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Active Focal Zone Sharpening for High-Precision Treatment Using Histotripsy

Tzu-Yin Wang,

Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI
(tzuyin@umich.edu).

Zhen Xu[Member, IEEE],

Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI.

Timothy L. Hall,

Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI.

J. Brian Fowlkes[Member, IEEE],

Departments of Radiology and Biomedical Engineering, University of Michigan, Ann Arbor, MI.

William W. Roberts, and

Department of Urology and Biomedical Engineering, University of Michigan, Ann Arbor, MI.

Charles A. Cain[Fellow, IEEE]

Departments of Biomedical Engineering and Electrical Engineering and Computer Science,
University of Michigan, Ann Arbor, MI.

Abstract

The goal of this study is to develop a focal zone sharpening strategy that produces more precise lesions for pulsed cavitation ultrasound therapy, or histotripsy. Precise and well-confined lesions were produced by locally suppressing cavitation in the periphery of the treatment focus without affecting cavitation in the center. The local suppression of cavitation was achieved using cavitation nuclei preconditioning pulses to actively control cavitation in the periphery of the focus. A 1-MHz 513-element therapeutic array was used to generate both the therapy and the nuclei preconditioning pulses. For therapy, 10-cycle bursts at 100-Hz pulse repetition frequency with P−/P+ pressure of 21/76 MPa were delivered to the geometric focus of the therapeutic array. For nuclei preconditioning, a different pulse was delivered to an annular region immediately surrounding the focus before each therapy pulse. A parametric study on the effective pressure, pulse duration, and delivery time of the preconditioning pulse was conducted in red blood cell-gel phantoms, where cavitation damage was indicated by the color change resulting from local cell lysis. Results showed that a short-duration (20 μ s) preconditioning pulse at a medium pressure (P−/P+ pressure of 7.2/13.6 MPa) delivered shortly before (30 μ s) the therapy pulse substantially suppressed the peripheral damage by $77 \pm 13\%$ while complete fractionation in the focal center was maintained. High-speed imaging of the bubble cloud showed a substantial decrease in the maximum width of the bubble cloud by $48 \pm 24\%$ using focal zone sharpening. Experiments *ex vivo* in livers confirmed that highly confined lesions were produced in real tissues as well as in the phantoms. This study demonstrated the feasibility of active focal zone sharpening using cavitation nuclei preconditioning, allowing for increased treatment precision compared with the natural focal width of the therapy transducer.

I. Introduction

Histotripsy is a cavitation-based tissue ablation technology that mechanically fractionates soft tissues using ultrasound pulses of high intensity (peak negative pressure >8 MPa) and

short duration ($<50\text{ }\mu\text{s}$) delivered at low duty cycles ($<1\%$) [1]–[4]. Lesions produced by histotripsy have size and shape approximately matching those of the focal zone of the therapy transducer. A $\sim 1\text{-mm}$ wide transition zone with scattered damaged spots is typically present at the lesion boundary [3], [5].

The goal of this study is to develop a focal zone sharpening strategy that produces highly confined lesions compared with the natural size of the focal zone without sacrificing the treatment efficiency. Our previous studies have demonstrated that the histotripsy process is highly correlated with the presence of cavitation bubble clouds [1], [6]–[10], suggesting that these bubble clouds are the causative agents of the mechanical tissue disruption. A more recent study has demonstrated that the size and shape of the lesions matches well with the dimensions of the bubble clouds [11]. Accordingly, we hypothesize that highly confined lesions may be produced by limiting the spatial extent of the cavitation bubble clouds. This may be achieved using local cavitation suppression in the periphery of the focus.

Various schemes have been proposed to suppress excess cavitation damage in cavitation-based therapies. Willis *et al.* have found that, in lithotripsy, the protection of a local selected area is possible by delivering several pretreatment low-intensity shockwaves [12]. Using this strategy, the renal damage produced by shockwave lithotripsy can be significantly reduced. The mechanism is hypothesized to be physiologic, i.e., vasoconstriction triggered by the low-intensity shockwaves. Other researchers have demonstrated that application of overpressure or a time-reversed waveform may suppress the cavitation bubble activity, thus reducing cell or tissue injuries induced by shockwave lithotripsy [13]–[16]. The possible drawback of these approaches is global suppression of cavitation, which may cause less-efficient treatments for target objects [13], [17]. To address this issue, local suppression of cavitation is necessary. The local suppression of cavitation may be achieved either by injecting cavitation suppressing agents, as suggested by Kawabata *et al.* [18], or by delivering specially designed insonation waveforms, as observed by Chapelon *et al.* [19].

