gels. High-speed photography was used to observe the evolution of the bubble cloud during the focus steering and to perform a limited parameter optimization. Using parameters of BH pulses that ensured the desired formation of the cavitation clouds in gels, the method was then applied to ex vivo bovine cardiac tissues to generate volumetric lesions of different sizes. The ablation rates achieved using this new approach were compared to the standard BH protocol without focus steering.

#### 867

## II. MATERIALS AND METHODS

# A. BH System

The BH transducer used in this work was a 1.5 MHz, 256-element spiral array made from composite piezoelectric material (Imasonic, Voray sur l'Ognon, France), and described in detail in our previous studies [30], [31], [32]. Briefly, the array was spherically focused with a radius of 120 mm, had an outer diameter of 144 mm, and a central opening of 40 mm diameter for mounting an inline ultrasound imaging probe with a -6 dB bandwidth between 2.2 and 5.2 MHz (3PE, Humanscan, Gyeonggi-do, South Korea). The elements of the array were circular with a diameter of 7 mm, and arranged in 16 spiral branches with a minimum of 0.5 mm spacing between the elements.

The array was electrically matched and connected to a four-board Verasonics V1 system (V-1 Ultrasound Acquisition platform, Verasonics Inc, Kirkland, WA, USA) with HIFU option. The Verasonics system was modified by adding seven electrolytic capacitors (B41560A9159M000, EPCOS, Munich, Germany) identical to the internal dc power supply in parallel with the external 1200 W dc power supply from the HIFU option (QPX600DP, Aim-TTI, Huntingdon, U.K.)

This BH system has been fully characterized in nonlinear regime and at acoustic power outputs relevant to BH in a previous publication [32]. Specifically, it was shown that boiling could be reached in polyacrylamide (PA) gels and ex vivo tissues within a 10 ms BH pulse at the acoustic power of 251 W. At this power, the peak positive pressure in free field in water at the focus was 96 MPa, the peak negative pressure was -17 MPa, and the dimensions of the focal lobe for the peak positive pressure at -6 dB level were 3.7 mm axially and 0.32 mm laterally. When used for volumetric BH lesions, the electronic steering of the system was limited to a maximum of  $\pm 6$  mm transversely and  $\pm 6$  mm axially around the geometric focus [7].

The inline ultrasound imaging probe was connected to a separate two-board Verasonics V1 system. The B-mode imaging rate was 27 Hz, and during each BH pulse, the probe was passively recording at a sampling rate of 18 MHz the backscattered BH waves and broadband noise emissions from cavitation bubbles, thus serving for passive cavitation detection (PCD).

#### B. Steered BH

The concept of a modified BH method investigated in this work is illustrated in Fig. 1 for a 10 ms BH pulse. First, a vapor cavity (boiling bubbles) must be generated at the focus within the length of the BH pulse. As such, the acoustic power required to reach boiling in the gel or tissue before the steering starting time  $t_s$  had to be found. Experimentally, the time-to-boil  $t_b$  was determined by looking at the transducer array backscattered signal-here recorded by the ultrasound imaging probe and referenced as PCD signal. When boiling starts, the PCD signal becomes noticeably stronger, with a substantial increase of broadband noise and harmonics level as a result of the cavitation in front of the vapor cavity and reflections of nonlinear BH pulse from bubbles at the focus [28], as shown in Fig. 2. As there was a certain variability in the time-to-boil  $t_b$ , it was verified to be less than 80% of  $t_s$  during a treatment



Fig. 1. Illustration of the cavitation cloud extension within a 10 ms pulse of steered BH. The black cross indicates the current position of the transducer array focus. (a) Beginning of a BH pulse rapidly heats a small region at the focus up to boiling temperature. (b) At  $t_b$ , a vapor bubble is created and its subsequent interaction with upcoming shocks of the BH pulse generates an initial layer of bubble cloud prefocally as a result of shock scattering. (c) At  $t_s$ , the focus is electronically steered toward the transducer array with a step  $\Delta z$ . Shock scattering interactions with the previously created bubble cloud generates an ew layer of bubble cloud. (d) and (e) Previous step is repeated *n* times for every time step  $\Delta t$  until the end of the BH pulse, here 10 ms.



Fig. 2. Example of the normalized PCD signal recorded by the central element of the inline imaging probe during a BH pulse (top) with its corresponding spectrogram (bottom). Boiling and subsequent reflections of nonlinear BH waves and cavitation cause a noticeable increase in broadband noise and harmonics level [3], [28].

of eight pulses at five different positions. The pressure level at the focus for that acoustic power was then obtained from previous characterization of that BH transducer array [32].

Once the vapor cavity was created, reflection of the shocks generated an initial layer of a bubble cloud prefocally. Then, at  $t_s$  when this first layer of bubbles had already been formed, the focus was electronically steered toward the transducer array with a step  $\Delta z$ . A new cloud of bubbles was then generated by scattering the upcoming shocks in the BH pulse off the previously created bubble cloud, and extended it further toward the transducer. This process of steering the BH focus axially, and thus extending the bubble cloud length through shock-scattering, was repeated *n* times with the same  $\Delta z$  step for every time step  $\Delta t$  until the end of the 10 ms BH pulse. Because the axial steering of the BH focus played a major role in the resulting cavitation cloud and lesion formation, this method will be referred to as "steered boiling histotripsy" or steered BH, throughout the manuscript.

