DISINTEGRATION OF TISSUE USING HIGH INTENSITY FOCUSED ULTRASOUND: TWO APPROACHES THAT UTILIZE SHOCK WAVES

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Introduction

Surgery is moving more and more toward minimally-invasive procedures – using laparoscopic approaches with instruments inserted through tiny incisions or catheters placed in blood vessels through puncture sites. These techniques minimize the risks to the patient such as bleeding complications or infection during surgery. Taken a step further, high-intensity focused ultrasound (HIFU) can provide a tool to accomplish many of the same procedures without any incision at all.[1-5] With HIFU, an ultrasound transducer can be positioned outside the body and focused through the skin and overlying tissue to deliver high-amplitude ultrasound to a target structure such as a tumor (Fig. 1). Absorption of acoustic energy within the focal volume is high enough to rapidly heat the tissue, effectively 'cooking' it within seconds or even a fraction of a second. This procedure also removes the need for a sterile operating room: without the risk of infection, HIFU noninvasive therapy could be done in the doctor's office or outpatient clinic.

"Ultrasound-induced tissue disintegration opens a new direction in development of HIFU medical technology"

For many years, HIFU surgery was centered on utilizing a thermal effect—tissue heating and denaturation caused by absorption of ultrasound.[6] As the heating rate is dependent on local acoustic intensity, the temperature rises significantly enough to ablate tissue only in the focal region. While thermal ablation is the dominant interaction at lower HIFU focal intensities, higher intensities can introduce other bioeffects (Fig. 2). If the temperature rises to 100°C during sonication, boiling bubbles appear in the tissue, inducing additional mechanical as well as thermal damage. At higher focal intensities, mechanical effects of the ultrasound wave itself become significant.[7,8] The large tension phase of the wave can cause sporadic inertial cavitation or even a cloud of cavitation bubbles in the focal region in tissue—a process where the small gas bubbles grow and violently collapse, creating destructive effects on the tissue. Nonlinear propagation effects result in formation of high-amplitude shock waves around the focus which themselves create mechanical stress in the tissue. In addition, significantly enhanced heat deposi-

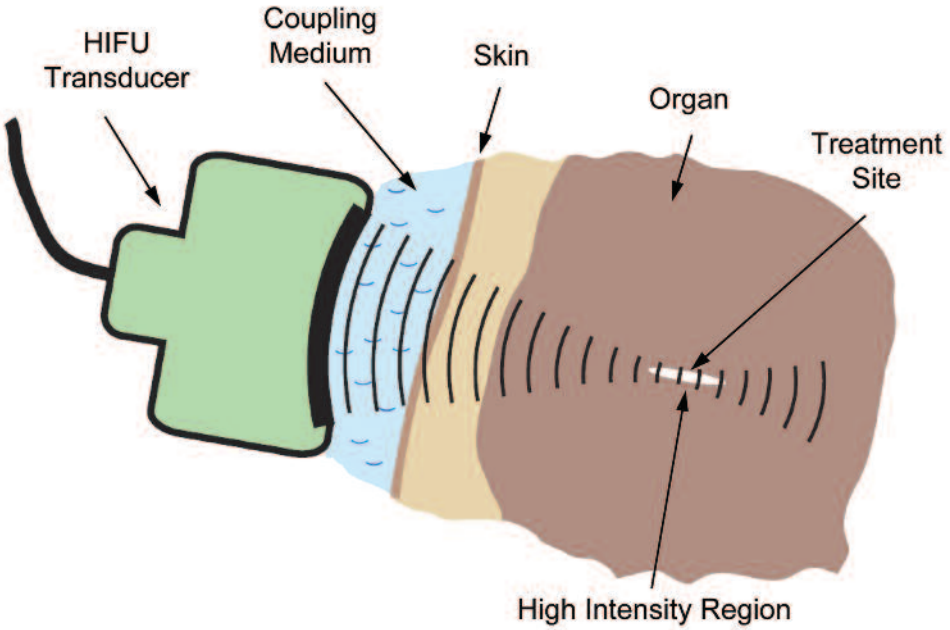

Fig. 1. Diagram of HIFU surgery. The transducer emits a focused ultrasound beam through the overlying tissue layers to create a high intensity region within the organ. The focus can be translated to ablate the entire volume of interest. (Adapted from part of a figure in reference 6)

tion at the shocks can induce boiling in tissue in milliseconds, much faster than typical HIFU exposures. Extracorporeal shockwave lithotripsy uses such focused shock waves and cavitation to break up kidney stones.[9] Recent HIFU studies have shown that the presence of shocks and cavities, induced by HIFU either as a cavitation cloud or millisecond boiling, can be also used to break up or mechanically fractionate soft tissues to tiny debris—an outcome similar to disintegration in a "remote" blender.

This ultrasound-induced tissue disintegration opens a new direction in development of HIFU medical technology. The technique has been dubbed '*histotripsy*' (the prefix *histo-* translated from Greek to mean tissue), as an analog to lithotripsy. Two separate techniques to perform histotripsy with ultrasound shock waves have been demonstrated thus far: one using a cloud of cavitation bubbles and another that uses boiling bubbles. The cavitation-based approach has been developed over the last 11 years at the University of

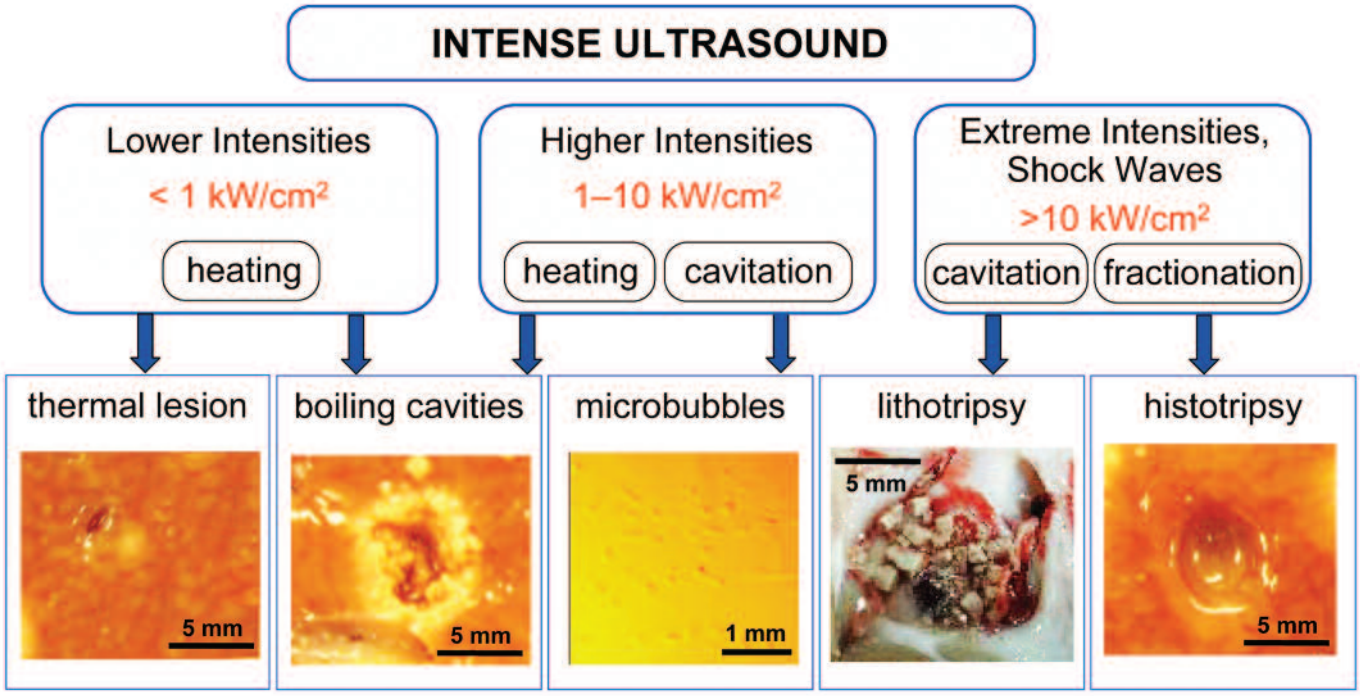

Fig. 2. Bioeffects of focused ultrasound at different focal intensity levels. At lower intensities, heating through acoustic absorption is the dominant mechanism, denaturing proteins within the tissue, leaving a blanched appearance. Boiling cavities form in the lesion when the temperature reaches 100°C. At higher intensities, heating combined with microbubble cavitation can cause mechanical trauma to the tissue structure. At very high intensities, shockwaves form at the focus and the wave itself can impart significant mechanical damage such as comminution of kidney stones (lithotripsy) or fractionation of soft tissues (histotripsy).