We propose a strategy for focal zone sharpening, where cavitation in the periphery of the focus may be suppressed using cavitation nuclei preconditioning. Because cavitation depends on a distribution of appropriately sized cavitation nuclei [20], [21], it is plausible that cavitation may be actively suppressed by altering the cavitation nuclei distribution. Our unpublished work shows that the distribution of the cavitation nuclei (possibly the microbubbles persisting from previous therapy pulses [22], [23]) may be changed using histotripsy pulses at a reduced intensity. Based on this observation, we propose a concurrent spatial-temporal pulsing strategy or focal zone sharpening. An ultrasound pulse is delivered to the periphery of the focus before each therapy pulse. This pulse is hypothesized to precondition the cavitation nuclei such that cavitation may be locally suppressed in the periphery.

In this paper, we investigated the feasibility of focal zone sharpening using the proposed pulsing strategy. We first explored effective pulse parameters by which complete damage in the focal center and minimum damage in the peripheral region occurred. To study effects of nuclei preconditioning on the spatial extent of cavitation, the cavitating bubble clouds generated with and without nuclei preconditioning were observed using high-speed photography. Experiments were performed both in red blood cell (RBC) phantoms and *ex vivo* livers. The former allowed rapid evaluation of the effective pulse parameters; the latter provided validation in real tissues. The focal zone sharpening technique could have significant clinical applications in which a target tissue is to be disrupted but the critical structures immediately adjacent to it are to be preserved.

II. Materials and Methods

A. Cavitation Damage Indication Phantom Preparation

Cavitation damage indication phantoms consisted of a thin (<1 mm) RBC-gel layer suspended in between two 2-cm-thick transparent gel layers. The phantoms were prepared using a mixture of high-clarity low-gelling-temperature agarose powder (Type-VII, Sigma-Aldrich, St. Louis, MO) and canine RBCs in 0.9% isotonic saline. Canine blood was obtained from healthy adult subjects and preserved with an anticoagulant solution (citrate-phosphate-dextrose C1765, Sigma-Aldrich) at 4°C . The RBCs were extracted from the whole blood before the preparation of the phantoms. The agarose powder was mixed with saline at a 1% w/v concentration, and heated until the agarose powder completely melted. The solution was placed in a vacuum chamber for 20 min to remove excess air bubbles in the solution. After air bubbles were removed, a 2-cm layer of agarose solution was poured in a 13 cm (width) $\times$ 7.5 cm (length) $\times$ 4 cm (height) polycarbonate holder which had a thin optically and acoustically transparent polyester membrane on the bottom. The holder was stored at 4°C to allow the agarose layer to solidify. A small volume of agarose solution was taken from the remaining solution, and the RBCs were mixed in this volume using 5% v/v concentration at 42°C . A thin layer of the RBC-gel solution was uniformly deposited onto the bottom layer. After the RBC-gel layer solidified, the remaining agarose solution was poured to completely fill the holder. More details on the RBC phantom are provided in [11].

B. Experimental Setup

The experimental setup is shown in Fig. 1. A 1-MHz 513-element 2-D therapeutic phased array transducer (Imasonic, Voray sur l'Ognon, France) was used to generate both the therapy and preconditioning pulses. The 2-D phased array is a 145-mm-diameter section of a spherical shell, and has a 150 mm geometric focal length and a 50-mm-diameter hole in the center [Fig. 2(a)].

Before experimentation, the geometric focus of the therapeutic array was located using a field scan with a custom-built fiber optic probe hydrophone (FOPH) [24]. The fiber tip was placed at the geometric focus after the field scan. Two 1-mm-wide 5-mW laser beams were generated using laser diode modules (Calpac lasers, Steamboat Springs, CO). The two laser beams, one along and the other perpendicular to the ultrasound beam, were placed to cross at the tip of the FOPH, indicating the geometric focus of the therapeutic array. The FOPH was then removed from the tank. The location of the geometric focus was confirmed by generating bubble clouds at the cross-section of the two lasers with a brief excitation of the transducer. After locating the geometric focus, the RBC phantom was placed in the tank such that the RBC-gel layer was perpendicular to the ultrasound beam. Multiple treatments were performed in a single RBC phantom. Each lesion was generated using multiple pulses delivered to a single focal location. The spacing between the adjacent lesions was at least 10 mm to avoid interference from different treatments.

C. Ultrasound Generation and Focal Pattern Synthesis

The driving phase and intensity of each element on the 513-element 2-D phased array can be individually controlled by an array control system designed and constructed in our group [25]. Therapy pulses were generated with all elements driven in phase focused at the geometric focus.