In this method, four parameters might impact the creation of the bubble cloud and the lesion generated, namely the total length of the BH pulse, the time  $t_s$  when the steering starts, the spatial step  $\Delta z$ , and the temporal step  $\Delta t$ . As this work focuses on the feasibility of the proposed method as an alternative to the standard BH exposure, most of those parameters were constant. As such, the length of the BH pulse was set constant and equal to 10 ms, as it is the most commonly used value in the BH exposure protocols [17]. The time  $t_s$  depends on the value of the time-to-boil,  $t_b$ , that has to be determined experimentally. However, previous studies have shown that boiling can be reached in less than 1 ms [9], [10]. The value of the spatial step  $\Delta z$  was variable and its range was verified experimentally. If chosen too large, the shock-scattering effect might not occur and thus the bubble cloud would not be extended. The maximum value of the spatial step was also limited by the electronic steering capabilities of the array. Here, the maximum axial steering was chosen as  $\pm 6$  mm around the geometric focus as in previous BH studies done with this array on BH volumetric lesions [7]. Finally, the temporal step  $\Delta t$  was set as constant and equal to 0.5 ms. Previous work on shock scattering demonstrated that only a small number of acoustic cycles-between 5 and 20-was needed to extend the bubble cloud to its maximum size, reaching the point where the peak negative pressure in the scattered wave does not exceed the intrinsic threshold [4], while BH lesions could be made with 1 ms pulse, including time-to-boil [9], [10]. This suggest that 0.5 ms would be sufficient for both the extension of the bubble cloud and the generation of lesion typical for BH.

## C. High-Speed Photography in Gel Phantoms

High-speed photography of steered BH exposures in transparent gel phantoms was performed to directly observe the initiation of boiling and cavitation cloud formation. A diagram of the experimental setup is shown in Fig. 3. The experiments were performed at room temperature of 20 °C in a glass-wall tank filled with deionized water, degassed to below 20% oxygen saturation with an in-house built degassing system. The BH array was fixed on one side of the tank, and a polyurethane rubber acoustic absorber was placed on the opposite side to minimize reverberations. The gel samples were placed in a custom 3-D-printed holder and positioned in the tank using a three-axis positioning system (Velmex Inc., Bloomfield, NY, USA). A high-speed camera (Fastrax APX-RS, Photron, San Diego, CA, USA) in combination with



Fig. 3. Experimental setup for high-speed optical imaging of the steered BH sonications in transparent gels.

a diffuse LED light on the other side of the tank were used to record the bubble activity resulting from the steered BH pulses inside the gel samples positioned in-between. The photographs were captured with a shutter speed of 4  $\mu$ s in a plane collinear to the axis of the BH transducer array. A 105 mm lens (Nikon, Melville, NY, USA) was used to obtain a resolution of 27  $\mu$ m per pixel. Recordings were made at 20 and 100 kfps with a field of view of 512 × 256 pixels (13.8 × 6.9 mm) and 256 × 32 pixels (6.9 × 0.9 mm), respectively.

Different steered BH exposures were tested in PA gel phantoms [33] without bovine serum albumin. This gel has acoustic properties very close to tissues and allows for visualization of the vapor and shock scattering bubbles during BH sonications. After BH sonications, the areas damaged by cavitation were visibly darker [28], [34], allowing for visualization of the region affected by cavitation during the treatment. The gel samples were prepared within 48 h of the experiments into plastic molds of  $80 \times 50 \times 50$  mm. The samples were then cut in half to a final size of  $80 \times 50 \times 25$  mm before being placed in the sample holder inside the water tank. For all the treatments, the geometric focus of the BH transducer array was 20 mm deep inside the gels. As a consequence of the gel samples being cut, and also due to small bubbles present at the gel/mold interface during polymerization, some artifacts could be seen on the high-speed photographs. These artifacts were purely visual, easily recognizable, and did not affect the experiment in any way.

Repeatable boiling in PA gels was reached in less than 2 ms for the acoustic power of 608 W, and thus  $t_s$  was set equal to 2.5 ms for all the following experiments. The focal beam shape of the peak positive and negative pressures, as well as two cycles of the focal waveform, which correspond to this acoustic power, were matched with a previous characterization of the transducer made using acoustic holography and nonlinear modeling [32] and are shown in Fig. 4. At this power, the peak positive pressure in free field in water at the focus was 132 MPa and the peak negative pressure was -20 MPa with a shock amplitude of 136 MPa, and the dimensions of



Fig. 4. Focal characteristics of the BH pulse at 608 W acoustic power, obtained by acoustic holography and nonlinear modeling [32]. Distributions of peak positive and peak negative pressures: (a) transversely and (b) axially. (c) Two cycles of the pressure waveform at the focus.

the focal lobe for the peak positive pressure at -6 dB level were 4.7 mm axially and 0.35 mm laterally.

High-speed imaging of a standard 10 ms BH treatment (i.e., no steering) was made to have a comparison point. For all gel experiments, a treatment consisted of up to eight pulses focused on the same position, with 1 min between each pulse to allow for bubble nuclei to dissolve and avoid any heat accumulation. The number of pulses per focus was chosen based on the results of previous study where eight BH pulses were needed to generate a complete lesion in cardiac tissue using the same BH array [35]. Then, multiple steered BH treatments were performed and recorded at different locations in the gel for different values of the spatial step  $\Delta z$ . A steered BH treatment was considered successful if for every pulse the continuous trail of shock-scattering bubbles was generated.

#### D. Ex Vivo Tissue Volumetric Treatments

The experimental arrangement used for the ex vivo exposures was the same as in Fig. 3, without the camera and light, and by replacing the gel samples with ex vivo bovine cardiac tissue samples. Bovine heart tissue was used, as it allowed to easily make gross evaluation of the BH lesions [35], [36]. A fresh bovine heart was obtained from a local abattoir and kept on ice during transportation and before the experiments. The heart was cut into samples of about  $70 \times 40 \times 40$  mm size, and any pericardial fat was removed from the samples if present. The heart tissue samples were then placed into cold degassed saline solution and degassed in a desiccant chamber for over an hour. Agarose solutions were prepared in parallel by mixing agarose powder (UltraPure Agarose, Invitrogen) into deionized water (1.5% wt./vol agarose/water), and was then boiled in a microwave oven to displace any dissolved gases present. The agarose solution was then poured into plastic molds of  $80 \times 50 \times 50$  mm and left to cool. Once the temperature of the agarose solution reached 40 °C, the tissue samples were placed into the molds and left to polymerize in a cold water bath for about 30 min.