Michigan,[10-12] while the boiling-based method was discovered a few years ago at the University of Washington.[13-15] The mechanisms of generating bubbles through each mode are quite different, but surprisingly, both techniques produce similar lesions through tissue disintegration.

Histotripsy could be employed as a noninvasive treatment for many diseases, such as malignant tumors, benign prostatic hyperplasia (BPH), deep vein thrombosis, and congenital heart defects. The unique ability of histotripsy to actually liquefy the tissue (rather than just thermally destroying it) means that the lesion content can be passed out of natural body orifices or easily reabsorbed by surrounding tissue. For instance, excess prostate tissue for BPH can be passed through the urinary system, offering immediate decompression and relief of symptoms. Thus far, both cavitation and boiling techniques have been demonstrated in animal studies.[16-18] This article discusses the acoustics of both types of histotripsy – including the processes of generation and focusing of intense ultrasound, the formation of cavitation clouds and rapid boiling in tissue, and the interactions of ultrasound shock waves with bubbles leading to tissue disintegration.

Background

The majority of HIFU sources (including those for histotripsy) are piezoelectric, made from ceramics such as lead-zirconate-titanate (PZT) or composites of PZT with passive materials. High-voltage periodic signals are applied to the piezoelectric element by a radiofrequency amplifier to generate ultrasound vibration of the transducer surface. Focusing is accomplished by several techniques. One method is to simply form the piezoelectric material to the shape of a spherical bowl with a natural focal point at its radius of curvature (Fig. 3). An alternative to this approach is to couple an acoustic lens to a flat source, which creates similar focusing without the need to precisely form the piezoelectric material. Finally, focusing can be achieved electronically using array transducers with multiple distinct elements. The phase of the output between different elements is controlled to create constructive interference at a desired focal point. The advantage of this last technique is that the focus can be electronically steered to different locations without physically changing the position of the device. Ultrasound imaging probes that typically comprise lensing and array focusing are often combined with HIFU transducers to create high-resolution images of the treatment site and provide treatment feedback to the operator.

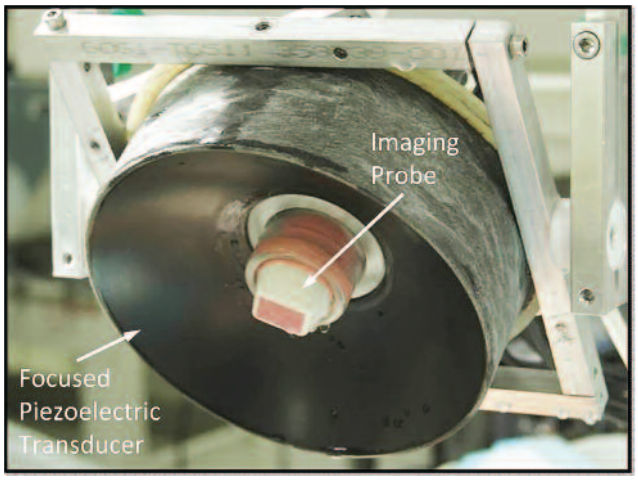

Fig. 3. A spherically-focused piezocomposite HIFU transducer of 0.75 MHz frequency, with a 15-cm diameter and 12-cm radius of curvature used for cavitation-cloud histotripsy. An imaging probe is positioned in its central hole to visualize the focal region, providing valuable feedback for targeting and monitoring the treatment progress. Visualization is based on high echogenicity of cavitation bubbles that are strong scatters of ultrasound.

Sources used for histotripsy studies are highly focused having similar apertures and radii of curvature ranging from about 5 to 15 cm. The sources operate at high power outputs to provide intensity levels at the focus from 10 to >30 kW/cm^2. Although initially sinusoidal waves are irradiated from the transducer, they become distorted while propagating to the focus due to combined nonlinear and diffraction effects.

The sound speed of high amplitude acoustic waves depends on the local pressure causing nonlinear propagation effects. The speed of sound is increased under compressive pressure and decreased for rarefactive pressure in comparison with the ambient sound speed, c_0, which leads to distortions of acoustic waveform. These nonlinear distortions accumulate over the propagation distance as a gradual steeping of the wave front and finally result in formation of shocks. For an initially harmonic wave, the shock formation distance x_{sh} is $x_{sh} = c_0^3\rho_0/(2\pi p_0 f_0 \beta)$, where ρ_0 is the density, p_0 is acoustic pressure amplitude, f_0 is the ultrasound frequency, and β is the nonlinear parameter of the propagation medium. For example, the shock formation distance in water for an ultrasound wave of 2 MHz frequency and 15 MPa pressure amplitude (8 kW/cm^2) is 5 mm. High amplitude focal regions of HIFU transducers are typically longer than this distance and focal intensities even higher than 30 kW/cm^2 have been reported, therefore formation of shocks is typical for histotripsy and very probable in some other clinical HIFU situations. In addition, the waveform achieves a strong positive/negative pressure asymmetry caused by a different diffraction phase shift between harmonics of the fundamental frequency generated in the beam, leading to high shock amplitudes (Fig. 4).[10,19]

Both cavitation and boiling histotripsy employ pulse-periodic schemes of irradiation (Fig. 4). However, in cavitation-based histotripsy, the operational frequency is relatively low (typically from 0.75 MHz to 1 MHz), the pulses are short (3-20 cycles) and delivered often (10 Hz – 1 kHz). In this regime, each pulse excites a cloud of cavitation microbubbles to expand and collapse in response to the acoustic pressure. Usually, a focal volume is treated with 10^3 - 10^4 pulses for complete ablation.[10] Focal peak pressures are approximately p_- = 15 – 25 MPa, and p_+ > 80 MPa. In boiling histotripsy, the frequency is higher (1 - 3 MHz), the pulses are much longer (3000-10000 cycles) and delivered less often (0.5 – 1 Hz) (Fig. 4b). The peak pressures are lower, about p_- = 10 – 15 MPa and p_+ > 40 MPa. In this regime, boiling is initiated within each millisecond-long pulse due to effective tissue heating by shocks. Interaction