To deliver preconditioning pulses to the annular region immediately surrounding the treatment center, a direct focal pattern synthesis technique was used. The array elements were divided into four sectors as a sector vortex array, which produces multi-foci patterns by applying a specially designed phase delay to each sector [26], [27]. In the present study, a

phase delay of 0 , $\pi/2$, π , or $3\pi/2$ was assigned to each sector [Fig. 2(b)]. This particular phasing simultaneously excited 4 foci in the annular region surrounding the central axis while maintaining a zero intensity all along the central axis. Fig. 2(c) shows the 4-foci pattern simulated by summing the contribution from each rectangular radiator on the array using the Rayleigh-Sommerfeld integral [28]. It is noted that continuous wave source and linear propagation were assumed for the simulation. Nonlinear propagation and transient response were not incorporated. As shown in Fig. 2(c), gaps exist between the four foci in the annular region. The annular region would not be uniformly treated with a single 4-foci pattern. To more uniformly treat the entire annular region, 4 multi-foci patterns were generated. Each pattern contained 4 foci as shown in Fig. 2(c), but was rotated 0° , 22.5° , 45° , or 67.5° around the central axis of the array. The four patterns were fired sequentially with zero delay between patterns.

D. Ultrasound Calibration

Acoustic waveforms were calibrated in degassed water using the FOPH with a 100- μm -diameter active element. The peak negative (P $-$) and peak positive (P $+$) pressures were measured. The -6-dB beamwidths were calculated on both P $-$ and P $+$ pressure profiles.

For therapy pulses, the P $-$ /P $+$ pressures were measured to be 21/76 MPa [Fig. 3(a)]. The lateral and axial -6-dB beamwidths were measured at a reduced P $-$ /P $+$ pressure of 10/45 MPa. The lateral -6-dB beamwidth measured on the P $-$ and P $+$ pressure profiles were 2.0 mm and 0.7 mm, respectively. The axial -6-dB beamwidth measured on the P $-$ and P $+$ pressure profiles were 19.0 mm and 7.5 mm, respectively. The beamwidths at higher pressures could not be successfully measured because cavitation may occur within a few pulses and damage the fiber tip during the pressure profile scan. The measurements were performed both with and without the therapeutic array firing the preconditioning pulses. The beamwidths were identical in both cases. A small variation in the peak pressures (<1 MPa) was found to occur when preconditioning pulses were fired. Because the pressure of the therapy pulse was much greater than the threshold for producing histotripsy lesions [2], this pressure variation was considered negligible.

For preconditioning pulses, a full 2-D field scan on the focal plane was performed with total pulse duration of 20 cycles (i.e., 5 cycles for each pattern) at P $-$ /P $+$ pressure of 7.2/13.6 MPa. At each sample location on the focal plane, the pressure waveforms of the preconditioning pulse was recorded [a representative waveform is shown in Fig. 3(b)]. Spatial pressure distributions of the preconditioning pulses are displayed in Fig. 3(c)–(d). The -6-dB beamwidth on the P $-$ pressure profile approximately covered an annular region with a 0.7 mm inner diameter and a 4.3 mm outer diameter; the -6-dB beamwidth on the P $+$ pressure profile approximately covered an annular region with a 1.3 mm inner diameter and a 3.5 mm outer diameter.

E. Ultrasound Exposure Conditions

A concurrent pulsing strategy was investigated for focal zone sharpening. A preconditioning pulse was delivered to the annular region surrounding the focus before each therapy pulse. A schematic of the pulse sequence is illustrated in Fig. 4. In all experiments, 10-cycle therapy pulses were delivered to the geometric focus with a constant pressure at P $-$ /P $+$ pressure of 21/76 MPa. The pulse repetition frequency (PRF) in this paper refers to the repetition frequency of the entire two-pulse sequence, and was held constant at 100 Hz. Both the therapy and the preconditioning pulses were delivered at 1 MHz. Each lesion was produced by a total of 5000 pulse sequences.

To find effective pulse parameters for focal zone sharpening, a parametric study was performed on the effects of 1) pressure, 2) pulse duration, and 3) delivery time of the preconditioning pulses. The pressures of the preconditioning pulses ranged from below to slightly above the threshold for inducing histotripsy lesions (P-/P+ pressure ~8/17 MPa as suggested in [2]). The pulse durations were tested in the range commonly used in histotripsy ($<50 \mu\text{s}$). The delivery times of the preconditioning pulse were tested within the pulse repetition period of the therapy pulse. A total of 107 treatments in the RBC phantoms were included for the parametric study. The exposure conditions of the three experimental series are summarized in Table I. Effective pulse parameters for focal zone sharpening were derived from the parametric study and used in the subsequent studies.

