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Enhanced Shock Scattering Histotripsy with Pseudo-Monopolar Ultrasound Pulses

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Abstract

Shock scattering histotripsy involves a complex interaction between positive and negative phases of an acoustic burst to initiate a robust cavitation bubble cloud. To more precisely study these effects and optimize shock scattering histotripsy therapy, we constructed a frequency compounding transducer to generate pseudo-monopolar ultrasound pulses. The transducer consisted of 113 individual piezoelectric elements with various resonant frequencies (250 kHz, 500 kHz, 750 kHz, 1 MHz, 1.5 MHz, 2 MHz, and 3 MHz). For each resonant frequency, an extremely short pulse could be generated. Pseudo-monopolar peak positive pulses were generated by aligning the principal peak positive pressures of individual frequency components temporally so that they added constructively, and destructive interference occurred outside the peak-positive-overlapped temporal window. After inverting the polarity of the excitation signals, pseudo-monopolar peak negative pulses were generated similarly by aligning principal peak negative pressures. Decoupling the positive and negative acoustic phases could have significant advantages for therapeutic applications enhancing precision and avoiding cavitation at tissue interfaces by using mostly positive pressure pulses. For example, we show that 16 shock scattering bubble clouds can be generated using only peak positive pulses following a single peak negative pulse that initiates a pressure-release “seed cloud” from which the first shock front is “scattered”. Subsequent positive only pulses result in a precise elongated lesion within red-blood-cell phantoms.

Index Terms—

cavitation; frequency compounding; histotripsy; shock scattering

I. Introduction

SHOCK scattering histotripsy is a noninvasive ultrasound therapy that uses very short, high-pressure ultrasound pulses to generate robust cavitation clouds to achieve mechanical tissue fractionation. A traditional shock scattering histotripsy pulse consists of 3 to 20 cycles with multiple compressional (positive) and rarefactional (negative) half-cycles that must interact with each other to produce therapeutically effective bubble clouds in a predictable and controllable manner [1]–[6], attributes not usually associated with cavitation phenomena. To

work properly, the peak pressure magnitude of the negative half cycles should exceed about 15 MPa (negative) and the positive half-cycles should be reasonably well-developed shock fronts exceeding about 30 MPa (positive). Mechanistically, Maxwell *et al.* [7] showed that initial negative half-cycles of a histotripsy pulse can generate incidental bubbles which act as pressure-release surfaces from which the positive shock fronts are scattered. Incidental bubbles are single bubbles that are sparsely concentrated and can be generated by multiple sub-intrinsic threshold negative pulses, whose negative pressures (e.g. 18 MPa) are below an intrinsic threshold of about 26 to 30 MPa (negative), based on previous studies [8]–[10]. The incidental bubbles are likely seeded from the pre-existing dissolved sub-micrometer gas bubbles or weak pockets [9]. The scattering process inverts the positive shock fronts that now propagate back towards the transducer and add constructively with the next counter propagating negative half-cycle of the histotripsy pulse. If the overall pressure of this composite waveform exceeds the intrinsic threshold, therapeutically effective dense energetic bubble clouds are generated at the focus. Alternatively, for very short histotripsy pulses (less than 2 cycles), a dense cavitation cloud can be initiated directly when the peak negative pressure exceeds the intrinsic threshold. This “intrinsic threshold histotripsy” approach usually gives superior results in terms of the precision of the location of the bubble clouds being generated. The location is precisely the region where the local negative pressure exceeds the intrinsic threshold. But, the threshold often cannot be achieved when the target volume is deep with an entry window which restricts the usable transducer aperture. Shock scattering histotripsy then becomes one of the alternatives that can be used. Much longer pulses at lower peak intensities can produce therapeutically effective bubble clouds by producing high temperatures close to the boiling point. Thus, “boiling histotripsy” is another approach when peak intensities that can be reached in the target volume are limited [11]–[13]. Cavitation bubble cloud due to the backscattering of HIFU from a laser-induced bubble was studied by Ogasawara *et al.* [14]. Yoshizawa *et al.* demonstrated control of shock scattering cavitation clouds with positive enhanced and negative enhanced waveforms, which were achieved by applying dual-frequency ultrasound sequences [15]. Shock scattering histotripsy in other contexts has been studied by several other groups [16]–[22].

There are a few limitations of standard shock scattering histotripsy that restrict us from studying the shock scattering mechanism thoroughly. First, for a multicycle shock scattering histotripsy pulse, the shock fronts are normally separated by a very short time (the period of the fundamental frequency), nominally around 1 μ s [7]. As a result, the bubble cloud generated in front of the next incoming shock wave does not have enough time to evolve to a fully-grown cloud. Also, the reflected shock waves will have to interfere with the following negative pressure phases within the pulse for shock scattering to happen, which adds complexity to studying the process. Therefore, the shock scattering process might not be optimal. To overcome those limitations, we generated independent pseudo-monopolar peak positive pulses and pseudo-monopolar peak negative pulses with variable, controllable delays, i.e., we temporally and spatially decouple the negative and positive half-cycles in the shock scattering process.

