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Suppressing Bubble Shielding Effect in Shock Wave Lithotripsy by Low Intensity Pulsed Ultrasound

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Abstract

Extracorporeal shock wave lithotripsy (ESWL) has been used as an effective modality to fragment kidney calculi. Because of the bubble shielding effect in the pre-focal region, the acoustic energy delivered to the focus is reduced. Low pulse repetition frequency (PRF) will be applied to dissolve these bubbles for better stone comminution efficiency. In this study, low intensity pulsed ultrasound (LIPUS) beam was aligned perpendicular to the axis of a shock wave (SW) lithotripter at its focus. The light transmission was used to evaluate the compressive wave and cavitation induced by SWs without or with a combination of LIPUS for continuous sonication. It is found that bubble shielding effect becomes dominated with the SW exposure and has a greater significant effect on cavitation than compressive wave. Using the combined wave scheme, the improvement began at the 5th pulse and gradually increased. Suppression effect on bubble shielding is independent on the trigger delay, but increases with the acoustic intensity and pulse duration of LIPUS. The peak negative and integral area of light transmission signal, which present the compressive wave and cavitation respectively, using our strategy at PRF of 1 Hz are comparable to those using SW alone at PRF of 0.1 Hz. In addition, high-speed photography confirmed the bubble activities in both free field and close to a stone surface. Bubble motion in response to the acoustic radiation force by LIPUS was found to be the major mechanism of suppressing bubble shielding effect. There is a 2.6-fold increase in stone fragmentation efficiency after 1,000 SWs at PRF of 1 Hz in combination with LIPUS. In summary, combination of SWs and LIPUS is an effective way of suppressing bubble shielding effect and, subsequently, improving cavitation at the focus for a better outcome.

Keywords — shock wave lithotripsy (SWL), cavitation, bubble shielding effect, low-intensity pulsed ultrasound (LIPUS), acoustic radiation force

1. Introduction

Since the introduction of extracorporeal shock wave lithotripsy (ESWL) in the early 1980s, this noninvasive technology has revolutionized the urology worldwide for significantly reduced morbidity and mortality via open surgery for removal of upper urinary tract stone [1]. At present, about 80% of kidney stone diseases are treated by ESWL alone or in conjunction with the other modalities [2]. Recently, shock waves (SWs) could also provide additional benefits in rehabilitation and orthopedics for the treatment of musculoskeletal diseases, such as Achilles tendonitis, heel spurs, and nonunion stress fracture [3]. Despite its great success, both *in vitro* and *in vivo* investigations also illustrate some of its shortcomings [4]. For example, if the stone is in an anatomically difficult position (i.e., in the collecting system of lower pole of the kidney) or its size is larger than 20 mm, the performance of ESWL is not satisfactory. About 30% of patients need re-sessions [5]. In addition, renal injuries characterized by the rupture of vessels and capillaries are usually found **on** the proximal surface of the kidney after ESWL. Although debate exists for the association between hypertension and diabetes mellitus with ESWL [6, 7], renal trauma caused by ESWL could lead to irreversible long-term complications and patients with pre-existing renal injury are at high risk [8, 9]. Therefore, work is being carried out to understand the underlying mechanism of ESWL and to improve its performance, increasing the stone fragmentation and reducing the associated side-effect.