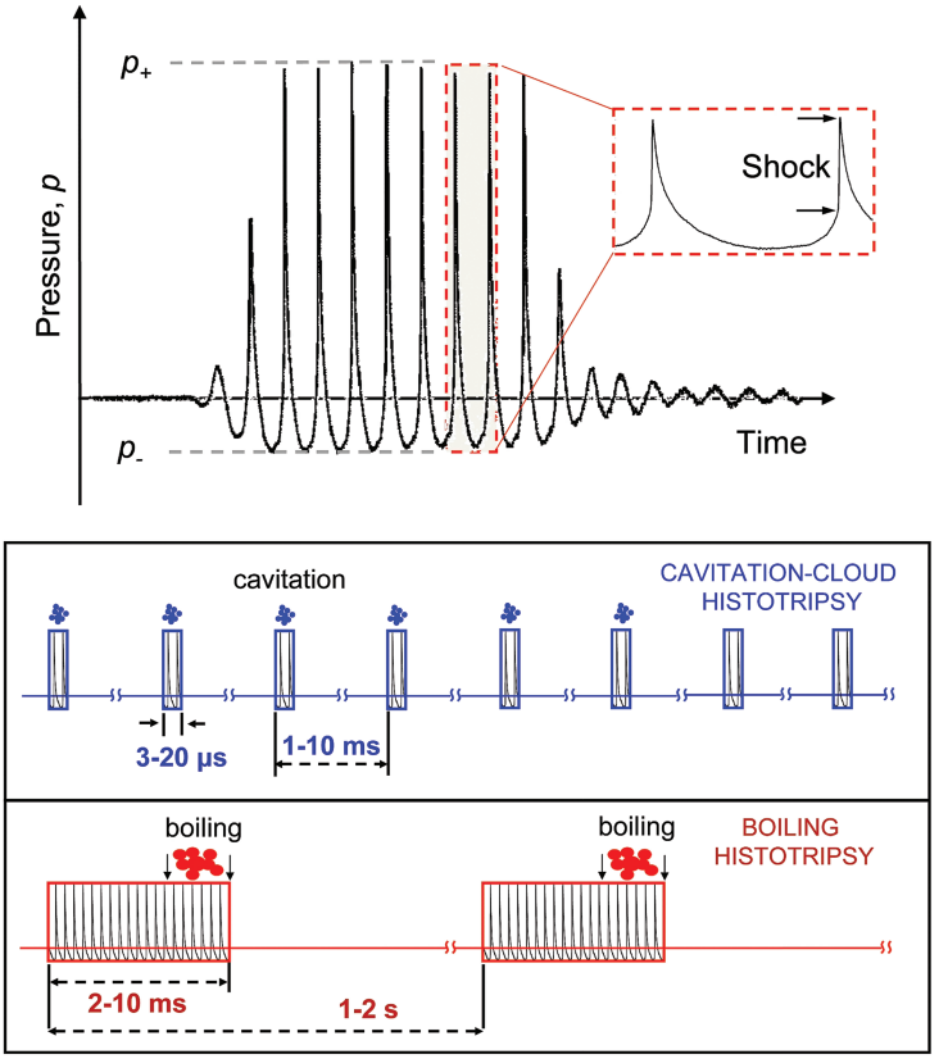

Fig. 4. (Top) Representative focal pressure waveform used for histotripsy. The pulse is initially a sinusoidal tone burst, but at the focus it is distorted by the combined nonlinear propagation and diffraction effects to produce the asymmetric waveform with higher peak positive pressure (p_+), lower-amplitude peak negative pressure (p_-), and high-amplitude shocks formed between negative and following positive phase as shown in the inset frame. (Bottom) Pulse-periodic timing schemes for two forms of histotripsy. The blue sequence shows the cavitation-cloud histotripsy scheme with microsecond-long pulses applied at 100-1000 Hz. The red sequence shows the boiling histotripsy scheme, employing millisecond-long pulses at a rate of 0.5 - 1 Hz.

of shocks with this vapor cavity causes mechanical damage of tissue before thermal effects become significant. Usually, 10 to 50 pulses are sufficient to fractionate the focal volume.[15] In both pulsing schemes, ultrasound is only being delivered to the focus about 1% of the treatment time. The periods in which the transducer is not emitting give the tissue time to cool, thus preventing accumulation of heat and thermal damage within the tissue volume. In this way, a completely mechanical effect is preserved.

Cavitation cloud histotripsy

Acoustic cavitation

Acoustic cavitation occurs when bubbles expand and contract in response to a pressure waveform. At low pressure amplitude, this behavior is relatively mild and results in fractional oscillation in the bubble radius *versus* time. However, at higher pressure amplitudes, the bubble can undergo a huge expansion as tension is applied to the liquid, followed by a violent collapse as the mass of the moving liquid forces the bubble to implode. As this motion is dominated by the momentum of the bubble wall, it is termed "inertial cavitation." Inertial cavitation is a threshold phenomenon—it requires certain pressure amplitude, dependent on the initial bubble size, to undergo the explosive expansion. In cavitation-cloud histotripsy, this large growth and collapse of bubbles creates a transient strain on the surrounding tissue, resulting in its fractionation.

The tensile pressure required to create the bubble nucleus for inertial cavitation in water is enormous—theoretically estimated at ~50 – 140 MPa.[20,21] However, the threshold to expand a pre-existing bubble in water or tissues is lower; inertial cavitation can occur even at modest pressures of p_- ~ 1 MPa at ultrasound frequencies.[22-24] Similarly, divers encounter decompression sickness through outgassing of bubbles in the blood after exposure to relatively small overpressures. These observations suggest the body harbors small pre-existing gas nuclei which can be driven to undergo explosive growth. However, free bubbles are generally not stable by themselves—they tend to dissolve over time due to the Laplace pressure created by surface tension of the liquid on the bubble. Instead, they are thought to be stabilized by different mechanisms such as crevices in solid particles or even macromolecules which house tiny gas pockets.[25,41] Inertial cavitation thresholds *in vivo* can largely vary depending on the existence and distribution of these nuclei.

Cloud cavitation in histotripsy

During histotripsy, many cavitation bubbles are expanded forming a dense cloud over the focal volume (Fig. 5). The cloud does not continuously increase in density as the acoustic pressure increases, but forms suddenly at a distinct pressure threshold. The value of this threshold, however, is about an order of magnitude larger than reported thresholds for inertial cavitation from single bubbles at 1 MHz. Interestingly, the formation of clouds is also probabilistic—that is, the cloud will not necessarily form on the first pulse applied above the threshold, but rather can take hundreds or thousands of prior pulses before a cloud will suddenly form, despite each pressure pulse being essentially identical. In this sense, cloud formation is "all-or-nothing."[12] When the pressure amplitude is sufficiently high (p_- > 20MPa), the bubble