“Unipolar” pulses generated by optimizing the electrical excitation signal of a piezoelectric transducer were explored by Rougny *et al.* [23] and Sferruzza *et al.* [24],[25]. Bailey *et al.*

used an electrohydraulic lithotripter to generate positive pressure pulses and negative pressure pulses and studied the bioeffects of those pulses *in vivo* [26]. The generation of pseudo-monopolar peak positive pulses and peak negative pulses based on the concept of frequency compounding was investigated by Lin *et al.* [27]. In the study, a relatively small and hemisphere-shaped frequency compounding transducer was built, and pseudo-monopolar peak positive pulses and peak negative pulses were successfully generated. However, the driving system of the transducer does not allow us to apply consecutive pseudo-monopolar pulses with time delays of tens of microseconds, which makes it very difficult to study the shock scattering mechanism. Also, since the transducer is relatively small and in a hemisphere geometry, the operation window around the focus is very limited and not open. In this study, we aim to design and build a new frequency compounding transducer with a driving system that allows us to generate consecutive pseudo-monopolar pulses with adjustable time delays as short as tens of microseconds. Also, this transducer will have a “dome” shape instead of being a hemisphere, so the operation window around the focus is completely open. Previous studies also investigated frequency compounding as a method for speckle reduction in ultrasound images [28]–[31] and optical coherence tomography [32]; however, the compounding is done at the level of image frames, not the imaging pulses, each of which has a different center frequency.

By adjusting time delays of individual frequency components to allow their principal peak positive pressure ($P+$) to align temporally, high-pressure peak positive pulses are generated by constructive addition or compounding. Destructive interference occurs outside the peak-positive-overlapped temporal window, resulting in a good approximation of a pseudo-monopolar (nearly half-cycle) pulse with a sharp high-pressure positive phase and low-amplitude, temporally smeared out negative phase. A similar pseudo-monopolar pulse with a sharp dominant negative phase can be generated in a similar way by constructive compounding of all principal peak negative pressure ($P-$) pulses from all the elements.

To study the shock scattering mechanism more precisely, we first initiate a primary bubble cloud (“seed cloud”) at the focus by applying a single pseudo-monopolar peak negative pulse whose peak negative pressure exceeds the intrinsic threshold in the focal zone. A pseudo-monopolar peak positive pulse then arrives at the approximate peak for the expansion curve of the “seed cloud” where it is pressure-release “scattered” producing a high negative pressure phase counter-propagating with respect to the original positive monopolar pulse. A dense therapeutically effective shock scattering bubble cloud is generated when this counter-propagating negative pressure exceeds the intrinsic threshold. Since every secondary shock scattering bubble cloud can provide a pressure-release interface for another pulse, we also propose to generate a series of shock scattering bubble clouds (a pearl chain) by using multiple subsequent peak positive pulses after a single initial peak negative pulse. We hypothesize that these shock scattering bubble clouds can cause more precise controllable lysis when compared to more chaotic standard shock scattering histotripsy, particularly since the spatial and temporal relationship between successive pulses can now be precisely controlled.

II. Materials and Methods

A. Frequency Compounding Transducer and Generation of Pseudo-Monopolar Pulses

The frequency compounding transducer (Fig. 1) consists of 113 individual piezoelectric elements with 7 various resonant frequencies. The frequencies used are 250 kHz (39 elements), 500 kHz (17 elements), 750 kHz (10 elements), 1 MHz (19 elements), 1.5 MHz (6 elements), 2 MHz (10 elements), and 3 MHz (12 elements). Each 250-kHz element consists of two 500-kHz, 20-mm-diameter piezoelectric discs (PZ36, Ferroperm, Kvistgaard, Denmark) bonded together with epoxy (LOCTITE E-00NS, Henkel, Dusseldorf, Germany). Each 500-kHz element consists of two 1 MHz, 20-mm-diameter piezoelectric discs. All higher frequencies use single 20-mm-diameter piezoelectric discs (PZ36, Ferroperm). The selection of the frequencies, the number of elements used for each frequency, and the relative ratio of pressure outputs among all frequencies was based on market availability of piezoelectric discs and it was optimized by a Monte-Carlo-method-based optimization program in Matlab (MathWorks, Natick, MA, USA). Pseudo-random combinations were generated by the program, each of which resulted in a frequency-compounded acoustic pulse. Then, parameters including the peak pressure level and the P+ over P- ratio were examined. Also, the overall shape of the compounded pulse was considered. We decided the combination of frequencies, element numbers and the relative ratio of pressure outputs upon obtaining a satisfactory overall waveform that met all the requirements mentioned earlier. The optimization was mainly done for generating monopolar peak positive pulses. Monopolar peak negative pulses resulting from the optimized combination were adequate since by inverting the polarity of the excitation signals, the individual short pulses were highly symmetrical to those generated for producing peak positive pulses. However, this process left considerable room for further optimization.

The housings and matching layers of all individual elements were fabricated using 3-D rapid prototyping [33]. Housings for all elements were 3-D prototyped using stereolithography (SLA) with Somos 9120 material (Proto Labs, Inc., Maple Plain, MN, USA). All elements featured two matching layers. A first matching layer was bonded to the piezoelectric disc and a second matching layer was then bonded to the first matching layer, both with epoxy (LOCTITE E-00NS, Henkel). For matching layers, all elements except those in 750 kHz featured a first matching layer 3-D prototyped using SLA with NanoTool material (Proto Labs). All elements in 750 kHz featured a first matching layer made of FR-4 sheet (G10/FR4, McMaster-Carr, Elmhurst, IL, USA), whose material is usually used for making printed circuit boards (PCB). All elements featured a second matching layer 3-D prototyped using SLA with Somos 9120 material (Proto Labs). The thickness of matching layers was a quarter wavelength for optimal acoustic transmission. All elements were backed with slow-curing marine epoxy (A-side Resin 314 + B-side Slow Hardener 143, TAP Plastics, Inc., San Leandro, CA, USA).