The acoustic power required to reliably reach boiling in the bovine heart tissue in less than 2 ms was found to be the same as in PA gels, and thus the same value of  $t_s = 2.5$  ms as in the previous section was used. Then, volumetric treatments using different spatial step  $\Delta z$ , with values in the range found earlier to be successful in PA gels, and including the case  $\Delta z = 0$ , i.e., standard BH, were made. All volumetric treatments were made according to a methodology previously published [7], [32], [35], by electronically steering the focus over a rectangular



Fig. 5. Treatment plane with the numbering order of each pulse. The plane is orthogonal to the BH transducer axis, and the dashed-dotted line represents the imaging plane.

grid of  $13 \times 5$  points, for a total of 65 points, with a spacing of 1 mm between each point in a plane orthogonal to the axis of the BH array. The order in which each point was treated was chosen randomly, as shown in Fig. 5, to minimize the heat accumulation and the risks of prefocal cavitation from a previously treated neighboring points. The acoustic power of the pulses was scaled for each steered focus to reach similar level of the shock amplitude, and thus time-to-boil, as detailed in a previous publication [32]. Each point in the plane received a steered BH pulse, and the process was repeated until all points received a certain number of pulses (pulses per point, PPP). The pulse repetition frequency (PRF) of the treatment was 1 Hz (resulting in a duty cycle of 1%), and thus the full plane was treated in 65 s. Therefore, from the perspective of one point in the treatment plane, the BH exposure would be similar to that of previous experiments in PA gel with a steered BH pulse exposure once every 65 s, i.e., the duty cycle for each sonicated point was 0.015%.

After the steered BH treatment, high-resolution U.S. imaging of the samples was done (Sonix RP, Ultrasonix, Richmond, Canada, and L14-5W probe operating at 14 MHz) in two orthogonal planes. The lesions were recognizable on B-mode images as homogeneous, hypoechoic, rectangular regions, and their sizes (width, height, and depth) were measured. The samples were then cut along the imaging plane (represented as a dash dotted black line in Fig. 5), and the liquefied tissue inside the lesion was gently washed away using a saline solution. Note that the lesion size measurements were taken from the high-resolution U.S. imaging rather than directly performed on bisected samples, as soft tissue is prone to slight shape changes upon bisection and handling. For each value of  $\Delta z$ , the treatment was considered successful if no solid tissue structures were left in the lesion. If the lesioning was unsuccessful, 2 more steered BH PPP were applied to subsequent lesions with the same value of the  $\Delta z$  parameter. Once a value of PPP has been found to yield successful lesions, the treatment was repeated eight times at different locations for the lesion size statistics (n = 8).

## **III. RESULTS**

# A. BH Exposure in Gel Phantoms

An example of high-speed imaging at 20 kfps of a standard 10 ms BH treatment with a 0.0167 Hz PRF (1 pulse/min) is shown in Fig. 6 and in the supplemental video (file: standard\_bh.avi). The first pulse of the treatment generated a boiling bubble at 0.67 ms, with a visible shock scattering



Fig. 6. Treatment with a standard, i.e. fixed focus position represented here by a red dot, 10 ms BH pulse with a PRF of 0.0167 Hz. The scale bar represents 2 mm, and the BH pulse was incident from the right side of the images. At 0.67 ms post BH exposure, a vapor bubble (blue arrow) with prefocal cavitation (red arrow) due to shock scattering is visible. Secondary vapor bubbles (blue arrows) appear behind the first one at 1.32, 1.72, and 4.07 ms, respectively. Bottom right: lesion as seen in PA with HIFU off after eight pulses.

bubble cloud in front of it-i.e., toward the transducer. Diffraction at the vapor bubble and the prefocal bubble cloud allowed for more boiling bubbles to appear behind previous vapor bubbles after 1.32, 1.72, and 4.07 ms of the BH exposure. During the 10 ms of each BH pulse, a prefocal bubble cloud generated by the shock scattering effect, as well as boiling bubbles themselves, were in constant movement-pushed along the BH transducer axis while also moving randomly in the transverse direction due to the acoustic radiation force exerted on them. This resulted in a slow growth of the cavitation bubble cloud in front of the boiling cavity toward the BH transducer, as well as perpendicularly to the transducer axis. Bubbles appearing from the side of the vapor cavity could also be seen starting from 1.72 ms. After 5.52 ms, the radius of the vapor bubbles was slowly decreasing as a result of the shielding of the now large prefocal bubble cloud, with the largest vapor bubble losing around 66% of its radius, but never to the point of not being visible by the end of the 10 ms pulse.

After delivering of a total number of eight BH pulses, the area in the PA gel damaged by cavitation had a comet shape-a dark, almost circular head with a gradually lighter shade trail behind it, with a total length of 6 mm and maximum width of 1.9 mm. A notable particularity during this treatment and visible in the supplemental video was that at the third and fifth pulse no boiling happened, but instead shock scattering cavitation started immediately when the BH pulse reached the focus due to bubble nuclei still present there. In the sixth pulse, the same shock scattering cavitation also started immediately; however, boiling can be seen happening moments later behind the prefocal cavitation. While boiling was visible at 0.67 ms in the first BH pulse, it would happen later in the following



Fig. 7. Steered BH treatment in PA gel with  $\Delta z$  set at 800  $\mu$ m. The white bar represents 2 mm, the BH pulse was arriving from the right side, and the red dot represents the focus position. At 1.57 ms ( $< t_s$ ) post BH exposure a vapor bubble is visible. At 2.52, 3.02, and 3.52 ms, respectively, the focus was steered by  $\Delta z = 800 \ \mu$ m relative to the previous picture. At 5.52, 7.52, and 9.52 ms, respectively, the focus had been steered four times by  $\Delta z = 800 \ \mu$ m relative to the previous picture is the lesion as seen in PA gel with HIFU off after eight pulses.

pulses: 0.77 ms for the second pulse, 0.92 ms for the fourth pulse, 1.32 ms for the seventh pulse, and 1.52 ms for the eighth and last pulse. This treatment was representative of others' treatments in PA, where all those phenomena would happen as well.