The dominating mechanism of ESWL is synergy of both mechanical stress induced directly by lithotripsy shock wave (LSW), including the superposition of longitudinal waves for stone spallation [10], circumferential stresses on the stone boundary for squeezing [11], and shear waves at the stone corners [12], and cavitation produced by the tensile component of LSW [13-15]. The stress wave causes the fracture of kidney calculi and usually dominates at the beginning of treatment. In contrast, cavitation and its associated formation of high-speed microjet produce fine fragments from the stone surface later, which is critical for spontaneously discharge although at a slower rate [16]. The pulse repetition frequency (PRF) for the delivery of SWs is usually 1 Hz, and the total number of SWs delivered in one session required by the Food and Drug Administration (FDA) is no more than 2,000. In order to reduce the treatment time, fast PRF was tried [17, 18]. However, less stone comminution and more renal injuries were found, which may be due to the shielding effect of bubble cloud in the pre-focal region (i.e., water in the coupling cushion) [19, 20]. In the **acoustic** cavitation, non-condensible gas dissolves into the bubble and increases its equilibrium radius during the growth. In the collapse stage, **a** bubble may be broken into many “daughter” bubbles, which dissolve slowly into the surrounding medium in seconds. If the interval time of SW delivery is shorter than the bubble dissolution time (i.e., higher PRF), these remnant small bubbles will grow to large sizes and shield the propagation of the incident tensile component of LSW, but selectively transmit the leading compressive component, which is called the bubble shielding effect [21]. As a result, cavitation in the focal region surrounding the stone will be reduced significantly [22]. Meanwhile, strong backscattering will also be produced by the pre-focal bubble cloud, which may be the reason of the presence of most SWL-induced renal injury **on** the proximal surface of the kidney. Although reducing PRF results in the improved stone comminution and less complication [23-25], the cost is the elongated treatment duration.

If the bubble shielding effect can be reduced (fewer number or less density of cavitation nuclei along the LSW pathway) between successive SWs, higher PRF can be applied without negatively affecting stone comminution. It is noted that bubble proliferation is a critical issue after delivery of several SWs. Cavitation nuclei can be suppressed by vacuum water degassing [26]. A jet of degassed water with an exit velocity of 62 cm/s could remove cavitation nuclei from the coupling cushion between successive SWs [27]. Consequently, the lifetime of pre-focal bubble nuclei was reduced from 7 s to 0.3 s detected in B-mode ultrasound image, and the stone fragmentation efficiency increased from 22±6% to 33±5% after 250 shocks at PRF of 1 Hz. If a weak preceding shock wave is delivered at an sufficiently long interval delay before the subsequent major one that the cavitation cluster generated by the first SW has already collapsed, a significantly pronounced bubble activity with high void fraction could be produced by the second SW [28]. Low frequency pulses (350 kHz) with pulse duration in the order of milliseconds were delivered between LSWs to effectively enhance the bubble coalescence with amplitude larger than 250 kPa [29, 30]. Bubble removal pulses reduced the bubble excitation along the SW axis and drastically enhanced the stone comminution at the higher rates (120 and 60 SW/min).

Several approaches have been utilized to capture the bubble dynamics. Light transmission is an easy and reliable method to measure bubble activities in the illumination area [31], but it cannot be used *in vivo*. Meanwhile, optical detection of tiny bubble nuclei is not as sensitive as acoustic approach because of the much more similarities in the optic index between water and air (1.33 vs. 1.0) than that of acoustic impedance (1.5 MRay vs. 416 Ray). Therefore, light transmission or photography cannot discern the remnant bubbles between SW intervals. Active cavitation detection (ACD), such as using B-mode ultrasound image, illustrated the lifetime of detectable bubble nuclei in the lithotripter field after 20 SWs delivered at PRF of 3 Hz is ~7s [27]. SW-induced echogenic areas enlarged with the increase of delivered pulses, discharge voltage and PRF both *in vitro* and *in vivo* [32], which is believed to be in the pre-focal region. Passive cavitation detection (PCD) has a characteristic double-burst structure and shows the presence of bubble cavitation by ESWL in animal experiment [33] and in clinics [34]. Correlation was found between the appearance of echogenic regions and the cavitation signals in PCD [35]. Using an ultrasound array, microbubble emission could be passively measured and dynamically focused at multiple depths. Agreement was found between the real-time passive imaging of cavitational acoustic emission and single or contiguous and disjoint cavitation regions [36, 37].

Low intensity pulsed ultrasound (LIPUS) is a medical technology, using ultrasound pulses at 1-2 MHz with a pulse duration much longer (> 10 ms) than that of diagnostic one at the intensity of no more than ≤ 2 W/cm^2. It is becoming popular in the rehabilitation and has been approved by FDA for use in orthopedics, such as promoting bone-fracture healing, treating orthodontically induced root resorption, regrow missing teeth, enhancing mandibular growth in children with hemifacial microsomia, promoting healing in various soft tissues such as cartilage, inter vertebral disc, and improving muscle healing after laceration injury [38].