The elements were fixed on a scaffold to allow their working distance to be approximately 15 cm. The scaffold of the transducer was 3-D prototyped using selective laser sintering (SLS) with nylon material (Stratasys Direct Manufacturing, Valencia, CA, USA). After

assembly, the aperture of the transducer was 25 cm. As a result, the F-number of this transducer was 0.6.

A 256-channel high-voltage pulser system was built in-house to drive all the elements. Each individual element had two driving channels in parallel. One of them was responsible for generating short acoustic pulses with a principle peak positive pressure and the other was responsible for generating short acoustic pulses with a principle peak negative pressure. The pulser system was connected to a set of field-programmable gate arrays (FPGA) (DE0-Nano, Terasic Inc., Hsinchu, Taiwan) programmed to generate the necessary timing of outputs. To generate pseudo-monopolar peak positive pulses, the pulser sends excitation signals to all elements to output individual short pulses with a principal peak positive pressure. By inverting the polarity of the excitation signals, we could make all elements generate individual short pulses with a principal peak negative pressure so that pseudo-monopolar peak negative pulses could be generated. The system allows us to customize the pressure amplitudes and time delays of the short pulses generated by individual elements, which leads to the generation of customizable pulsing sequences consisting of arbitrary combinations of monopolar peak positive pulses and peak negative pulses, which is not feasible with the previous transducer studied by Lin *et al.* [27]. A fiber-optic probe hydrophone (FOPH) [34] was used to measure the ultrasound waveforms of all frequency components as well as frequency compounded pseudo-monopolar peak positive pulses and peak negative pulses at the focus of the transducer in deionized, degassed water (gas saturation below 20%). The waveforms were processed with Matlab. The gas saturation was monitored by using a portable meter (Orion Star A323 RDO/DO, Thermo Fisher Scientific, Waltham, MA, USA).

B. Experiments for Observation of Cavitation Generated by Enhanced Shock Scattering Histotripsy

We performed experiments for observation of cavitation generated in different scenarios, so we could better understand various shock scattering phenomena in different settings. A diagram of the experiment setup is shown in Fig. 2. The transducer was submerged in a water tank filled with deionized, degassed water (gas saturation below 20%). Cavitation was generated around the focal zone. A high-speed camera (Phantom v210, Vision Research Inc., Wayne, NJ, USA) with a focusing lens (AT-X M100 AF PRO D, Tokina, Tokyo, Japan) was used to take high-speed photography of the cavitation generated during various experiments. The field of view of the photographs was in the axial-elevational plane. The camera featured a 1280×800 CMOS sensor and the active pixel size was 20 μm . The FPGA sent trigger signals to both the highvoltage pulser and the high-speed camera so that photography and cavitation activities were synchronized. A white-light LED was used for continuous, back-lit illumination. Frame rates varied with specific experiments from 53,000 frames per second (fps) to 210,000 fps, depending on the resolution required to observe certain cavitation phenomena. Raw video files were recorded and then saved to a computer. We then selected single frames to form a set of consecutive photographs to present the results.

1) One Monopolar Positive Pulse Following an Initial Monopolar Negative

Pulse: For observing the cavitation generated by enhanced shock scattering histotripsy, our first-step goal was to generate a single secondary bubble cloud by shock scattering from a primary “seed” bubble cloud and to observe the complete evolution process. Thus, we started from a simple scenario where only one pseudo-monopolar peak positive pulse was applied following an initial pseudo-monopolar peak negative pulse. The time delay between the two pulses was 30 μs , which was approximately the peak time for the expansion curve of the primary bubble cloud. Similar strategy was used in studies of the effects of the time delay between shock waves in lithotripsy by Bailey *et al.* [35], Neisius *et al.* [36], Zhong *et al.* [37], and Handa *et al.* [38]. The initial peak negative pulse was applied to generate a primary bubble cloud at the focus and the following peak positive pulse was applied to generate a secondary bubble cloud by shock scattering from the primary bubble cloud. To generate reliable cavitation, we increased the pressure levels for both the peak positive pulse and the initial peak negative pulse. The pressures applied were measured in deionized, degassed water (gas saturation below 20%) by using the FOPH. They remained unchanged for later experiments, including the red-blood-cell (RBC) phantom results. The pulse repetition frequency (PRF) was set to 1 Hz for all experiments to eliminate memory effects [39]. The frame rate used for photography was 210,000 fps. The exposure time for a single frame was 2 μs for all experiments.