F. Lesion Analysis

Because the RBCs were lysed in the local area treated with histotripsy, more light could penetrate through the damaged area, resulting in increased brightness. Therefore, the damaged area could be clearly visualized through the transparent gel layers [Figs. 5(a)–5(c)]. The lesions were imaged using a digital camera (Coolpix 4500, Nikon, Tokyo, Japan) with backlighting provided from a white light table (Porta-Trace, Gagne, Johnson City, NY). Quantitative analysis of the lesion images was performed using Matlab (The MathWorks Inc, Natick, MA). The presence of damage at each pixel was determined when the pixel intensity exceeded a threshold of $\text{mean} + 3 \times \text{standard deviation}$ intensity in the unaffected area. Using this threshold, the original bright-field lesion images were converted to binary lesion images [Figs. 5(d)–5(f)]. The damaged areas in the treatment center and in the peripheral annular region were measured separately. To define the treatment center and the peripheral annular region, the centroid of the entire lesion was located on the binary lesion images. A ring centered at the centroid of the lesion with a 1.3 mm inner diameter and a 3.5 mm outer diameter was defined as the peripheral annular region [Figs. 5(e) and 5(f)]. This ring area was the overlapped region of the -6-dB beamwidths on the P- and P+ pressure profiles, i.e., approximate focal zone, of the preconditioning pulses. The area surrounded by the ring was defined as the treatment center. The damaged area was calculated by integrating the pixels in the presence of damage for each region.

G. High Speed Photography of Bubble Clouds

Bubble clouds generated with or without focal zone sharpening were imaged using a 12-bit, 1280×960 pixel high-speed camera (SIM02, Specialised Imaging Ltd., Hertfordshire, UK). The bubble clouds were generated in an optically transparent agarose phantom prepared without the RBCs. Backlighting was provided using a high-power short-duration white light flash lamp (SIL 500, Specialised Imaging Ltd., Hertfordshire, UK). A projection of the bubble cloud on an axial-lateral plane of the therapeutic array was captured. Bubble clouds were imaged from $6 \mu\text{s}$ before the therapy pulse's arrival at the focus, to $14 \mu\text{s}$ after the pulse ended, with an interframe delay of $2 \mu\text{s}$ and an exposure time of 100 ns . This imaging duration ensured the observation of the maximum spatial extent of the bubble cloud, because the maximum size of the bubble cloud has been found to occur at the end of the pulse [10], [29].

The spatial extent of the bubble cloud was measured using the maximum width of the bubble cloud in the lateral direction of the therapeutic array. The pixels representing bubbles were determined as those for which the pixel intensity was below a threshold of $\text{mean} - 3 \times \text{standard deviation}$ of the background pixel intensity. A histogram was calculated for the lateral positions of the pixels representing bubbles. The width of the bubble cloud was defined as distance between the 5th and 95th percentile of the histogram. A maximum width of the bubble cloud was calculated for each bubble cloud. A mean and standard deviation of the maximum width were obtained from 8 independently generated bubble clouds with and

without focal zone sharpening. Because the area of the lesion matched well with that of the bubble cloud [11], the maximum width of the bubble cloud should be proportional to the square root of the maximum lesion area.

H. Treatments in Ex Vivo Tissues

A total of 4 *ex vivo* treatments were performed in freshly excised canine livers to validate the effects of focal zone sharpening in real tissues. The canine liver tissues were obtained from healthy adult research subjects, preserved in degassed saline at room temperature, and used within 3 h of harvest. The liver tissues were sectioned into 9 cm (width) $\times$ 5 cm (length) $\times$ 5 cm (thickness) samples, sealed in Ziploc bags filled with saline, and placed where the RBC phantom was in Fig. 1. The acoustic parameters used for the *ex vivo* tissue treatments were the same as those derived from the parametric study described previously. Each lesion was produced using 5000 therapy pulses. After treatments, the tissue samples were fixed in formalin and prepared for hematoxylin and eosin (H&E) sections. The lesions were sectioned transversely with respect to the ultrasound beam. Multiple 5- μ m thick H&E sections were made through the entire lesion. The sections with the maximum spatial extent of damage were examined with comparisons between those with and without focal zone sharpening.