Next, steered BH exposures with varying the parameter  $\Delta z$  were performed. It was observed that a new bubble cloud resulting of shock-scattering was generated reliably with  $\Delta z$  value of up to 1.2 mm. However, due to steering limitations of the array and for a 10 ms pulse with a  $\Delta t$  value set at 0.5 ms, the maximum value of  $\Delta z$  was 800  $\mu$ m, resulting in a total steering of 12 mm along the HIFU beam axis.

High speed photographs of the bubble cloud evolution using  $\Delta z = 800 \ \mu \text{m}$  value are shown in Fig. 7 and also in supplemental video (file: sbh\_800um.avi). The pulse started with a focus electronically steered 6 mm behind the geometric focus, and was then moved a total of 15 times by a spatial step of 800  $\mu$ m toward the HIFU transducer every temporal step of  $\Delta t = 0.5$  ms. During the first pulse, boiling was reached at 1.62 ms, and after each  $\Delta z$  spatial step, the bubble cloud was seen extending axially by values comprised between 603 and 1140  $\mu$ m locally. This high variability of the growth of the bubble trail can be explained by the strong acoustic radiation force that was exerted by the BH pulse, with the region affected seen as pushed along the transducer axis, but also slightly off-axis (up and down on the photographs). The affected area would then move back progressively to its initial position as the focus was steered away from it, and later as the BH pulse was turned off. As the focus was moving further away from the initial boiling bubbles, their radius was seen progressively decreasing, some of them disappearing before the end of the 10 ms pulse. The same was observed for bubbles resulting from shock scattering. However, bubbles that were in close proximity to the current BH focus position could be seen oscillating and collapsing, even with the prefocal shielding. This behavior could be better observed at 100 kfps as shown in the supplemental video (file: sbh\_800um\_100kfps.avi). Finally, as observed earlier in standard BH, remnants of bubble nuclei from the previous BH pulse at the focus would sometimes initiate the formation of a cavitation cloud immediately at the start of the BH pulse prior to, or even on occasions without, any boiling. In those cases, with or without boiling, the shock scattering bubble trail was still created consistently, as shown in the supplemental video (file: sbh 800um.avi) at the fifth and seventh pulse. The lesion in PA had a maximum width of 1.6 mm and a total length of 15.4 mm.

Lesions smaller in the axial direction were generated by reducing the value of  $\Delta z$ , as shown in Fig. 8 and the supplemental video (file: sbh 400um.avi), where its value was set to 400  $\mu$ m. Similar to the previous treatments, displacement of the bubble clouds under the influence of the acoustic radiation force could be observed. However, the displacement perpendicular to the BH transducer axis was larger than for the 800  $\mu$ m case, so much that in some cases it would delay the shock scattering cloud as seen at 3.02 ms, or also the next bubble cloud would start from the upper or lower part of the previous cloud, yielding this zigzag shape bubble trail seen at 9.52 ms. Also similar to the previous treatments was the progressive decrease in radius of the original boiling bubble as the focus moved away. After eight pulses, the lesion's total length was 10.6 mm. The difference of about 2 mm length between the picture at 9.52 ms for the first pulse and the picture after eight pulses showed that the acoustic radiation force pushed and compressed the gel and bubble cloud axially during the treatment. The width of the lesion was slightly larger close to the boiling area, measuring 1.8 mm there compared to 1.6 mm further prefocal, which was the same as in the case of a  $\Delta z$  of 800  $\mu$ m. This width variability can be attributed to the accrued "wiggling" of the bubble cloud during the pulse exposure. Overall, any values of  $\Delta z$  that were less than 800  $\mu$ m generated repeatably the bubble cloud trail.

### B. Volumetric Steered BH Exposures in Ex Vivo Tissues

Based on the previous results in PA gels, four different values of  $\Delta z$  were selected for evaluation: 0 (i.e., standard



Fig. 8. Steered BH treatment in PA gel with  $\Delta z$  set at 400  $\mu$ m. The white bar represents 2 mm, the HIFU pulse was arriving from the right side, and the red dot represents the focus position. At 0.77 ms ( $< t_s$ ) post HIFU exposure a vapor bubbles are visible. At 2.52, 3.02, and 3.52 ms, respectively, the focus was steered by  $\Delta z = 400 \,\mu$ m relative to the previous picture. At 5.52, 7.52, and 9.52 ms, respectively, the focus had been steered four times by  $\Delta z = 400 \,\mu$ m relative to the previous picture. The last picture is the lesion as seen in PA gel with HIFU off after eight pulses.

BH), 400, 600, and 800  $\mu$ m. Achieving completely fractionated lesions with fixed-focus BH exposures required 8 PPP, as previously reported for bovine heart tissue [35]; achieving complete lesions in steered BH exposures with  $\Delta z =$ 400  $\mu$ m required 10 PPP, and with  $\Delta z =$  600 and 800  $\mu$ m required 12 PPP. Using a lower number of PPP resulted in residual connective tissue inside some of the lesion, as shown in Fig. 9.

The bubbles resulting from each BH pulse were visible on the inline B-mode imaging right after the pulse and quickly faded away in less than a second as shown in Fig. 10 and the supplemental videos (files:  $\Box$ bmode\_bh.mp4,  $\Box$ bmode\_steered\_bh\_400um.mp4,  $\Box$ bmode\_steered\_bh\_600um.mp4 and  $\Box$ bmode\_steered\_ bh\_800um.mp4). For a steered BH pulse with  $\Delta z > 0$ , a line of hyperechoic bubbles was distinguishable as shown in Fig. 10(b). The length of this B-mode line would variate at each pulse. As the treatment progressed, and for all the values



Fig. 9. Photograph of an incomplete lesion in ex vivo bovine heart tissue. The treatment parameters were  $\Delta z = 800 \ \mu m$  and 10 PPP. The targeted area is outlined with dashed lines; residual tissues that were not liquefied are visible in that area.