In this study, a novel therapy strategy was proposed and tested by combining SWs and LIPUS, which were aligned confocally and delivered different acoustic pulses in turn. Light transmission signal through the focal region was used to evaluate the compressive wave and cavitation, two major mechanisms of stone comminution in ESWL, in the free field during the SWL treatment. The bubble shielding effect produced in the pre-focal region was found to have much more influence on cavitation than the compressive wave, but can be suppressed using the new strategy, which is dependent on the trigger delay between SWs and LIPUS, the duration and acoustic intensity of LIPUS and the energy flux of SWs. High-speed images illustrated bubble activities using SWs alone or combination of SWs and LIPUS both in the free field and close to a stone surface. Motion of remnant bubble nuclei during LIPUS sonication illustrated the mechanism of suppression bubble shielding effect. As a result, there is a 2.6-fold increase in the stone fragmentation efficiency using the novel strategy *in vitro* while LIPUS alone had negligible influence. It suggests that this approach can effectively suppress the bubble shielding effect in ESWL and, subsequently, improve the performance.

2. Materials and Method

2.1. Acoustic Sources

SWs were generated by a focused piezoelectric transducer (FB10 G4, PiezoSon 100 plus, Richard Wolf GmbH, Knittlingen, Germany) with an aperture of 100 mm and a focal length of 40 mm, the energy flux in the range of 0.03 to 1.05 mJ/mm^2, the measured focal peak pressure in the range of 11 to 126.3 MPa, and 6 dB beam size of 1.1-3.2 mm in radius and 6.1-14.8 mm in length [39]. LIPUS was generated by a flat and circular transducer (Model X, Rich-Mar, Chattanooga, TN, USA) with an emission area of 10 cm^2. These two transducers were immersed into a testing tank (L×W×H = 36×22×25 cm) filled with degassed and deionized water ($O_2 <$ 4 mg/L, T = 25 °C, measured by DO700, Extech Instrument, Waltham, MA, USA) and aligned perpendicular to each other (see Fig. 1). A LabView (National Instruments, Austin, TX, USA) program on a personal computer (PC) was written to control the delivery of SW and LIPUS by setting the transistor-transistor logic (TTL) level of the trigger circuit of these two devices through a data acquisition (DAQ) board (USB-6008, National Instruments). Variations of SW and LIPUS parameters used in this study are listed in Table 1. Trigger delay is determined as the delay time of triggering SW and LIPUS at the same PRF and is kept consistent throughout the whole sonication. At least 60% of the maximum output of SW (~0.63 mJ/mm^2) is required to produce detectable cavitation in our experiment.

2.2. Cavitation Detection

A broadband 10 MHz polyvinylidene fluoride (PVDF) focused membrane transducer (PA381, Precision Acoustics, Dorchester, UK) with a diameter of 19 mm and a focal length of 46.7 mm was aligned confocally with the SW transducer and used as a PCD transducer. The received acoustic emission (AE) signals, which are associated with bubble dynamics [40, 41], were amplified by a broadband pulser/receiver (5077PR, Olympus-IMS, Waltham, MA, USA) with a gain of 20 dB and a high-pass filtering frequency of 1 MHz to eliminate signals caused by the vibration of PCD transducer [42]. Furthermore, bubble activities during the pulse exposure could also be monitored by light transmission technique in a free field [31] (see Fig. 1). An illumination Helium-Neon laser light (1507-2, λ = 632.8 nm, 0.95 mW, JDSU, Milpitas, CA, USA) was expanded by a combination of **lenses** (F_1 = -12 mm, F_2 = **60** mm, Thorlabs, Newton, NJ, USA) to a parallel beam with a diameter of 15 mm, transmitted through the focal zone of SW transducer, and subsequently focused onto a fast photo-detector (30 dB gain, 3.6 mm sensor size, bandwidth from DC to 10 MHz, noise-equivalent power (NEP) of $2.1\times10^{-12} – 7.7\times10^{-11}$, PDA36A-EC, Thorlabs) through a concave lens (F_3 = 150 mm, Thorlabs). -6 dB beam size in the axial and lateral direction of SW focal zone is 13 mm and 4 mm, respectively, so that the illumination light beam width is sufficiently large to cover the whole focal region. Both acoustic emission and light transmission signals were recorded by a digital oscilloscope (WaveSurfer 44MXs-B, LeCroy, Chestnut Ridge, NY, USA) at a sampling rate of 100 MHz and then transferred to the PC for further data analysis in Matlab (MathWorks, N. Nortick, MA, USA). At least 5 minutes were set between measurements for complete bubble dissolution.