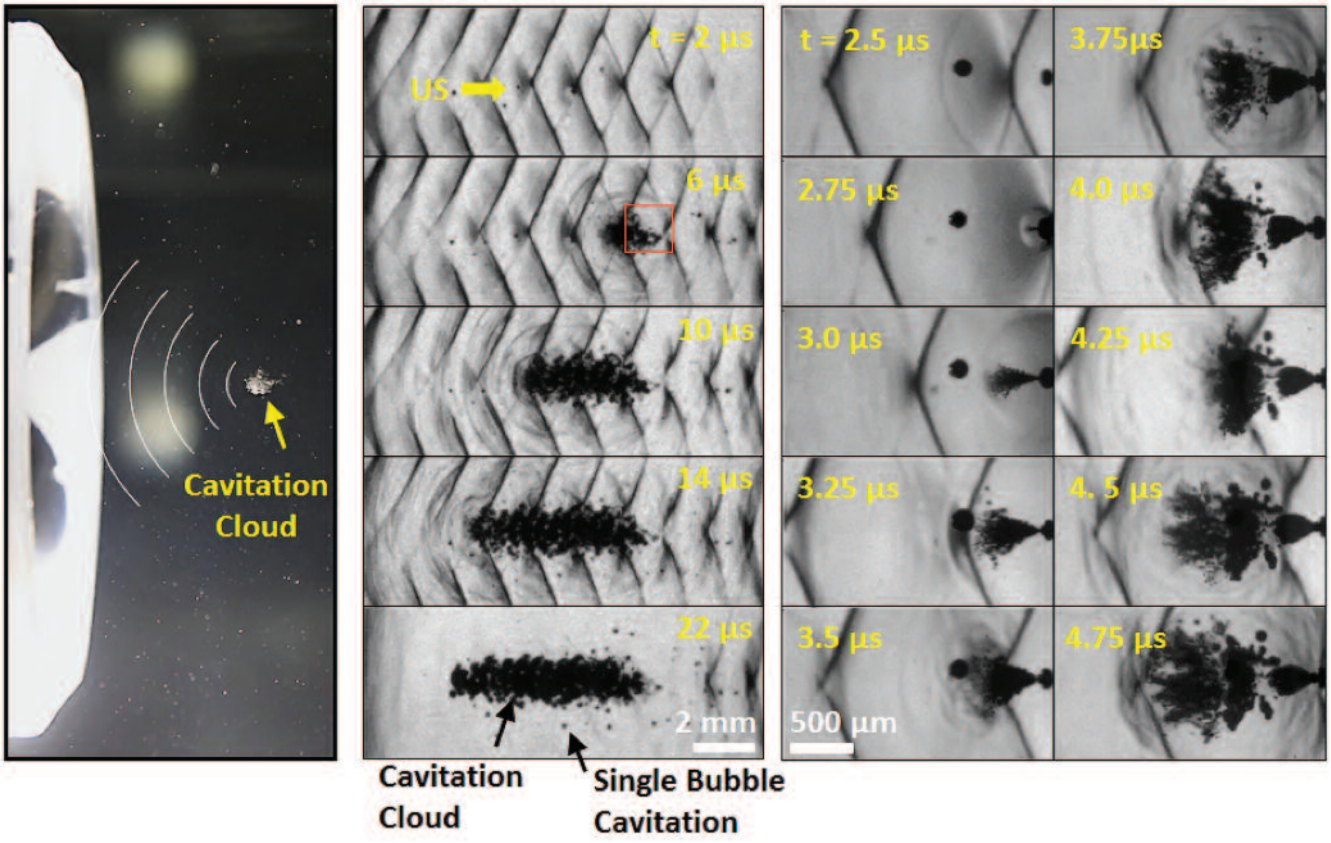

Fig. 5. Cavitation cloud generated at the focus of a transducer. (Left) A bubble cloud as it appears in a water bath. (Center) Formation of a cavitation cloud observed by high-speed photography in a gelatin tissue-mimicking phantom. The ultrasound propagation is from left to right, and the cloud grows opposite this direction throughout the pulse. Shock fronts are visible as dark lines. (Right) Initiation of a cloud during 3 acoustic cycles of a pulse. A cluster of cavitation appears after the incidence of a shock on a single bubble at the focal center. Another cluster appears each cycle after the shock wave impinges on the previously formed one. (Adapted from reference 26).

cloud can be formed within one or a few pulses.

As the presence of a cloud facilitates histotripsy tissue damage, much work has gone into studying the dynamics of how this cloud forms. In particular, high-speed photography has provided valuable information regarding the interaction of the pulsed waveform with cavitation bubbles to form the cloud.[26] In these experiments, tissue-mimicking optically-transparent 7% gelatin samples were used to visualize cavitation activity during application of a single histotripsy pulse. The pulses of 5-20 cycles in length were applied from a 1-MHz circular transducer with diameter d = 10 cm and radius of curvature F = 9 cm. The peak pressures measured in water for these pulses using a fiber-optic probe hydrophone were p_- = 19 MPa and p_+ = 85 MPa, with a waveform similar to that in Fig. 4. The camera (SIM02, Specialized Imaging, Hertfordshire, UK) is capable of taking 16 images at frame rates up to 100 million frames per second, providing information on pulse propagation as well as bubble dynamics. To observe cavitation, the images were backlit to create a shadowgraph. Bubbles appear as black regions against a bright background. Additionally, the index of refraction changes with the density of the gelatin (created by the pressure waveform), which causes the shock fronts to be displayed as dark lines in these images (Fig. 5).

At the pressure amplitude used in this study, a cavitation cloud was not observed for every pulse regardless of the pulse length. However, single microbubbles undergoing inertial cavitation were generally observed to grow and collapse as the pulse passed over the focal region. The single bubbles expanded to ~100-200 µm, depending on their location around the focus (which determines the pressure they experienced). Cavitation clouds, on the other hand, were comprised of perhaps hundreds or thousands of cavitation bubbles, and the structure of the cloud often occupied a significant part of the focal volume when expanded (Fig. 5). Most distinctly, the cloud 'initiated' from a distal position in the focal region (furthest from the transducer) and grew throughout the pulse towards the transducer (against the direction of acoustic propagation). Longer pulses tended to form larger clouds which occupied a greater percentage of the focal volume. However, the clouds were always confined to the focal region, and did not continue to grow beyond its limits.

Images recorded at higher magnification indicate that cloud growth initiates by scattering of the shock fronts from one or more single bubbles (Fig. 5). The initial tension phase of the incident pulse causes this bubble to expand. When a shock front impinges on the bubble, it is reflected from its surface. As the acoustic impedance of the bubble is very low compared with the tissue, the reflection occurs as that from a pressure-release surface and the reflected wave is inverted. The incident shock thus transforms into a high amplitude tensile wave—ideal for inciting cavitation. As can be seen in Fig. 5, a cluster of cavitation bubbles forms behind this back-

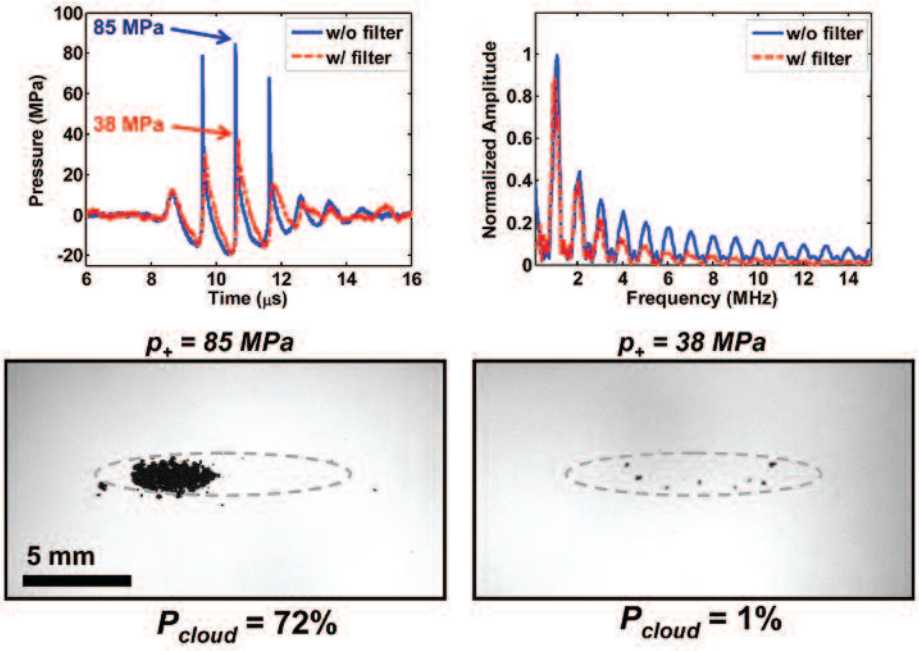

Fig. 6. Experiment demonstrating the role of shocks in forming cavitation clouds. (Top) Pulses focused without an acoustic filter have significant shock amplitude (blue) while the filtered waveforms have reduced shock amplitude and p_+ (upper left). Both waveforms have the same p_-. In the frequency domain (upper right), this translates to a reduction in the high-frequency harmonics of the pulse while the lower frequency content remains. (Bottom) The reduction in shock amplitude results in significant reduction in the probability of generating a cloud during a pulse (P_{cloud}), although single microbubble cavitation from the negative pressure of an incident wave is still observed.

propagating wave. This cluster acts as a scatterer for the next shock in the incident pulse, which creates a second cluster of cavitation in front of the first. The reflected shock incites a larger region of cavitation, and this cavitation serves to scatter more effectively the following shock, in a cascade effect which is only terminated when no additional shocks are available (either the pulse ends or the cloud grows outside the focal region where the shocks do not occur). This seeding effect causes the cloud to emerge from a single bubble and grow explosively back toward the transducer. The cloud takes on a layered appearance, each layer occurring from one shock front of the pulse.