Fig. 10. B-mode images of one treatment with  $\Delta z = 600 \ \mu$ m. The BH pulses were arriving from the right. (a) Image with the inline probe right before the treatment started. (b) Image with the inline imaging probe after the first pulse of the treatment. The bubbles trail (red arrow) can be seen as hyperechoic. (c) Image with the inline imaging probe just after the treatment. Hyperechoic layer of bubbles (red arrow) can be seen at the distal part of the lesion. Lesion appears as hypoechoic. (d) Image of the lesion that appears as a hypoechoic rectangular area 10 min after treatment, obtained using the high-resolution U.S. imaging system.

of the spatial step  $\Delta z$  including fixed-focus BH with  $\Delta z = 0$ , the likelihood of cavitation cloud forming instantly increased, which was manifested as high PCD noise level immediately at the start of BH pulse. In particular, PCD signals shown in Fig. 2, characteristics of BH with clear backscatter before the boiling and highly noisy backscatter after the boiling were rarely observed after delivering more than 2 PPP. After about three quarters of the treatment time for steered BH, swirling movement of scatterers inside the lesions was visible on B-mode. Also during the treatment in all cases, a hyperechoic layer was progressively seen appearing on B-mode at the distal part of the lesion as shown in Fig. 10(c). Once the HIFU



Fig. 11. Photographs of lesions in ex vivo bovine heart tissue using different values of  $\Delta z$ . The BH pulses were arriving from the right. Two lesions using the same parameters were produced next to each other to illustrate the repeatability of the method. (a)  $\Delta z = 0$ , 8 PPP. (b)  $\Delta z = 400 \ \mu m$ , 10 PPP. (c)  $\Delta z = 600 \ \mu m$ , 12 PPP. (d)  $\Delta z = 800 \ \mu m$ , 12 PPP.

was turned off, this layer slowly faded and disappeared after about 5–10 min. This behavior has been previously reported for standard BH volumetric treatments as well [7]. The lesions appeared as hypoechoic on B-mode imaging, either with the inline imaging probe as shown in Fig. 10(c) or with the high-resolution U.S. imaging system as shown in Fig. 10(d), allowing for accurate measurements.

The mean and standard deviation of the measured lesion dimensions for the different values of  $\Delta z$ , as well as the average ablation rate, are presented in Table I. Photographs where two lesions using the same parameters were made next to each other to illustrate the repeatability of the method

TABLE I Ex Vivo Lesion Dimensions

$\begin{array}{ c c } \Delta z \\ (\mu \mathrm{m}) \end{array}$	width (mm)	height (mm)	length (mm)	PPP	rate (cc/h)
0	$13.5 \pm 0.4$	$6.3 \pm 0.3$	$3.4 \pm 0.3$	8	2.0
400	$13.6 \pm 0.7$	$6.5 \pm 0.5$	$8.3 \pm 0.4$	10	4.0
600	$13.3 \pm 0.6$	$6.4 \pm 0.3$	$11.2 \pm 0.5$	12	4.3
800	$13.2 \pm 0.8$	$6.4 \pm 0.3$	$14.0 \pm 0.7$	12	5.5

The width and height correspond to the lesion dimensions in the treatment plane (see Fig. 5), while the length corresponds to the lesion dimension along the BH transducer axis. The mean and standard deviation were obtained from a sample size n=8, and the values for ablation rate were obtained from average lesion dimensions. The length of all the steered BH lesions are statistically significantly different from the standard BH lesions ( $p < 10^{-13}$  per two-tailed Student's t-test) while the other two dimensions are not (p > 0.2).

are shown in Fig. 11. The width and height correspond to the dimensions of the treatment plane (see Fig. 5), while the length corresponds to the dimension along the BH transducer axis. The borders of the lesions made with  $\Delta z$  set as 0 and 400  $\mu$ m were sharp and well defined, and presented thin lightly blanched rim, characteristic of changes in heme iron caused by low temperature increase as observed in previous BH lesions [36]. In contrast, for  $\Delta z$  set as 600 and 800  $\mu$ m, thin remnants of connective tissue were observed at the borders. Adding two more PPP to the treatment did not seem to improve the smoothness of the lesion border. More pronounced blanching of the rim was also observable compared to the treatment with lower value of  $\Delta z$ , including some patches of thermal damage as well. All lesions had a notably more irregular distal border, corresponding to the boiling lesion "tails," as previously reported [7], [35].

The lesion size in the treatment plane was almost the same among all lesions, but its length was significantly affected by varying the parameter  $\Delta z$ . Compared to fixed focus BH, the lesion length in steered focus BH with  $\Delta z = 400 \ \mu m$ increased by 4.9 mm on average, while further addition of 200  $\mu$ m of  $\Delta z$  resulted in the increase of the lesion length of almost 3 mm in average, corresponding to the BH focus steering difference. Since larger lesions necessitated more PPP, volumetric ablation rate was calculated for all treatments as overall treatment volume divided by the treatment time. In that regard, steered BH with  $\Delta z = 400 \ \mu m$  yielded an ablation rate of 4.0 cc/h, for  $\Delta z = 800 \ \mu m$  it reached 5.5 cc/h-twofold and almost threefold increase compared to fixed-focus BH (2.0 cc/h), respectively.