III. Results

A. Parametric Study for Pulse Sequence Development

Representative lesion images are shown in Fig. 5. In an untreated area, the RBC phantom appeared translucent [Fig. 5(a)]. The RBCs in this area also appeared intact under microscopic examination. In a treated area, the lesion was clearly visualized as the damaged locations turned transparent. The lesions produced with and without focal zone sharpening appeared significantly different. Lesions produced without focal zone sharpening had a $\sim$ 2 mm diameter damaged area in the center with an irregular boundary. Immediately surrounding the center was a $\sim$ 1 mm transition zone of round or elliptically shaped scattered damaged spots. The diameters of these scattered damaged spots ranged from 50 to 200 μ m each. Very few, if any, damage spots were observed outside the transition zone [Fig. 5(b)]. In contrast, highly confined lesions were produced using focal zone sharpening. The damaged area was $\sim$ 1.5 mm in diameter with a smoother boundary and very few peripheral damaged spots [Fig. 5(c)].

1) Effects of Pressure of Preconditioning Pulses—Fig. 6 shows representative binary lesion images and the damaged area as a function of the peak negative pressure of the preconditioning pulses. Student's *t*-test and one-way ANOVA were performed to compare the calculated damaged area for each case. Results indicated that: 1) the damaged area in the center was similar for all pressures except for the lowest pressure, 4.6 MPa ($p < 0.01$, $N = 7$ to 24; ANOVA); 2) the damaged area in the peripheral annular region was reduced for all pressures, and decreased with decreasing pressures within 4.6 to 11.5 MPa ($P < 0.01$ for each pair, $N = 7$ to 24; *t*-test). The preconditioning pulses at the lowest pressure (4.6 MPa) reduced the damage in the peripheral annular region most significantly but also resulted in incomplete treatment in the center. Therefore, a medium pressure level, 7.2 MPa, was chosen to achieve focal zone sharpening without interfering treatment in the center.

2) Effects of Pulse Duration of Preconditioning Pulses—Fig. 7 shows representative binary lesion images and the damaged area as a function of the pulse duration of the preconditioning pulses. Results showed that: 1) the damaged area in the center was similar for all cases ($p > 0.2$, $N = 6$ to 24; ANOVA); and 2) the damaged area in the peripheral annular region was reduced with preconditioning pulses using all 4 pulse

durations, and the smallest damaged area was achieved at pulse duration of 20 cycles ($p < 0.06$ for each pair, $N = 6$ to 24; t -test).

3) Effects of Separation Time Between Preconditioning and Therapy Pulses—

Fig. 8 shows representative binary lesion images and the damaged area as a function of the separation time between preconditioning and therapy pulses. Here, the separation time refers to the interval from the end of the preconditioning pulse to the beginning of the therapy pulse. Results indicated that: 1) the damaged area in the center was similar for all cases ($p > 0.05$, $N = 6$ to 24; ANOVA); 2) the damaged area in the peripheral annular region was reduced with a separation time no longer than half pulse repetition period, i.e., 5000 μs ($p < 0.01$ for each pair, $N = 6$ to 24; t -test); the minimum was found at the shortest tested separation time, 10 μs ($p < 0.01$ for each pair, $N = 6$ to 24; t -test); no discernible difference was found among separation times of 100 to 5000 μs ($p > 0.2$, $N = 6$ to 24; ANOVA); the damaged area in the periphery was similar to the control when the preconditioning pulse was delivered long before (9900 μs) the therapy pulse, or shortly (100 μs) after the previous therapy pulse ($p > 0.6$, $N = 6$ to 24; t -test).

Based on these results, we found an effective pulse sequence for focal zone sharpening consisting of a 20-cycle pulse delivered to the peripheral annular region at P-/P+ pressure of 7.2/13.6 MPa before the therapy pulses with a separation time of 10 μs . This pulse sequence was used for the subsequent studies.

B. High Speed Photography of Bubble Clouds

The bubble clouds produced with and without focal zone sharpening shared the same evolutionary trend (Fig. 9). The bubble cloud grew along the direction of ultrasound as the ultrasound pulse propagated through the focus. After the ultrasound pulse ceased, the bubble cloud shrank in size and gradually disappeared on the optical images. The maximum spatial extent of the bubble cloud was achieved at the end of the ultrasound pulse. Individual bubbles in the cloud formed and grew during the pulse. The individual bubbles grew to $\leq 200 \mu\text{m}$ in radius by the end of the pulse, and gradually dissolved after the pulse ended.

The shape and size of the bubble clouds produced with and without focal zone sharpening were significantly different. Without focal zone sharpening, the bubble cloud was composed of sparsely distributed individual bubbles in a cigar-shaped region [Fig. 9(a)]. With focal zone sharpening, the majority of individual bubbles appeared in a more confined region along the central axis, resulting in a much narrower and denser bubble cloud. Fewer bubbles were present in the periphery [Fig. 9 (b)]. The maximum width of the bubble cloud was calculated with and without focal zone sharpening (Table II). The results indicated that the maximum width of the bubble cloud decreased by $48 \pm 24\%$ using focal zone sharpening ($p < 0.01$, $N = 8$; t -test).