2) Multiple Monopolar Positive Pulses Following an Initial Monopolar

Negative Pulse without Moving the Focus by Phasing: To study the shock scattering mechanism within the context of spatial limitations, we examined the number of secondary bubble clouds we could generate by applying consecutive peak positive pulses without moving the focus by phasing. Therefore, we performed an experiment where multiple peak positive pulses were applied following an initial peak negative pulse. In this case, all peak positive pulses applied following the peak negative pulse were focusing at the same geometric focus. For this experiment, 3 peak positive pulses were applied following an initial peak negative pulse. The time delay between the initial peak negative pulse and the first peak positive pulse was 30 μs . Then, 40 μs time delay, which was approximately the peak time for the expansion curve of the secondary bubble cloud, was applied between adjacent peak positive pulses. The frame rate used for photography was 140,000 fps.

3) Multiple Monopolar Positive Pulses Following an Initial Monopolar

Negative Pulse with Moving the Focus by Phasing: After studying the case without phasing, we investigated the focus moving case, where we wanted to generate a series of consecutive secondary bubble clouds with the focus moving towards the transducer. We phased the peak positive pulses step-by-step axially towards the transducer. With this pulsing strategy we can achieve enhanced shock scattering histotripsy using almost all positive pressure shock fronts, the advantage of which will be discussed later.

To achieve step-by-step phasing, the first peak positive pulse arrived at the geometric focus. Then, the second peak positive pulse arrived at a point that was 0.9 mm closer to the transducer in the axial direction. The step was chosen based on the approximate maximum diameter of a single secondary bubble cloud. Each succeeding pulse arrived 0.9 mm closer

to the transducer. For these experiments, 18 peak positive pulses were applied following an initial peak negative pulse. The time delay between the initial peak negative pulse and the first peak positive pulse was 30 μ s. Then, 40 μ s time delay was applied between adjacent peak positive pulses. The frame rate used for photography was 53,000 fps.

C. Experiments for Therapeutic Feasibility Test with Red-Blood-Cell (RBC) Phantoms

RBC tissue-mimicking phantoms were used to test the therapeutic feasibility of enhanced shock scattering histotripsy. RBC phantoms were used to visualize damage induced by cavitation [40]. We made RBC phantoms based on the methods described in previous studies [27],[40]. The agarose-saline mixture was made of low-EEO/multipurpose agarose powder (BP160–500, Fisher Scientific, Hampton, NH, USA) and degassed phosphate buffer saline. The ratio of the mixture was 1:100 (w:v). The central layer of the phantom that contained RBCs was made to be around 500 μ m to 600 μ m in thickness. The ratio of RBCs to agarose-saline mixture was 6:44 (v:v) to obtain a sufficient contrast between undamaged and damaged regions. During the experiments, the phantom was held by a gel holder and the gel holder was firmly attached to a 3-axis stepper motor positioning system for mobility. Two axes of the system featured 17MDSI stepper motors (Anaheim Automation, Anaheim, CA, USA) and one axis featured a 23MDSI stepper motor (Anaheim). The gel holder was positioned such that the central layer of the phantom was aligned with the axial direction of the transducer and the layer overlapped with the focal zone. The alignment was confirmed by successfully generating a sample lesion at the beginning of every experiment.

To generate a lesion in an RBC phantom using enhanced shock scattering histotripsy, 16 peak positive pulses with step-by-step phasing were applied after an initial peak negative pulse. The time delay between the initial peak negative pulse and the first peak positive pulse was 30 μ s. Then, 40 μ s time delay was applied between adjacent peak positive pulses. Up to 400 repetitions of those pulses were applied. The PRF was set to 1 Hz. 16 peak positive pulses were chosen based on the results from the cavitation observation experiment with phasing. Photographs were taken after 10, 100, 200, 400 repetitions were applied to observe the progression of the lesion. A reference photograph was also taken under the pretreatment condition.

D. Experiments for Observation of Pre-Focal Cavitation at a Tissue Interface with Peak Positive Pulses and Peak Negative Pulses

To help discuss pre-focal cavitation issues, we obtained a piece of fresh pig skin tissue from an unrelated study and observed the cavitation at the water-tissue interface when multiple peak negative pulses and peak positive pulses were applied, respectively. The dimensions of the tissue cut were 4 cm in width, 8 cm in height, and 3 mm in thickness. It was positioned 1.5 cm closer to the transducer in the axial direction with respect to the focus. The interior layer of the pig skin was facing the transducer to provide a pre-focal, water-tissue interface for incident ultrasound pulses. The experiments were conducted within the same day of the harvest of the tissue. For peak negative pulses, the focal peak negative pressure was 44.7 MPa. 100 pulses were applied at 100 Hz PRF. For peak positive pulses, the focal peak positive pressure was 45.7 MPa, which was kept at the same pressure level as the peak

negative pulses. 100 pulses were applied at 100 Hz PRF. The high-speed camera was used to observe potential cavitation activities.

III. Results

A. Generation of Pseudo-Monopolar Peak Positive Pulses and Pseudo-Monopolar Peak Negative Pulses

For generation of pseudo-monopolar peak positive pulses, we measured the temporal focal waveform from each individual frequency component and a frequency compounded peak positive pulse. Representative waveforms are shown in Fig. 3. All waveforms were measured directly by using the FOPH in deionized, degassed water. As shown in Figs. 3(a1)–3(a7), for each resonant frequency, we could generate a short pulse with a principal peak positive pressure and they could be aligned temporally with correct time delays. Fig. 3(b) shows a pseudo-monopolar peak positive pulse. For the peak positive pulse, the peak negative pressure was 5.7 MPa and the peak positive pressure was 36.5 MPa. The peak negative pressure was from a negative phase right in front of the high-pressure positive phase. The waveform in Fig. 3(b) was measured when all frequency components were firing simultaneously. It was not a linear summation of the waveforms shown in Figs. 3(a1)–3(a7) due to nonlinear distortion.