#### IV. DISCUSSION AND CONCLUSION

In this work, a proof of concept of a new approach for extending BH lesions axially by steering the focus during the delivery of each BH pulse was presented. Realization of the approach requires a multi-element phased array HIFU transducer with axial steering capability, either a 2-D array having a large number of small elements, as in the current study, or an annular (1-D) array having multiple elements. Such an array needs a driving circuit with the ability to quickly, on the order of microseconds, change the delay on its elements to avoid too long an interruption in the process of emitting a BH pulse. The main goal of this study was to show that a prefocal bubble cloud generated in the standard BH after initiation of boiling can be extended by moving the focus axially toward the transducer. Such discrete movement and generation, step by step, a sequence of proximal additions to the original bubble cloud can lead to higher volumetric ablation rate. This approach therefore enhances some of the mechanisms involved in BH mechanical tissue ablation.

High-speed optical imaging in transparent gels showed that another prefocal bubble cloud can be generated off a previous bubble cloud by shock scattering, effectively extending it. While the first prefocal bubble cloud was generated after boiling started by scattering from the vapor cavity, its further extension was mainly caused by scattering from cavitation cloud formed at each previous step of focus steering. For the following BH pulses, in some cases the full trail of bubbles was seen even without initiation of boiling, as long as bubble nuclei were present at the focus-in our case, remnants of the previous BH pulse. Steering limitations combined with the fixed length of the pulse and fixed temporal step  $\Delta t$  resulted in a maximum spatial step  $\Delta z$  of 800  $\mu$ m, yielding a 12 mm total steering and a maximum lesion length in PA gels of 15.4 mm, 2.6 times longer than standard BH lesions obtained with the same array without focus steering.

Optical observations also showed an important role of the acoustic radiation force in lesion formation in PA gels. For all cases, the gel and bubble clouds were pushed and compressed in the axial direction of the BH transducer, resulting in lesion length longer that the bubble cloud itself. Another observed effect was that the longer in time the area was exposed to the BH pulse, the wider was the final lesion. This resulted from shock-scattering happening not only in the axial direction. In addition, the bubble cloud itself was pushed in seemingly random directions perpendicular to the BH transducer axis, allowing for the creation of more bubbles on the sides of the cloud.

Axial steering of the HIFU focus during the BH pulse delivery successfully increased the length of volumetric lesions in ex vivo bovine heart, while still allowing single lesions to merge transversely. For all cases of  $\Delta z$ , the length of the lesion in tissue was less than observed in PA gel. This can be explained by the difference between the two media: PA gel stiffs and do not liquefy when exposed to BH pulses, while tissue progressively liquefies [7]-as observed here with incomplete lesions as shown in Fig. 9. Once liquefaction starts, other physical mechanisms such as acoustic streaming, microjetting, and atomization inside the vapor cavity, which cannot be observed in PA gels, take place along with cavitation. However, as the formation of prefocal bubble clouds plays an important role, at least at the start of the treatment, before partial liquefaction of the tissue, PA gel experiments are still important to find and optimize the parameters of the steered BH exposures.

While the volume of lesions in bovine cardiac ex vivo tissue increased with the value of the spatial step  $\Delta z$ , so did the number of pulses required to reach a full liquefaction of the volume targeted. Extra pulses were most likely required for complete liquefaction of stiff structures inside the tissue, as well as for proper merging each steered BH treatment spot, as it was shown in the PA gel experiments that the width of the bubble cloud was inversely proportional to the spatial step value. Even so, the ablation rate still increased in relation with the value of  $\Delta z$ , up to a maximum of close to threefold for  $\Delta z = 800 \ \mu m$ . However, the increase of the value of the spatial step and the number of PPP also come with increased visible spread of thermal damages on all borders of the lesion, as well as less-defined borders, especially on the distal side of the lesions where the boiling happened. As cavitational and BH methods typically aim for precise and purely mechanical tissue ablation, these undesired thermal effects, if present, may limit the applications of steered BH. Some BH applications such as hematoma and abscess treatment might benefit greatly from the increased ablation rate of steered BH while its extra thermal effects would not be a concern, whereas the less-defined borders and increased thermal damages might be critical for applications such as precise tissue liquefaction or tumor removal. This would only apply for large values of the spatial step as here the value  $\Delta z = 400 \ \mu m$  presented no significant thermal effects and well-defined borders of the lesions, and could thus potentially be applied to all standard BH applications.

The work presented here was a limited proof-of-concept study, and as such only one parameter-the spatial step  $\Delta z$ -was set as variable. However, the method depends on other parameters such as the steering starting time  $t_s$ , the temporal step  $\Delta t$ , the acoustic power, and the overall total pulselength. Each of those parameters might impact the ablation rate differently in specific tissues, as well as the thermal effects observed here for large spatial steps. Therefore, further studies are needed to optimize various parameters used in this approach. Other challenges might arise when applying steered BH in vivo, in particular how variation in phase aberrations might impact the steering, especially for large spatial steps, as well as how cardiac and respiratory motion affect the lesion process.

#### REFERENCES

- T. D. Khokhlova, M. S. Canney, V. A. Khokhlova, O. A. Sapozhnikov, L. A. Crum, and M. R. Bailey, "Controlled tissue emulsification produced by high intensity focused ultrasound shock waves and millisecond boiling," *J. Acoust. Soc. Amer.*, vol. 130, no. 5, pp. 3498–3510, Nov. 2011.
- [2] V. A. Khokhlova, M. R. Bailey, J. A. Reed, B. W. Cunitz, P. J. Kaczkowski, and L. A. Crum, "Effects of nonlinear propagation, cavitation, and boiling in lesion formation by high intensity focused ultrasound in a gel phantom," *J. Acoust. Soc. Amer.*, vol. 119, no. 3, pp. 1834–1848, Mar. 2006.
- [3] M. S. Canney, V. A. Khokhlova, O. V. Bessonova, M. R. Bailey, and L. A. Crum, "Shock-induced heating and millisecond boiling in gels and tissue due to high intensity focused ultrasound," *Ultrasound Med. Biol.*, vol. 36, no. 2, pp. 250–267, Feb. 2010.
- [4] A. D. Maxwell et al., "Cavitation clouds created by shock scattering from bubbles during histotripsy," J. Acoust. Soc. Amer., vol. 130, no. 4, pp. 1888–1898, Oct. 2011.
- [5] K. J. Pahk, S. Lee, P. Gélat, M. O. de Andrade, and N. Saffari, "The interaction of shockwaves with a vapour bubble in boiling histotripsy: The shock scattering effect," *Ultrason. Sonochem.*, vol. 70, Jan. 2021, Art. no. 105312.
- [6] J. C. Simon, O. A. Sapozhnikov, V. A. Khokhlova, Y.-N. Wang, L. A. Crum, and M. R. Bailey, "Ultrasonic atomization of tissue and its role in tissue fractionation by high intensity focused ultrasound," *Phys. Med. Biol.*, vol. 57, no. 23, pp. 8061–8078, Dec. 2012.
- [7] M. Song et al., "Quantitative assessment of boiling histotripsy progression based on color Doppler measurements," *IEEE Trans. Ultrason.*, *Ferroelectr., Freq. Control*, vol. 69, no. 12, pp. 3255–3269, Dec. 2022.