This mechanism explains the "all-or-nothing" behavior of the cloud. If a single bubble nucleus is not serendipitously positioned within the center of the focal region where the shocks form, there is no scatterer to initiate the cloud. While the incident p_- is responsible for forming the single bubbles, the shocks, which only form locally within the high pressure focal region, are responsible for initiating the cloud. One experiment which illustrates this particularly well is the introduction of an acoustic low-pass filter between the transducer and focal zone. In this experiment, the filter was constructed from thin sheets of brass which effectively attenuate the high-frequency harmonics that create the shocks. Meanwhile, the fundamental frequency transmission that determines p_- is minimally altered (Fig. 6). With the filter in place, the shock amplitude was reduced from 85 to 38 MPa, while p_- was 19 MPa in both cases. This filter suppressed the probability of generating a cloud during a pulse from $P = 0.72$ to $P = 0.01$.

The acoustics at the initial phase of this process can be modeled by the classic problem of a plane wave scattering from a spherical fluid target.[27,28] Such a model demonstrates the importance of the characteristic of the shock front to the process. The individual seed bubbles are considerably smaller than the fundamental wavelength ($\lambda = 1.5$ mm in the gel) and scattering at this frequency is weak. However, the high frequency components of the waveform scatter strongly and

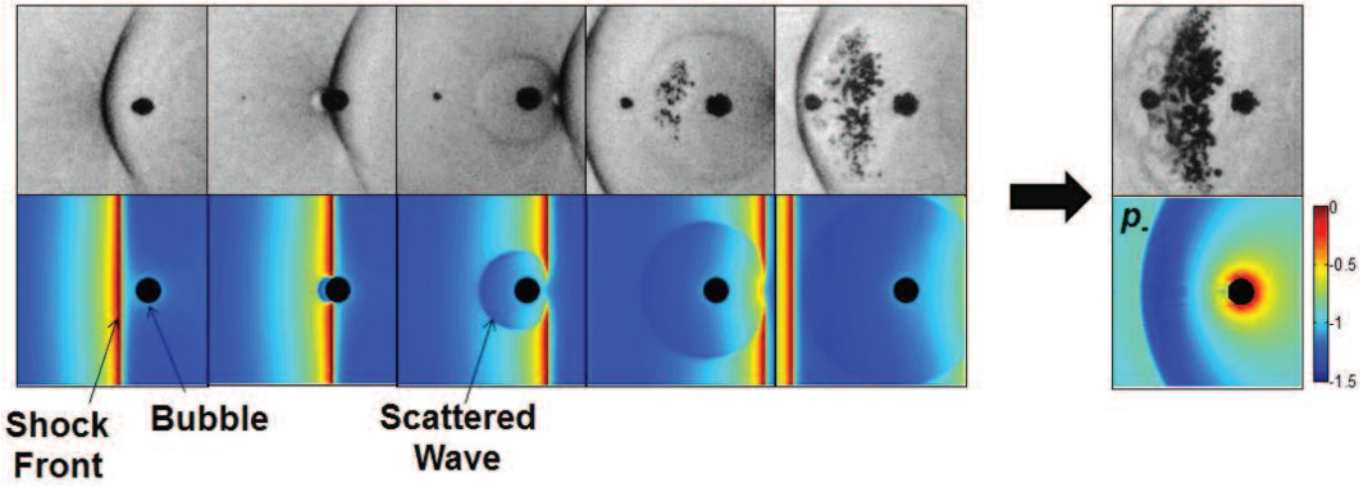

Fig. 7. Photographs (top) and simulations (bottom) of a shock scattering from a bubble. The shock is focused in the experiment but is approximated as a plane wave in the simulation. The constructive interference of the scattering wave and the rarefaction phase of an incident wave creates a region where the tensile pressure is greatest, which coincides with the location cavitation is observed in the field. The 5 frames of simulations on the left show the transient pressure distribution and the image on the right shows the peak negative pressure achieved throughout the field over 1 cycle.

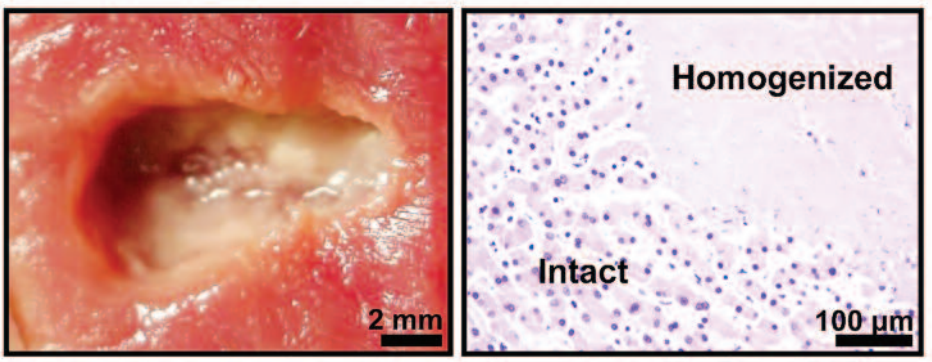

Fig. 8. (Left) Gross morphology of a histotripsy lesion created in myocardial tissue. The disintegrated liquid has been removed, creating a hole. (Adapted from part of a figure in reference 10) (Right) A microscopic view of intact cells from a section of liver in the lower left, and treated tissue in the upper right. The homogenized tissue is almost completely lacking structure, while less than a cell-length away, the tissue appears normal. The lack of structure in the homogenized region leads to a dark region on an ultrasound image because there are no significant scatterers remaining in this region. The hypoechogenicity is used as an indicator for treatment progression in histotripsy.

in phase—the characteristics of the focused shock—which causes the large tension upon reflection from its surface. Furthermore, the scattered shock constructively interferes with the incident trailing negative pressure to create a region where the tension is greatest. This process is akin to the "spallation" mechanism discussed in lithotripsy. The pattern of cavitation observed after scattering from the single bubble can be predicted based on the region where p_- is greatest over a cycle (Fig. 7).

Histotripsy lesions

The shock scattering process describes what happens during a single pulse to initiate the cloud for cavitation-based histotripsy. Generally speaking, ~10^3 - 10^4 pulses must be applied following this event to mechanically ablate the focal volume of tissue. Provided another pulse is applied quickly enough after the initiation of the cloud, the bubble nuclei which make up the cloud can be repeatedly expanded and collapsed. If the pulses are not applied often enough, the cloud nuclei will dissolve back into the medium, and another cloud must be formed through the shock-scattering process. This temporary susceptibility of the medium to be repeatedly cavitated is referred to as "cavitation memory."[29] Cavitation memory is also a prime explanation for why lithotripters operate more efficiently when pulses are applied at slow rates rather than fast rates—this gives the bubbles which would shield acoustic propagation of the shockwave time to dissolve between the pulses.