C. Treatments in Ex Vivo Tissues

The lesion histology demonstrated that highly confined lesions were produced in real tissues using focal zone sharpening as well as in the RBC phantoms.

Without focal zone sharpening, a completely fractionated region approximately 1.5 mm in diameter was observed in the center of the lesion. No recognizable tissue or cellular components were found in this region [Fig. 10(a)]. Scattered damaged spots were present in a ~ 0.8 mm transition zone outside the central damaged region [Fig. 10(c), for example]. The diameter of the peripheral damaged spots ranged from 60 to 200 μm each.

With focal zone sharpening, the central damage region was narrowed to approximately 0.8 mm in diameter [Fig. 10(b)]. Much smoother lesion boundaries with no significant scattered damaged spots were observed [Fig. 10(d)].

IV. Discussion and Conclusions

We have demonstrated that highly confined lesions can be produced using spatial control of the bubble cloud in histotripsy. Although damage in the periphery was suppressed, complete fractionation in the treatment center was achieved. The effect of focal zone sharpening has been demonstrated both in RBC phantoms and in *ex vivo* tissues. This technique could be useful in many clinical applications where precise and confined tissue ablation is needed, such as fetal or neonate surgery [1].

High-speed imaging of the bubble clouds illustrated that the preconditioning pulses substantially altered the appearance of the bubble clouds. The cigar-shaped bubble cloud produced without focal zone sharpening is consistent with our previous observations [9], [10] and with the general shape of the focal zone of the geometrically focused field. Because the lesion most likely occurred where the cavitation bubbles appeared [11], this cigar-shaped bubble cloud may account for the cigar-shaped lesions observed in our previous *in vitro* and *in vivo* studies [3], [5]. Using the focal zone sharpening strategy, much narrower and denser bubble clouds were generated. The significant change in the spatial extent of the bubble cloud may explain why more confined lesions were produced.

The mechanisms underlying focal zone sharpening may involve a combination of several effects that are incompletely understood. One possibility is that the preconditioning pulses may have changed the sizes of the cavitation nuclei in the periphery by inducing the growth or collapse of the cavitation nuclei (an effect similar to that in [30]–[32]). This change in the sizes of the cavitation nuclei may raise the local cavitation threshold [20], [21], and suppress local cavitation. Another possibility is that the cavitation nuclei may have been propelled away from the periphery by the radiation force generated in the acoustic field of the sector vortex configuration [33]. This may remove the available cavitation nuclei and prevent cavitation in the periphery. In addition, researchers have observed that the spatial extent of the bubble cloud may decrease with increased cavitation nuclei concentration [34]. It is possible that the preconditioning pulses may have excited excess cavitation nuclei such that a dense and narrow bubble cloud was formed. An investigation into the underlying mechanisms is underway.

The demonstration of local suppression of cavitation damage in a selected zone implies a more general application: active protection of an arbitrarily selected zone. Complete fractionation of target tissue volume while preserving critical structures has been an important goal for tissue ablation therapies. An intuitive way to protect the critical structures is to intentionally skip over those structures on treatment planning. With the local nuclei preconditioning technique, we may not only passively skip the critical structures, but also actively protect them using appropriate ultrasound pulses. The method would locally raise the threshold for cavitation damage in the selected tissue. As a result, the selected protection zone may be resistant to cavitation damage. Active protection for an arbitrarily selected zone is our ultimate goal and will be pursued in the future.

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Biographies

Tzu-Yin Wang is a graduate student in the Department of Biomedical Engineering at the University of Michigan, Ann Arbor, MI. She received her B.S. degree in 2004 and M.S.

degree in 2006, both in electrical engineering from National Taiwan University, Taipei, Taiwan. Her research interests include ultrasound therapy control and monitoring, mechanisms of cavitation-induced tissue fractionation, and phased array ultrasound transducers for therapeutics.

Zhen Xu (S'05–M'06) is an assistant professor in the Department of Biomedical Engineering at the University of Michigan, Ann Arbor, MI. She received the B.S.E. (highest honors) degree in biomedical engineering from Southeast University, Nanjing, China, in 2001, and her M.S. and Ph.D. degrees from the University of Michigan in 2003 and 2005, respectively, both in biomedical engineering. Her research is focusing on ultrasound therapy, particularly the applications of histotripsy for noninvasive surgeries. She received the IEEE Ultrasonics, Ferroelectrics, and Frequency Control Society 2006 Outstanding Paper Award. She was also selected as the best student paper competition finalist at the 2003 IEEE International Ultrasonics Symposium and 2005 International Symposium on Therapeutic Ultrasound.