- [8] T. D. Khokhlova et al., "Ultrasound-guided tissue fractionation by high intensity focused ultrasound in an in vivo porcine liver model," *Proc. Nat. Acad. Sci. USA*, vol. 111, no. 22, pp. 8161–8166, Jun. 2014.
- [9] Y.-N. Wang et al., "Mechanical decellularization of tissue volumes using boiling histotripsy," *Phys. Med. Biol.*, vol. 63, no. 23, Dec. 2018, Art. no. 235023.
- [10] T. D. Khokhlova et al., "Pilot in vivo studies on transcutaneous boiling histotripsy in porcine liver and kidney," *Sci. Rep.*, vol. 9, no. 1, pp. 1–12, Dec. 2019.
- [11] T. J. Matula et al., "Treating porcine abscesses with histotripsy: A pilot study," Ultrasound Med. Biol., vol. 47, no. 3, pp. 603–619, Mar. 2021.
- [12] T. D. Khokhlova, W. L. Monsky, Y. A. Haider, A. D. Maxwell, Y.-N. Wang, and T. J. Matula, "Histotripsy liquefaction of large hematomas," *Ultrasound Med. Biol.*, vol. 42, no. 7, pp. 1491–1498, Jul. 2016.
- [13] V. A. K. Khokhlova et al., "A novel method for non-invasive mechanical ablation of prostate tumors using pulsed focused ultrasound," *Urologiia*, vol. 6, pp. 67–73, Jan. 2020.
- [14] V. A. Khokhlova et al., "Initial assessment of boiling histotripsy for mechanical ablation of ex vivo human prostate tissue," *Ultrasound Med. Biol.*, vol. 49, no. 1, pp. 62–71, Jan. 2023.
- [15] J. R. Chevillet et al., "Release of cell-free MicroRNA tumor biomarkers into the blood circulation with pulsed focused ultrasound: A noninvasive, anatomically localized, molecular liquid biopsy," *Radiology*, vol. 283, no. 1, pp. 158–167, Apr. 2017.
- [16] K. J. Pahk, G. H. Mohammad, M. Malago, N. Saffari, and D. K. Dhar, "A novel approach to ultrasound-mediated tissue decellularization and intra-hepatic cell delivery in rats," *Ultrasound Med. Biol.*, vol. 42, no. 8, pp. 1958–1967, Aug. 2016.
- [17] V. A. Khokhlova et al., "Histotripsy methods in mechanical disintegration of tissue: Towards clinical applications," *Int. J. Hyperthermia*, vol. 31, no. 2, pp. 145–162, Feb. 2015.
- [18] P. B. Rosnitskiy, P. V. Yuldashev, and V. A. Khokhlova, "Effect of the angular aperture of medical ultrasound transducers on the parameters of nonlinear ultrasound field with shocks at the focus," *Acoust. Phys.*, vol. 61, no. 3, pp. 301–307, May 2015.
- [19] Z. Xu et al., "Controlled ultrasound tissue erosion," IEEE Trans. Ultrason., Ferroelectr, Freq. Control, vol. 51, no. 6, pp. 726–736, Jun. 2004.
- [20] W. W. Roberts, T. L. Hall, K. Ives, J. S. Wolf, J. B. Fowlkes, and C. A. Cain, "Pulsed cavitational ultrasound: A noninvasive technology for controlled tissue ablation (Histotripsy) in the rabbit kidney," *J. Urol.*, vol. 175, no. 2, pp. 734–738, Feb. 2006.
- [21] A. D. Maxwell, C. A. Cain, T. L. Hall, J. B. Fowlkes, and Z. Xu, "Probability of cavitation for single ultrasound pulses applied to tissues and tissue-mimicking materials," *Ultrasound Med. Biol.*, vol. 39, no. 3, pp. 449–465, Mar. 2013.
- [22] Z. Xu, T. L. Hall, J. B. Fowlkes, and C. A. Cain, "Effects of acoustic parameters on bubble cloud dynamics in ultrasound tissue erosion (histotripsy)," *J. Acoust. Soc. Amer.*, vol. 122, no. 1, pp. 229–236, Jul. 2007.
- [23] E. Vlaisavljevich et al., "Effects of ultrasound frequency and tissue stiffness on the histotripsy intrinsic threshold for cavitation," *Ultrasound Med. Biol.*, vol. 41, no. 6, pp. 1651–1667, Jun. 2015.
- [24] E. Vlaisavljevich et al., "Effects of temperature on the histotripsy intrinsic threshold for cavitation," *IEEE Trans. Ultrason., Ferroelectr., Freq. Control*, vol. 63, no. 8, pp. 1064–1077, Aug. 2016.
- [25] E. Vlaisavljevich, A. Maxwell, M. Warnez, E. Johnsen, C. A. Cain, and Z. Xu, "Histotripsy-induced cavitation cloud initiation thresholds in tissues of different mechanical properties," *IEEE Trans. Ultrason.*, *Ferroelectr., Freq. Control*, vol. 61, no. 2, pp. 341–352, Feb. 2014.
- [26] K. Lin et al., "Histotripsy beyond the intrinsic cavitation threshold using very short ultrasound pulses: Microtripsy," *IEEE Trans. Ultrason.*, *Ferroelectr., Freq. Control*, vol. 61, no. 2, pp. 251–265, Feb. 2014.
- [27] Y. Li, T. L. Hall, Z. Xu, and C. A. Cain, "Enhanced shock scattering histotripsy with pseudomonopolar ultrasound pulses," *IEEE Trans. Ultrason., Ferroelectr., Freq. Control*, vol. 66, no. 7, pp. 1185–1197, Jul. 2019.
- [28] K. J. Pahk, P. Gélat, D. Sinden, D. K. Dhar, and N. Saffari, "Numerical and experimental study of mechanisms involved in boiling histotripsy," *Ultrasound Med. Biol.*, vol. 43, no. 12, pp. 2848–2861, Dec. 2017.
- [29] Y.-S. Kim et al., "Volumetric MR-HIFU ablation of uterine fibroids: Role of treatment cell size in the improvement of energy efficiency," *Eur. J. Radiol.*, vol. 81, no. 11, pp. 3652–3659, Nov. 2012.