The outcome of repeatedly expanding and collapsing the cavitation cloud using microsecond-long shock pulses is a complete homogenization of the tissue structure into an acellular liquid with a sharp transition zone between completely intact or completely destroyed tissue (Fig. 8). The size of the debris remaining within the region where the cavitation cloud is generated is found to be very small, with about 97% of the volume consisting of fragments subcellular in size.[30] Because the cavitation cloud is spatially confined to the focal volume, this is the only region which is ablated. This feature is a distinct advantage of histotripsy as a therapy—there is no apparent risk of applying too great of a dose to the tissue. In contrast, applying too great of a dose in thermal therapy can result in damage to surrounding tissue through heat diffusion.

Boiling histotripsy

Shock wave heating

Nonlinear waveform distortion of an initially harmonic wave corresponds to generation of higher harmonics that are more readily absorbed and generate more heat. Thermoviscous absorption in water is weak but grows quadratically with frequency. In tissue, additional stronger absorption is caused by multirelaxation processes following a nearly linear frequency power law. Once shocks that contain very high frequencies develop, heating effects increase dramatically.[31,14] Heat deposition in tissue caused by absorption of a plane harmonic wave (H_{lin}) is proportional to the wave intensity I, i.e., to the pressure amplitude p squared: $H_{lin} = 2\alpha I$, where $I = p^2 / (2c_0\rho_0)$ and α is the absorption coefficient in tissue at the ultrasound frequency. On the contrary, absorption at the shocks (H_{shock}) is

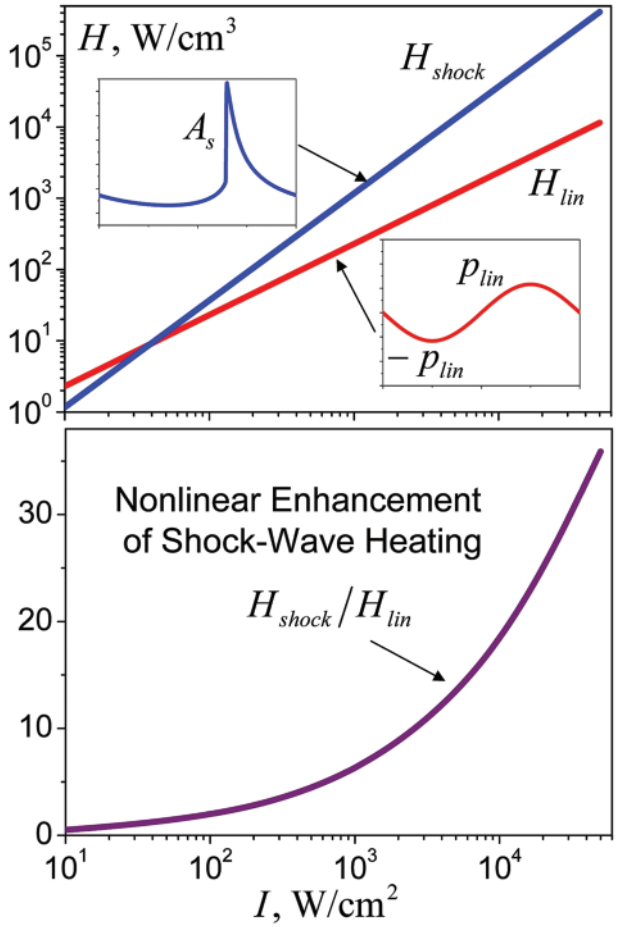

Fig. 9. Comparison of tissue heating using harmonic waves (H_{lin}) or shock waves (H_{shock}) of the same intensity I and frequency. (Top) Heat deposition caused by absorption of harmonic waves is proportional to their intensity (red), i.e., pressure amplitude squared, while energy absorption of shock waves is proportional to the shock amplitude cubed (blue). (Bottom) The difference in efficiency of heating increases at larger intensities and can be more than an order of magnitude higher for shock waves as compared to harmonic waves of the same intensity.

proportional to the shock amplitude A_s cubed: $H_{shock} = \beta f_0 A_s^3 / (6 c_0^4 \rho_0^2)$.[32] In addition, when shocks form at the focus of an acoustic beam, rather than in a plane wave, nonlinear effects combined with a different diffraction phase shift between harmonics lead to the asymmetry of the waveform and about 1.5 times higher shock amplitude than it would be expected for a plane wave.[33] Figure 9 compares heat deposition at the focus in tissue due to absorption of a harmonic wave H_{lin} (red curves) and shock waves H_{shock} (blue curves) against their intensity. Curves are calculated for a 2 MHz transducer, absorption in tissue α_0 = 0.5 dB/cm/MHz, sound speed c_0 = 1500 m/s, density ρ_0 = 1000 kg/m^3, and nonlinear parameter β = 4. Corresponding waveforms are presented in inset frames. The ratio of heating rates shows that at focal intensities > 10 kW/cm^2 heating efficiency from shock waveform is more than 20 times higher than that from the harmonic waves. This indicates that using shock waves is beneficial to accelerate thermal effects in HIFU and that intensity by itself cannot be used as a metric of the field to quantify heating if strong nonlinear effects and shocks are present. Moreover, rapid tissue heating by shocks can initiate boiling in milliseconds that, surprisingly, results in histotripsy rather than thermal ablation.

Millisecond boiling

Shock fronts are superfocused to a localized volume within the focal region of the HIFU beam leading to very precise heating at the focus. Simulations of acoustic fields from various HIFU transducers based on the Khokhlov-Zabolotskaya-Kuznetsov (KZK) nonlinear propagation model combined with the heat transfer equation have shown that if shock fronts of about 40 – 80 MPa develop at the focus, boiling temperatures are reached in milliseconds (Fig. 10).[14] Once shocks form, spatial distributions of ultrasound-induced heating (frame c) becomes much more localized than acoustic intensity (frame a). Even though heating by shocks is concentrated in a very small volume of about 0.1 mm radius, heat diffusion from volume of this size occurs in about 20 ms.[14] If boiling starts within several milliseconds, heat diffusion is almost negligible. Time-to-boil therefore can be easily predicted from the shock wave amplitude and thermal parameters of the medium.[15] Contrary to cavitation inception, which is a stochastic phenomenon and may occur in a much larger volume within the focus (frame b), shock heating and boiling are highly predictable and occur locally at the focal center, where shock amplitude is the largest. Tissue is heated to high temperatures in a very small volume of 0.2 mm width, then, a boiling bubble starts to grow (frame d) to a much larger volume creating a mm-sized vapor cavity. The incident shocks interact with the tissue–bubble interface, causing mechanical fragmentation of tissue in a much larger volume than that heated to create the initial bubble.

Boiling histotripsy lesions

Mechanically emulsified lesions without visible thermal damage can be produced under the conditions that the pulse length is not significantly greater than the time-to-boil and the pulse rate is low enough to provide tissue cooling between pulses.[13,15] The results of such a boiling-histotripsy protocol are very repeatable in terms of the location, shape, size, and the content of the lesions (Fig. 11). As an example, a sequence of four single lesions was produced in *ex-vivo* bovine liver using a typical pulsing protocol: 2-MHz HIFU frequency, 70 MPa shock amplitude at the focus, 10 ms pulse