For generation of pseudo-monopolar peak negative pulses, we measured the temporal focal waveform from each individual frequency component and a frequency compounded peak negative pulse. Representative waveforms are shown in Fig. 4. Again, all waveforms were measured directly by using the FOPH in deionized, degassed water. As shown in Figs. 4(a1)–4(a7), for each resonant frequency, we could generate a short pulse with a principal peak negative pressure by inverting the polarity of the excitation signals. They could still be aligned temporally with correct time delays. Fig. 4(b) shows a pseudo-monopolar peak negative pulse. For the peak negative pulse, the peak negative pressure was 9.7 MPa and the peak positive pressure was 3.0 MPa. The waveform in Fig. 4(b) was measured when all frequency components were firing simultaneously. It was not a linear summation of the waveforms shown in Figs. 4(a1)–4(a7) due to nonlinear distortion. The temporal full width at half maximum (FWHM) of the peak negative pulse was 0.30 μ s. It was between the FWHMs of the principal peak negative pressures of the 1.5 MHz (0.25 μ s) and 1 MHz (0.35 μ s) components.

B. High-Speed Photography of Cavitation Generated by Enhanced Shock Scattering Histotripsy

We first measured the pressure levels of the applied pseudo-monopolar peak negative pulses and pseudo-monopolar peak positive pulses. The pressure levels applied for the peak negative pulse were shown in Table. I. The focal pressure levels for individual frequency components were measured directly by using the FOPH. The P- pressure level for the peak negative pulse was from the linearly summed signal and it was not directly measured due to cavitation. A representative waveform of the applied peak positive pulse is shown in Fig. 5. The waveform was measured directly by using the FOPH. For the peak positive pulse, the peak negative pressure was 18.0 MPa and the peak positive pressure was 63.4 MPa. The

axial -6 -dB beamwidth was approximately 4 mm. We were unable to measure the beamwidth in the lateral direction and the delineation of the focal zone due to instantaneous cavitation on the FOPH during measurements.

1) Cavitation Generated by One Monopolar Positive Pulse Following an Initial Monopolar Negative Pulse: The cavitation generated by one peak positive pulse following an initial peak negative pulse is shown in Fig. 6. The transducer was on the left side of the field of view, so the ultrasound was propagating from left to right. The orientation was the same for later results. At $0 \mu\text{s}$, several small bubbles were generated at the focus by the peak negative pulse because its peak negative pressure exceeded the intrinsic threshold. The bubbles then coalesced into a primary bubble cloud. A white cross marks the approximate center location of those small bubbles to indicate their initiation location so that potential movement of the bubble cloud could be monitored, although quantitative analysis of the movement was not within the scope of this study. The cross remained at its original location throughout all subsequent frames. At $30 \mu\text{s}$, the peak positive pulse arrived at the focus and impinged on the primary bubble cloud. A resultant, secondary bubble cloud was generated by shock scattering. The initiation of the secondary bubble cloud was captured by the frame at $28.57 \mu\text{s}$ because the exposure time of each frame was $2 \mu\text{s}$ and the exposure covered the time point of the initiation. Right after its initiation, the dimension of the secondary bubble cloud in the elevational direction was larger than that in the axial direction. Then, the secondary bubble cloud expanded. It became almost round-shaped before collapsing and fragmenting into smaller residual bubbles. A second white cross marks the approximate initiation location of the secondary bubble cloud starting from the frame at $28.57 \mu\text{s}$. Hence, there was only one white cross in each frame for the first three frames and there were two white crosses for the rest of the frames. We observed that the primary bubble cloud moved slightly away from the transducer and the secondary bubble cloud didn't move significantly throughout its lifespan. We performed this experiment 40 times and every time the same process occurred.

2) Cavitation Generated by Multiple Monopolar Positive Pulses Following an Initial Monopolar Negative Pulse without Phasing: The cavitation generated by multiple peak positive pulses following an initial peak negative pulse without phasing is shown in Fig. 7. At $0 \mu\text{s}$, a small bubble was generated by the initial peak negative pulse. A white cross marks its approximate initiation location. Starting from the frame at $28.57 \mu\text{s}$, we could observe a first secondary bubble cloud marked with a second white cross. The bubble cloud expanded and gradually reached its maximum size before the next peak positive pulse arrived. Starting from the frame at $71.43 \mu\text{s}$, a second secondary bubble cloud marked with a third white cross was observed. In the frames of $71.43 \mu\text{s}$ to $100.00 \mu\text{s}$, we could observe that the primary bubble cloud and the first secondary bubble cloud coalesced into a complex shape and they seemed to be migrating away from the transducer. Finally, starting from the frame at $114.29 \mu\text{s}$, we could observe a third secondary bubble cloud marked with a fourth white cross. Overall, 3 secondary bubble clouds were generated by 3 peak positive pulses. After around 3 secondary bubble clouds, the process could no longer generate shock scattering bubble clouds because the peak positive pressure around the front edge of the

third secondary cloud was not sufficient due to movement of the clouds away from the focus. We performed this experiment 60 times and every time the same process occurred.