- [30] V. A. Khokhlova et al., "Design of HIFU transducers to generate specific nonlinear ultrasound fields," *Phys. Proc.*, vol. 87, pp. 132–138, Jan. 2016.
- [31] M. A. Ghanem et al., "Field characterization and compensation of vibrational nonuniformity for a 256-element focused ultrasound phased array," *IEEE Trans. Ultrason., Ferroelectr., Freq. Control*, vol. 65, no. 9, pp. 1618–1630, Sep. 2018.
- [32] C. R. Bawiec et al., "A prototype therapy system for boiling histotripsy in abdominal targets based on a 256-element spiral array," *IEEE Trans. Ultrason., Ferroelectr., Freq. Control*, vol. 68, no. 5, pp. 1496–1510, May 2021.
- [33] C. Lafon et al., "Gel phantom for use in high-intensity focused ultrasound dosimetry," *Ultrasound Med. Biol.*, vol. 31, no. 10, pp. 1383–1389, Oct. 2005.
- [34] T. D. Khokhlova, Y. A. Haider, A. D. Maxwell, W. Kreider, M. R. Bailey, and V. A. Khokhlova, "Dependence of boiling histotripsy treatment efficiency on HIFU frequency and focal pressure levels," *Ultrasound Med. Biol.*, vol. 43, no. 9, pp. 1975–1985, Sep. 2017.
- [35] G. P. L. Thomas, T. D. Khokhlova, and V. A. Khokhlova, "Partial respiratory motion compensation for abdominal extracorporeal boiling histotripsy treatments with a robotic arm," *IEEE Trans. Ultrason.*, *Ferroelectr., Freq. Control*, vol. 68, no. 9, pp. 2861–2870, Sep. 2021.
- [36] Y.-N. Wang, T. Khokhlova, M. Bailey, J. H. Hwang, and V. Khokhlova, "Histological and biochemical analysis of mechanical and thermal bioeffects in boiling histotripsy lesions induced by high intensity focused ultrasound," *Ultrasound Med. Biol.*, vol. 39, no. 3, pp. 424–438, Mar. 2013.



Tatiana D. Khokhlova (Member, IEEE) received the Ph.D. degree in physics from Moscow State University (MSU), Moscow, Russia, in 2008.

After graduation from the Ph.D. program she moved to the Applied Physics Laboratory, University of Washington (UW), Seattle, WA, USA, for postdoctoral training, and then completed a Research Fellowship with the Department of Medicine, UW, where she is currently a Research Assistant Professor. Her research interests include physical acoustics, therapeutic

ultrasound, and photoacoustic imaging.



Oleg A. Sapozhnikov received the M.S. degree in physics and the Ph.D. and D.Sc. degrees in acoustics from Moscow State University (MSU), Moscow, Russia, in 1985, 1988, and 2008, respectively.

He is currently a Professor with the Department of Acoustics, Physics Faculty, MSU. Since 1996, he has been with the Center for Industrial and Medical Ultrasound, Applied Physics Laboratory, University of Washington, Seattle, WA, USA. His research interests include physical

acoustics, nonlinear wave phenomena, medical ultrasound including shock wave lithotripsy, high-intensity focused ultrasound, and ultrasound-based imaging.



Gilles P. L. Thomas received the Engineering degree in general engineering from the École Centrale de Nantes, Nantes, France, in 2014, the Engineering degree in mechatronics engineering and the M.S. degree in control and automation engineering from the Polytechnic School, University of São Paulo, São Paulo, Brazil, in 2014 and 2015, respectively, and the Ph.D. degree in biomedical engineering with the Université Lyon 1, Lyon, France, in 2019.

He is with the Applied Physics Laboratory, University of Washington, Seattle, WA, USA, for postdoctoral training.



Vera A. Khokhlova received the M.S. degree in physics and Ph.D. and D.Sc. degrees in acoustics from Moscow State University (MSU), Moscow, Russia, in 1986, 1991, and 2012, respectively.

After graduation from the Ph.D. program she was appointed by Moscow State University, where she currently is an Associate Professor with the Department of Acoustics, Physics Faculty, MSU. In 1995, she is also with the Center for Industrial and Medical Ultrasound, Applied

Physics Laboratory (APL), University of Washington, Seattle, WA, USA. Her research interests include nonlinear acoustics, therapeutic ultrasound including metrology and bioeffects of high-intensity focused ultrasound fields, shock wave focusing, nonlinear wave propagation in inhomogeneous media, and nonlinear modeling.