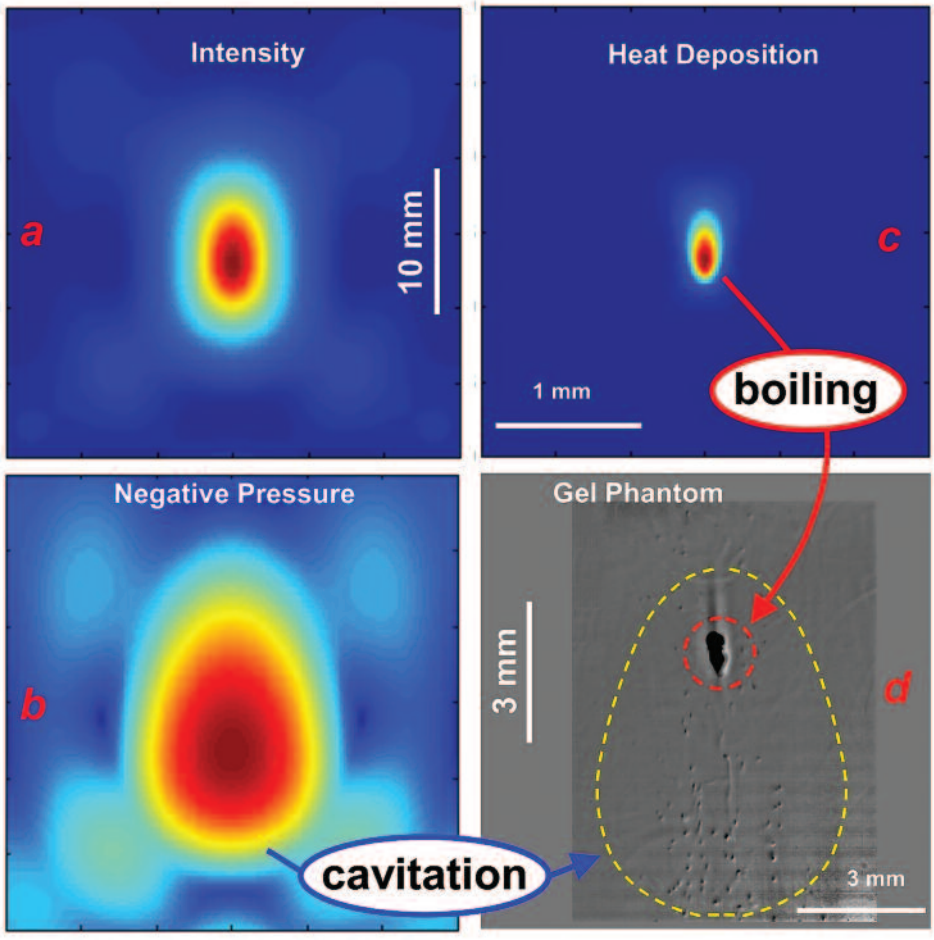

Fig. 10. Modeling of the acoustic field from a 2 MHz HIFU transducer of 4.4 cm diameter and focal length in a tissue-mimicking gel phantom (a-c) and corresponding visualization of initiation of boiling at the focus after 9 ms of exposure (d). Irradiation was from the bottom, 2 D distributions of intensity (a), peak negative pressure (b), heat deposition rate (c) were simulated in the axial plane of the transducer using the KZK equation. Focal intensity was 12 kW/cm^2, pressure waveforms with 70 MPa shocks formed at the focus. Cavitation was also observed in a larger volume around the focus following the peak negative pressure pattern, but did not affect heating at the focus. Modeling predicted heating by shocks to boiling temperature in 7 ms and initiation of boiling was detected in measurements in 9 ms. (10d adapted from part of a figure in reference 14)

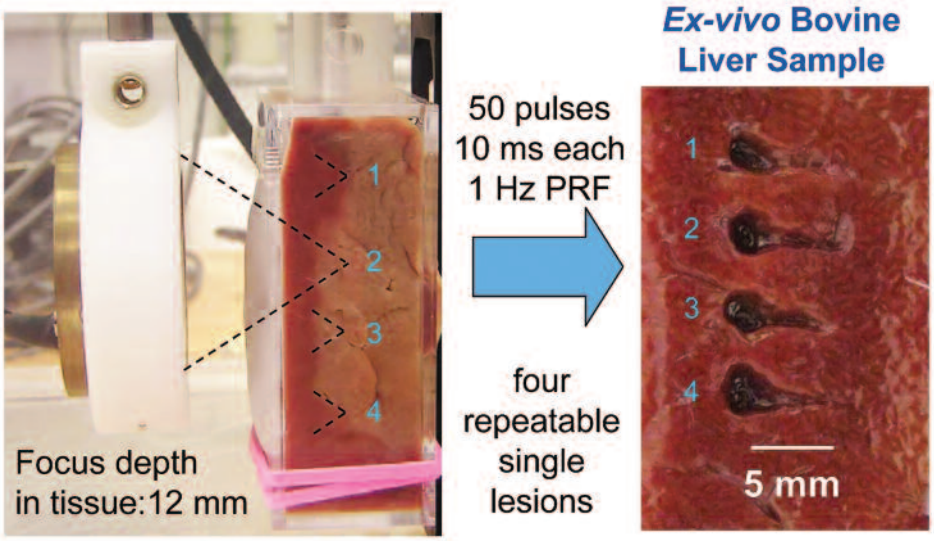

Fig. 11. Boiling histotripsy lesions lesions produced in excised bovine liver by four independent exposures using a 2 MHz HIFU transducer of 4.4 cm diameter and focal length. Shock amplitude at the focus was about 70 MPa and time-to-boil was 4 – 5 ms.

duration, and 0.01 duty factor. The time-to-boil was first predicted using weak shock theory and then used to define pulse lengths and duty factors. The sequence of 50 pulses produced a liquefied cavity in the tissue. Histological studies also confirmed that tissue thermal injury in such lesions is negligible compared to the mechanical injury caused by the exploding boiling bubble and its further interaction with shocks.[34]

In the experiment shown in Fig. 11, time-to-boil was predicted theoretically and occurrence of boiling within each pulse was also controlled in the experiment. As large boiling bubbles are strong scatters, onset of boiling at the focus provided a contrast for B-mode ultrasound imaging and also resulted in fluctuations of the HIFU source drive voltage recorded by a high-voltage probe.[35,14] No thermal damage was observed in the lesion content shown in Fig. 11. However, if pulse duration, the duty factor, or the focal pressures were increased, thermal denaturation of the lesion content was detected both visually as blanching and with histology.[34] It was therefore shown that boiling histotripsy can produce lesions with different degrees of thermal effects which can be controlled by varying parameters of the pulsing scheme.

Mechanisms of boiling histotripsy

Experimental studies have shown that boiling histotripsy can be induced in different types of soft tissues and using different frequencies of 1 – 3 MHz.[15] Mechanical fragmentation of tissue without thermal denaturation was realized if several key components of the exposure were combined together: shock fronts higher than 40 MPa were present at the focus, shock amplitude was high enough to initiate boiling in several milliseconds, pulses were a little longer than time-to-boil, and the repetition rate of the pulsing scheme was slow enough so that thermal effects did not accumulate. No histotripsy occurred if any of these components was absent. However, it was not clear how mm-sized vapor bubbles can fragment tissue into sub-micron pieces. Recently, it was proposed that the major mechanisms involved in this process are acoustic atomization and formation of a miniature fountain from tissue into the boiling bubble.[36,37]

Ultrasound atomization or the emission of small liquid droplets into the air creating a fog is a well-known phenomenon that occurs when an ultrasound wave passes through the liquid-air interface.[38,39] When high intensity ultrasound is focused at the interface, the acoustic radiation force pushes the liquid and creates a fountain. These effects have been used as a basis of air humidifiers and medical nebulizers. It was hypothesized that similar to liquids, tissues can be atomized and produce fountains. Based on this hypothesis, the following scenario of boiling histotripsy process was proposed and tested (Fig. 12).[40] High amplitude