3) Cavitation Generated by Multiple Monopolar Positive Pulses Following an Initial Monopolar Negative Pulse with Phasing: The cavitation generated by multiple peak positive pulses following an initial peak negative pulse with step-by-step phasing is shown in Fig. 8. 16 secondary bubble clouds were generated in total by 16 peak positive pulses phasing gradually towards the transducer. At 0 μs , several small primary bubbles marked with a white cross were generated. At 37.7 μs , a first secondary bubble cloud marked with a white arrow was observed. At 75.5 μs , a second secondary bubble cloud was observed. At 188.7 μs , the initiation of a 5th secondary bubble cloud was barely visible because for that frame, the 2- μs exposure time of the camera barely covered the initiation of the bubble cloud. However, at 226.4 μs , we could observe the 5th secondary bubble cloud clearly because the bubble cloud had been initiated and evolved. As time progressed, at 641.5 μs , a 16th secondary bubble cloud was observed. Overall, we could see that with each peak positive pulse, a new secondary bubble cloud was generated by shock scattering. The bubble clouds kept growing towards the transducer and the overall resultant cloud had an elongated shape. We found out that after the 16th peak positive pulse, there was no more shock scattering cavitation because the peak positive pulse was out of the steering range of the transducer and we did not include those results due to limited space. We performed this experiment 100 times and every time the same process occurred.

C. Therapeutic Feasibility Test of Enhanced Shock Scattering Histotripsy with Red-Blood-Cell (RBC) Phantoms

The lesion generated by enhanced shock scattering histotripsy is shown in Fig. 9. Prior to the first burst (pretreatment), the field of view was dark because the RBC layer blocked the back-lit illumination. After 10 repetitions, we could start to observe RBC lysis introduced by cavitation, especially around the geometric focus. The damage was seen in bright spots since illumination could then reach the camera. The last phasing position was also marked manually in the photographs to refer to the point where the last peak positive pulse was focusing. After 400 repetitions, we could observe an elongated, “cigar-shaped” lesion. The boundary between damaged and undamaged regions was clear and there was no significant damage outside of the lesion. We performed this RBC phantom experiment 3 times and every time the same process occurred.

D. Pre-Focal Cavitation at a Tissue Interface with Peak Positive Pulses and Peak Negative Pulses

The representative photographs of the water-tissue interface are shown in Fig. 10. (a) shows a representative photograph of the water-tissue interface when a P+ pulse was applied. No cavitation bubble was observed. (b) and (c) are two individual, representative photographs when a P− pulse was applied. Cavitation bubbles were observed in both frames, which are pointed out by a white arrow. Quantitatively, we found out that for P− pulses, the cavitation did not appear until several pulses were applied. From the three experiments we performed, the average number of P− pulses needed for cavitation to become observable was 5. Also, after the appearance of the first cavitation bubbles, the average percentage of P− pulses that

generated cavitation bubbles at the interface was 85.9%. For P+ pulses, there were 0% of pulses that generated observable cavitation bubbles.

IV. Discussion

There are two approaches, or methods, for doing short pulse (less than 20 cycles) histotripsy. These we have called “intrinsic threshold histotripsy” and “shock scattering histotripsy”. Intrinsic threshold histotripsy is the method that depends on creating focal waveforms part of which exceeds the intrinsic threshold (around 28 MPa negative). A very dense energetic bubble cloud can then be generated with nearly 100% cavitation probability. For shock scattering histotripsy, the negative pressures of the focal waveform usually do not directly exceed the intrinsic threshold. These lower negative pressures create sparse populations of incidental bubbles which do not effectively mechanically fractionate tissue. However, therapeutically effective bubble clouds are still generated in this method from the interaction of the shock waves with incidental bubbles and the negative phases within the pulses, which is addressed in detail earlier in the paper.

Intrinsic threshold histotripsy is by far the most effective and versatile method of creating dense therapeutically effective bubble clouds wherein at least one negative half-cycle of the focal waveform directly exceeds the intrinsic threshold. However, when the target volume is deep and occluded by gas bodies and/or bone, it is often impossible to directly exceed the intrinsic threshold. Fortunately, if the maximum peak negative focal pressure exceeds about 20 MPa (sometimes a little lower, but higher than 15 MPa), it is possible to generate energetic bubble clouds by shock scattering histotripsy. In this method, nonlinear propagation can generate positive shock fronts with peak pressures many times the magnitude of negative pressures. Nonlinear shock front generation can be thought of as a natural pulse amplification process making shock scattering histotripsy possible. These high positive pressures do not harm tissue unless they are reflected or back-scattered from a pressure release (gaseous) surface. The resulting pressure inversion can easily exceed the intrinsic threshold. In shock scattering histotripsy, the pressure release scattering bodies are created at the focus by the first several negative half cycles in the form of incidental bubbles. The process is made easier when the scattered shock front, a newly generated peak negative pressure, adds coherently with the next negative phase of the counter-propagating incident histotripsy waveform. The generated histotripsy bubble clouds are often rather chaotic and not very repeatable in shape but can be quite effective in fractionating tissue.