Timothy L. Hall was born in 1975 in Lansing, Michigan. He is currently an assistant research scientist in the Department of Biomedical Engineering at the University of Michigan. He received the B.S.E. degree in 1998 and M.S.E. degree in 2001, both in electrical engineering, and he received his Ph.D. degree in 2007 in biomedical engineering, all from the University of Michigan. He worked for Teradyne Inc., Boston, MA, from 1998

to 1999 as a circuit design engineer and at the University of Michigan from 2001 to 2004 as a visiting research investigator. His research interests are in high-power pulsed-RF-amplifier electronics, phased-array ultrasound transducers for therapeutics, and sonic cavitation for therapeutic applications.

Jeffery Brian Fowlkes (M'94–A'94) received his B.S. degree in physics from the University of Central Arkansas in 1983, and his M.S. and Ph.D. degrees from the University of Mississippi in 1986 and 1988, respectively, both in physics. Dr. Fowlkes is an associate professor in the Department of Radiology and in the Department of Biomedical Engineering at the University of Michigan, Ann Arbor, MI. He is currently directing and conducting research in medical ultrasound, including the use of gas bubbles for diagnostic and therapeutic applications. His work includes studies of ultrasound contrast agents for monitoring tissue perfusion, acoustic droplet vaporization for bubble production in cancer therapy and phase aberration correction, effects of gas bubbles in high-intensity ultrasound, and volume flow estimation for ultrasonic imaging. Dr. Fowlkes is a fellow of the American Institute of Ultrasound in Medicine and has served as secretary and as a member of its Board of Governors. He also received the AIUM Presidential Recognition Award for outstanding contributions and service to the expanding future of ultrasound in medicine. As a member of the Acoustical Society of America, Dr. Fowlkes has served on the Physical Acoustics Technical Committee and the Medical Acoustics and Bioresponse to Vibration Technical Committee. As a member of the IEEE, he has worked with the IEEE I&M Society Technical Committee on Imaging Systems. Dr. Fowlkes is a fellow of the American Institute of Medical and Biomedical Engineering.

William Woodruff Roberts was born in Charlottesville, VA, on July 26, 1970. He received his B.S. degree in physics from the Massachusetts Institute of Technology, Cambridge, MA, in 1992 and his M.D. degree from the Johns Hopkins University, Baltimore, MD, in 1997.

From 1997 to 2003, he pursued residency training in General Surgery and Urology at the Brady Urological Institute, Johns Hopkins Hospital, Baltimore, MD, and was appointed an Instructor in Urology in 2003. He joined the faculty at the University of Michigan in 2004 and is currently an assistant professor in the Department of Urology and in the Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI. He was certified by the American Board of Urology in 2006.

Dr. Roberts maintains a busy clinical practice focused on laparoscopy, endourology, and minimally invasive treatment of cancer and stone disease. His research is focused on the preclinical development and clinical application of focused ultrasound as an alternative to surgical and percutaneous interventions.

Charles A. Cain (S'65–M'71–SM'80–F'89) was born in Tampa, FL, on March 3, 1943. He received the B.E.E. (highest honors) degree in 1965 from the University of Florida, Gainesville, FL; the M.S.E.E. degree in 1966 from the Massachusetts Institute of Technology, Cambridge, MA; and the Ph.D. degree in electrical engineering in 1972 from the University of Michigan, Ann Arbor, MI. During 1965 through 1968, he was a member of the Technical Staff at Bell Laboratories, Naperville, IL, where he worked in the electronic switching systems development area.

During 1972 through 1989, he was in the Department of Electrical and Computer Engineering at the University of Illinois at Urbana-Champaign, where he was a professor of electrical engineering and bioengineering. Since 1989, he has been in the College of Engineering at the University of Michigan, Ann Arbor, as a professor of biomedical engineering and electrical engineering. He was the chair of the Biomedical Engineering Program from 1989 to 1996, the founding chair of the Biomedical Engineering Department from 1996 to 1999, and the Richard A. Auhll Professor of Engineering in 2002.

He has been involved in research on the medical applications of ultrasound, particularly high-intensity ultrasound for noninvasive surgery. He was formerly an associate editor of the *IEEE Transactions on Biomedical Engineering* and the *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control* and an editorial board member of the *International Journal of Hyperthermia and Radiation Research*. He is a fellow of the IEEE and the AIMBE.