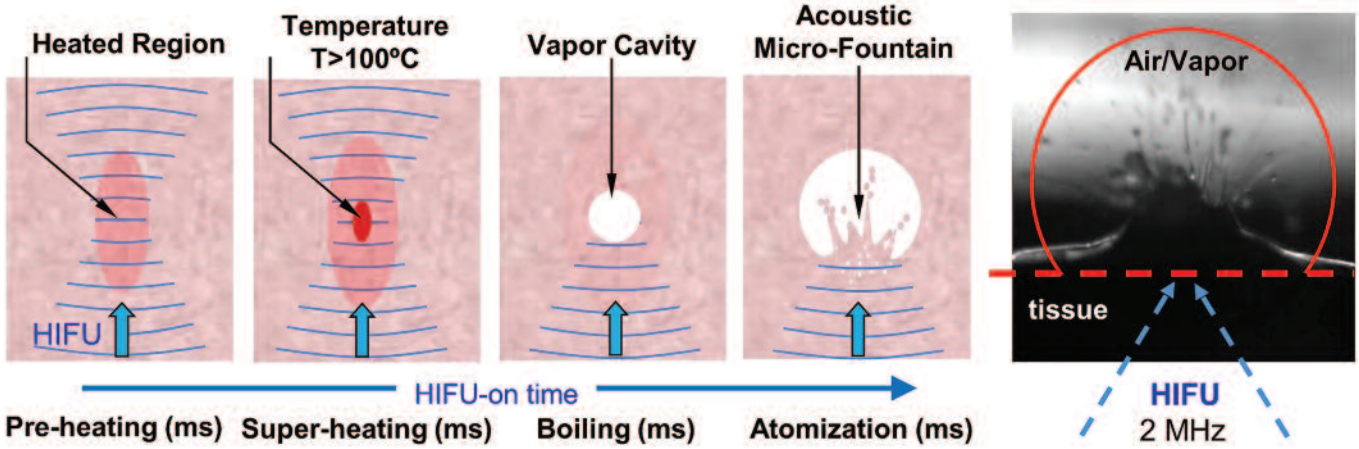

Fig. 12. Illustration of the proposed boiling histotripsy mechanism. (Left) Shock waves are superfocused and rapidly heat tissue to a boiling temperature in a small volume at the focus. The boiling bubble is initiated in milliseconds and grows to a millimeter size. Shock waves interact with the vapor cavity generating atomization and an acoustic fountain from the tissue interface into the cavity. (Right) Experiment mimicking histotripsy processes in the vapor cavity. A frame of high speed photography showing atomization and a fountain at the free tissue/air interface generated by focusing the ultrasound beam at the surface of bovine liver. (Adapted from part of a figure in reference 40)

shocks develop in a small volume within focal region of a HIFU beam and rapidly heat this volume to boiling temperatures. A boiling bubble is initiated in milliseconds and grows to a millimeter size. Shock waves interact with the vapor cavity generating atomization and an acoustic fountain from the tissue interface into the cavity. The experimental illustration mimicking the histotripsy process in the vapor cavity is presented on the right of the Fig. 12. A frame of high speed photography shows atomization and fountain production at the free tissue/air interface generated by focusing an ultrasound beam at the surface of *ex-vivo* bovine liver. Atomization and acoustic fountain production were therefore proposed as a mechanism of mechanical tissue damage: a large cavity is formed in tissue due to shock heating and boiling in milliseconds, and then interaction of shock waves with the tissue/cavity interface fragments the tissue.

Summary

High intensity focused ultrasound has been previously applied to ablate tissue noninvasively through absorption-induced heating. However, at very high focal pressure amplitudes, strong nonlinear effects manifest such as shock formation, cavitation, and rapid boiling resulting in mechanical effects. At their extreme, these phenomena can be applied to completely disintegrate tissue structures, i.e., to produce histotripsy. Both histotripsy technologies overviewed in this article may hold advantages over thermal therapy. While the dose must be tightly regulated in thermal therapy to control heat diffusion and collateral tissue damage, blood vessels can transfer heat away from the treatment site by convection, causing distortion of a thermal lesion. Cavitation clouds and shock-induced boiling are inherently self-limited to the focal volume by the processes described above. Because heat diffusion is not an essential component of histotripsy, the modalities described above may provide a much more compelling argument for the wider clinical acceptance of noninvasive, focused-ultrasound therapy. In addition, bubbles and tissue breakdown can also be visualized on ultrasound imaging as targeting feedback for the surgeon, while acoustic detection of heating is very difficult. Finally, the ability to actually disintegrate tissue rather than just causing necrosis may aid reabsorption into the body and allows new clinical applications which cannot be accomplished with thermal HIFU.

It may be surprising that the same effect can be achieved by two completely separate paths, using different acoustic pulsing schemes. However, both of these schemes utilize relatively large cavities (0.1 – 1 mm) created in the tissue to achieve the effect, generated in different ways. It may be stress induced by expansion and collapse of the bubbles or atomization that fractionate tissue. In reality, it is likely that each mechanism contributes in some degree to both cavitation and boiling histotripsy. Regardless, it is clear that nonlinear acoustic propagation and shock waves play a critical role in both the creation of the cavitation cloud and the vapor cavities of millisecond boiling, as well as providing mechanisms of ultrasound interaction between tissue and bubbles. These studies reflect the importance of acoustic principles in understanding and predicting the interactions that drive this new medical technology.

Acknowledgments

The authors greatly acknowledge support from the National Institutes of Health (NIH) under grants RO1 EB007643 (V. Khokhlova), R01 EB008998 (Z. Xu), and the T32 Multidisciplinary Training Program in Benign Urology at the University of Washington (A. Maxwell). The authors would like to thank Tzu-Yin Wang, Timothy Hall, William Roberts and many others from the Therapeutic Ultrasound Group at the University of Michigan who have contributed to development of cavitation-based histotripsy. We also thank Michael Canney, Tatiana Khokhlova, Julianna Simon, Wayne Kreider, Joo Ha Hwang, and Yak-Nam Wang who greatly contributed to developing boiling histotripsy technology at the University of Washington over the last several years.AT

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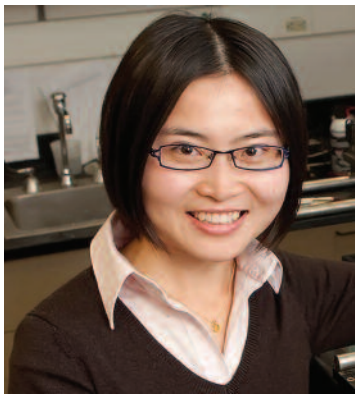

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Statement of Ownership, Management and Circulation

1. *Publication title:* Acoustics Today
2. *Publication number:* ISSN1557-0215
3. *Filing Date:* 1 October 2012
4. *Issue frequency:* Quarterly
5. *No. of issues published annually:* 4
6. *Annual subscription price:* $5
7. *Complete mailing address of known office of publication:* 2 Huntington Quadrangle, Melville, NY 11747-4502
8. *Complete mailing address of headquarters or general business offices of the publisher:* 2 Huntington Quadrangle, Suite 1NO1, Melville, NY 11747-4502
9. *Full names and complete mailing addresses of publisher, editor and managing editor:*
   Publisher: Acoustical Society of America, 2 Huntington Quadrangle, Suite 1NO1, Melville, NY 11747-4502
   Editor: Richard Stern, Acoustical Society of America, Suite 1NO1, 2 Huntington Quadrangle, Melville, NY 11747-4502
   Managing editor: none
10. *Owner (if the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a Partnership or other unincorporated firm, give its name and address as well as those of each individual owner. If the publication is published by a nonprofit organization, give its name and address:* Acoustical Society of America, Suite 1NO1, 2 Huntington Quadrangle, Melville, NY 11747-4502
11. *Known bondholders, mortgagees and other security holders owning or holding 1 per cent or more of total amount of bonds, mortgages or other securities:* None
12. *The purpose, function and nonprofit status of this organization and the exempt status for Federal income tax purposes:* The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes has not changed during preceding 12 months.
13. *Publication name:* Acoustics Today
14. *Issue date for circulation data below:* July 2012
15. *Extent and nature of circulation:*

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