In “enhanced shock scattering histotripsy”, which is proposed in this paper, we can choose to apply an initial peak negative pulse whose negative pressure directly exceeds the intrinsic threshold to generate a primary bubble cloud so that the subsequent shock scattering can happen. In a situation where it is difficult to do so, we could apply a few successive, sub-intrinsic threshold negative pulses to initiate incidental bubbles first. After those pulses, we can start applying only positive pulses to create cavitation bubble clouds by shock scattering as well. Although, under this specific condition, the enhanced shock scattering histotripsy method has the same limitation of precision as the standard shock scattering histotripsy method because the location and time of the generation of incidental bubbles are still unpredictable, this method can be used over the standard one since it could help solve the

problem of pre-focal cavitation because of the use of subsequent peak positive pulses after initial peak negative pulses.

A significant disadvantage of shock scattering histotripsy can be an unfortunate result of the many negative half cycles of the therapy pulse which is typically from 3 to 10 cycles in length. These negative half cycles are effective at generating the necessary incidental “seed” bubbles at the focus from which shock scattering occurs but can also generate many incidental bubbles pre-focally. Accumulation of these pre-focal bubbles can be treatment limiting as they can significantly attenuate the primary histotripsy pulse. Thus, pre-focal cavitation, particularly at tissue interfaces, is a major limiting factor in treatment of target volumes at depth with standard shock scattering histotripsy.

The enhanced histotripsy method presented in this paper was created partly to alleviate this problem. This approach decouples the generation of the seed cloud from the following positive shock front because they are separate independent waveforms. Moreover, using frequency compounding technology, both positive and negative pulses can be synthesized to approximate monopolar pulses wherein only a single principal negative or positive half cycle is generated. With independent temporal and spatial control of these quasi-monopolar pulses, the number of parameters that can be changed to optimize the shock scattering process becomes quite large.

For example, in the 16-pulse pearl-chain bubble cloud produced in this paper, an elongated therapeutically effective set of consecutive bubble clouds were generated with each 16-cloud pearl-chain requiring only one seed cloud forming negative half cycle greatly reducing pre-focal cavitation because virtually everything is accomplished with monopolar positive pulses. Contrast this with standard shock scattering histotripsy with an 8-cycle pulse. To generate a 16-cloud pearl-chain, 8×16 , or 128 negative half cycles, traverse the pre-focal zone greatly enhancing the potential for treatment limiting pre-focal cavitation. Compare this to only a single negative half cycle required for the pearl-chain formation exemplified in this paper. This result is magnified if multiple repetitions of the pearl chain are required to completely homogenize the tissue.

Another disadvantage of standard shock scattering histotripsy relates to the bubble cloud emission signals that can be received at the transducer. In intrinsic threshold histotripsy, a single negative half-cycle generates dense regular shaped bubble clouds that emit a large clean signal propagated back to the transducer due to the energetic initial expansion of the cloud [41]. These signals may be useful for aberration correction. However, the emission from standard shock scattering histotripsy clouds is rather chaotic and provides inconsistent timing information [42]. Since we use single pseudo-monopolar pulses for enhanced shock scattering histotripsy, the generated clouds are remarkably regular and repeatable in shape. The clean emission signals can provide accurate timing information for aberration correction, extremely useful from deep focal volumes wherein aberration correction can greatly increase the quality of the focal waveforms. This self-generation of accurate aberration correction “beacon” signals from the focus is an important feature of some forms of histotripsy.

A few limitations still exist for the transducer design presented in this paper. First, there are some pressure variations outside of the high-amplitude peak positive phase within the pseudo-monopolar peak positive pulse, which can be seen in Fig. 5. Further optimization can be performed to lower the pressure variation and increase the pressure amplitude of the shock front even higher. Also, the pulser system developed for this transducer does not allow us to generate successive pseudo-monopolar pulses with time delays of around 1 microsecond, which makes it difficult to directly compare the new technique proposed in this paper to standard shock scattering histotripsy. Future system can be designed to achieve this aim.

Finally, it should be noted that the spatial and temporal parameters used in this paper to generate the pearl-chain clouds are insensitive to even relatively large changes in both timing of the next pulse and its placement in the front of the previous pulse. We tried many variations in timing of succeeding pulses and the placement of their foci (with respect to the preceding cloud) with essentially the same interesting results.

V. Conclusion

In this study, a frequency compounding transducer was designed and constructed to generate pseudo-monopolar peak positive and peak negative pulses. Compared to standard shock scattering histotripsy, we were able to decouple the peak positive pulses from the peak negative pulses thus allowing precise spatial and temporal control between successive pulses in an optimized sequence. We applied multiple subsequent peak positive pulses following an initial seed cloud forming peak negative pulse, and successfully generated a series of secondary bubble clouds (pearl chain) by shock scattering. We then tested its therapeutic feasibility by generating a precise elongated lesion in an RBC phantom. Enhanced shock scattering histotripsy could greatly reduce pre-focal cavitation, which is a major limiting factor for standard shock scattering histotripsy, by reducing the necessary number of negative half cycles to only one. Essentially all the work is done by successive pseudo-monopolar positive shock fronts.

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Fig. 1.

Illustration of the frequency compounding transducer. (a) is a diagram showing the fully assembled transducer with a scaffold and individual elements color-coded for different resonant frequencies. (b) is a photograph showing the fully assembled transducer. The text on the surface of each element was used to label the resonant frequency and the number of that element.