Fig. 1.

Experimental setup. The 513-element therapeutic array and the motorized positioning system are controlled using a PC console. The therapeutic array is mounted to the tank, facing the RBC phantom. The crossing point of two laser beams, one along and the other perpendicular to the ultrasound beam, indicates the focus of the therapeutic array. The RBC layer is placed on the focal plane.

Fig. 2.

(a) Photograph and (b) element configuration of the 513-element phased array. Using a sector vortex phasing as indicated in (b), an annular focal pattern can be produced. (c) shows the simulation of the annular focal pattern with a color bar indicating the normalized pressure in a linear scale.

Fig. 3.

Calibration of (a) the therapy pulse and (b)–(d) the preconditioning pulse. The waveform of the therapy pulse is shown in (a). A representative waveform of the preconditioning pulse is shown in (b). The waveform of the preconditioning pulse is composed of 4 segments which correspond to the 4 sequentially fired multi-foci patterns. (c) and (d) show the spatial peak negative (P[−]) and peak positive (P⁺) pressure distributions on the focal plane of the 4 sequentially fired multi-foci patterns in the preconditioning pulse. The waveform in (b) was measured at the location indicated by the circles in (c) and (d).

Fig. 4.

A schematic drawing of the concurrent spatial-temporal pulsing sequence for active focal zone sharpening. The upper panels indicate the region where ultrasound pulses were focused (marked in gray). The lower panels show the temporal pulsing sequence. A total of 4 multi-foci patterns were sequentially delivered to the peripheral annular region before each therapy pulse. Effects of the pressure, P_r , and total pulse duration, PD , of the preconditioning pulses, and the separation time between preconditioning and therapy pulses, t_s , were studied.

Fig. 5.

Representative images of the lesions in RBC phantoms are shown in panels (a)–(c). The corresponding binary lesion images are shown in panels (d)–(f), where the damaged area is marked in white and the unaffected area is marked in black. The ring area outlined by the dashed lines indicates the focal zone (overlapped region of the -6 -dB beamwidths on the P^- and P^+ pressure profiles) of the preconditioning pulses.

Fig. 6.

Representative lesion patterns and calculated damaged area in the center and the peripheral annular region using preconditioning pulses at varying pressures. Data points are expressed in mean $\pm$ standard deviation (N = 6 to 24).

Fig. 7. Representative lesion patterns and calculated damaged area in the center and the peripheral annular region using preconditioning pulses at varying pulse durations. Data points are expressed in mean $\pm$ standard deviation ($N = 6$ to 24).

Fig. 8. Representative lesion patterns and calculated damaged area in the center and the peripheral annular region at varying separation times between preconditioning and therapy pulses. Data points are expressed in mean $\pm$ standard deviation ($N = 6$ to 24).

Fig. 9.

High speed optical images of bubble clouds generated (a) without or (b) with focal zone sharpening. The time is displayed with respect to the first cycle's arrival at the focus. The dark crossed lines are the shockfronts of the ultrasound.

Fig. 10.

Histology of lesions produced [(a) and (c)] without, and [(b) and (d)] with focal zone sharpening at different magnifications. At lower magnification [(a) and (b)], a completely homogenized area (H) was observed in the centers with and without focal zone sharpening. Tissue outside this transition zone appeared normal (N). At higher magnification, an irregular lesion boundary with radial projections was observed in lesions produced without focal zone sharpening (c). Lesions produced with focal zone sharpening present a more regular boundary with no significant peripheral damaged spots (d).

TABLE I

Ultrasound Exposure Parameters for Nuclei Preconditioning Pulses.

	Peak positive pressure (MPa)	Peak negative pressure (MPa)	Pulse duration per pattern (cycles)	Total pulse duration (cycles)	Separation time between preconditioning and therapy pulses, t_s (μ s)	Sample size
Control	N/A	N/A	N/A	N/A	N/A	24
Series 1.	8.8	4.6	5	20	10	6
Variable pressure	13.6	7.2				23
	30.2	11.5				12
Series 2.	13.6	7.2	3	12	10	6
Variable pulse duration			5	20		23
			7	28		6
			10	40		6
Series 3.	13.6	7.2	5	20	10	23
Variable separation time between preconditioning and therapy pulses					100	10
					500	12
					5000	7
					9900	6

TABLE II

Maximum Width of Bubble Clouds.

	Maximum width of bubble clouds (mm)	Sample size
No focal zone sharpening	1.35 ± 0.22	8
Focal zone sharpening	0.70 ± 0.32	8