Fig. 2.

A diagram (top view) of the experiment setup for cavitation observation experiments. The frequency compounding transducer was submerged in a water tank filled with deionized, degassed water. FPGA motherboard received commands from PC and sent driving signals to a high-voltage pulser system. The high-voltage pulser then sent excitation signals to all individual elements. A high-speed camera and a back-lit illumination were used to take high-speed photography of the cavitation generated around the focal zone. The FPGA also sent trigger signals to both the high-voltage pulser and the high-speed camera so that photography and cavitation activities were synchronized. The photographs were then saved to PC.

Fig. 3.

Representative temporal focal waveforms for individual frequency components and a frequency compounded pseudo-monopolar peak positive pulse. (a1)-(a7) are waveforms with a principal peak positive pressure for individual frequency components, measured in water directly by using the FOPH. (b) is the waveform for a frequency compounded pseudo-monopolar peak positive pulse, measured in water directly by using the FOPH. The peak negative pressure was 5.7 MPa and the peak positive pressure was 36.5 MPa.

Fig. 4.

Representative temporal focal waveforms for individual frequency components and a frequency compounded pseudo-monopolar peak negative pulse. (a1)-(a7) are waveforms with a principal peak negative pressure for individual frequency components, measured in water directly by using the FOPH. (b) is the waveform for a frequency compounded pseudo-monopolar peak negative pulse, measured in water directly by using the FOPH. The peak negative pressure was 9.7 MPa and the peak positive pressure was 3.0 MPa.

Fig. 5.

Representative temporal focal waveform for a pseudo-monopolar peak positive pulse applied in the cavitation observation experiments and RBC phantom experiments, measured in water directly by using the FOPH. The peak negative pressure was 18.0 MPa and the peak positive pressure was 63.4 MPa.

Fig. 6.

High-speed photography of the cavitation generated by a peak positive pulse following an initial peak negative pulse. The time delay between two pulses was 30 μ s. Ultrasound was propagating from left to right. At 0 μ s, several small bubbles marked with a white cross were generated at the focus by the peak negative pulse because its peak negative pressure exceeded the intrinsic threshold. From the frame at 28.57 μ s, a secondary bubble cloud marked with a second white cross was generated by shock scattering and observed (the exposure time was 2 μ s for each frame). The secondary bubble cloud expanded after being generated. It became almost round-shaped before collapsing. The white crosses indicated the initiation locations of the bubble clouds and remained at their original locations through all subsequent frames to provide a reference for observing potential bubble movement.

Fig. 7.

High-speed photography of the cavitation generated by multiple peak positive pulses following an initial peak negative pulse without moving the focus by phasing. All 3 peak positive pulses applied were focusing at the geometric focus. The time delay between the peak negative pulse and the first peak positive pulse was 30 μs . Then, 40 μs time delay was applied between adjacent peak positive pulses. A primary bubble cloud marked with a white cross was generated at 0 μs . From the frame at 28.57 μs , a first secondary bubble marked with a second white cross could be observed. From the frame at 71.43 μs , a second secondary bubble marked with a third white cross could be observed. From the frame at 114.29 μs , a third secondary bubble marked with a fourth white cross could be observed.

Fig. 8.

High-speed photography of the cavitation generated by multiple peak positive pulses following an initial peak negative pulse with step-by-step phasing. A step was uniformly 0.9 mm towards the transducer in the axial direction. The time delay between the peak negative pulse and the first peak positive pulse was 30 μs . Then, 40 μs time delay was applied between adjacent peak positive pulses. 16 secondary bubble clouds were generated in total and the overall bubble cloud kept growing towards the transducer, resulting in an elongated shape. A white cross marked the initiation location of the primary bubble cloud. Each secondary bubble cloud was marked with a white arrow. The shadows on the left and right side of each frame were areas outside of the boundary of the back-lit illumination.

Fig. 9.

Representative photographs of a lesion generated in an RBC phantom. Photographs were taken after 10, 100, 200, 400 repetitions of enhanced shock scattering histotripsy pulses. A reference photograph was also taken under the pre-treatment condition. The field of view was dark because the RBC layer blocked the back-lit illumination. After 10 repetitions, damage induced by cavitation could be observed, especially around the geometric focus. The geometric focus and the last phasing position were both marked with a white arrow. After 400 repetitions, an elongated lesion could be observed.

Fig. 10.

Representative photographs of the water-tissue interface when peak negative (P-) pulses and peak positive (P+) pulses were applied. The grey area is water and the dark area is the interior layer of the pig skin. (a) shows a representative photograph of the water-tissue interface when a P+ pulse was applied. No cavitation bubble was observed. (b) and (c) are two individual, representative photographs when a P- pulse was applied. Cavitation bubbles were observed in both frames, which are pointed out by a white arrow.

TABLE I
Applied Focal Negative Pressure Levels for Generating a Pseudo-Monopolar Peak Negative Pulse (MPa)

250 kHz	500 kHz	750 kHz	1 MHz	1.5 MHz	2 MHz	3 MHz	Focal Peak Negative Pressure of Linearly Summed Signal* (MPa)
3.2	5.0	6.5	6.5	4.1	6.2	5.0	34.5

*The pressure level in this column was the peak negative pressure of the linearly summed waveform. It was not directly measured.