2.3. High-Speed Photography

Bubble dynamics either in a free field or near a solid surface of cement stone phantom were captured by a high-speed camera (Ultima APX-RS fastcam, Photron, San Diego, CA, USA) with a lens (AF Micro Nikkor 60 mm 1:2.8 D, Nikon, Japan) under the illumination (100 W, Fiber-Lite MH100 Metal Halide Machine Vision Illuminator, Dolan-Jenner, Boxborough, MA, USA) at the frame rate of 30,000 fps and shutter speed of 1 μs. The camera lens was adjusted to achieve the vision field of 7 mm × 7 mm with image resolution of 256 pixel × 256 pixel in each frame. The light source and the camera were aimed at the focal region of SW and aligned both horizontally (see Fig. 1). A TTL signal generated by the DAQ board was used to trigger the camera and SW/LIPUS transducer simultaneously. Because the travel time of SW towards the focus (i.e., 26.7 μs) is shorter than the interval time of photography and no Schlieren mirror was used for shadowgraphy, no wavefront of SW was found in our high-speed images [31]. The motion of bubbles under LIPUS exposure was calculated using particle image velocimetry (PIV) method [43].

2.4. Stone Comminution

Stone comminution was evaluated using our established protocol [44]. Spherical stone phantoms are in size of 1 cm and made of cement with a powder to water mixing ratio of 2:1 by weight, which has acoustic impedance within the range of reported values for renal calculi [31]. The weight of each phantom in the dry state was measured by a digital balance (SBC-31, Scaltec Instruments GmbH, Germany). Before placing it into a customer-built holder and aligned with the focal point of SW, each stone phantom was immersed in degassed water for at least 1 hour until no visible bubbles coming out. A total of 1,000 SWs without or with a combination of LIPUS were delivered to the stone phantom at PRF of 1 Hz. Afterwards, all fragments were removed from the holder, spread out into a layer on paper, and let dry at room temperature for 24 hours. Dry fragments were then filtered through an ASTM standard sieve (W.S. Tyler, Mentor, OH, USA) with 2-mm grid. The comminution efficiency was determined by the percentage of fragments less than 2 mm, which can be discharged spontaneously after clinical ESWL.

2.5. Statistical Analysis

At least 10 data were collected in the cavitation measurement at each testing conditions, and 6 stone samples were used in comminution experiment. Student's *t*-test was performed in SigmaPlot 8 (Systat Software, San Jose, CA) to determine the statistical difference between the measurement groups that was fixed at $p < 0.05$.

3. Results

3.1. Cavitation Detection

Two distinct peaks were detected in the trace of measured AE signals (see Fig. 2a). The first peak (1’) is caused by the compression and the ensuing expansion of gas nuclei exposed by the incident LSW while the second one (2’) is due to the bubble collapse [40, 41]. The delay time between these two peaks is defined as the bubble collapse time, which correlates with the maximum expansion of the bubble cluster in both theoretical calculation and experimental measurement [41, 45]. Sometimes, one or more peaks were also found after 2’, which is generated at the collapse of rebounding bubble nuclei. However, two peaks in AE signals were not always captured by PCD clearly due to randomness of SW-induced cavitation [46] and acoustic blocking by remnant bubbles even with the application of dual PCD [47].

In comparison, light transmission is a more sensitive and reliable method of detecting the presence and dynamics of bubble cavitation [31]. Upon the arrival of LSW to the focal region, the strong compressive wave increases the optical index of the fluid and forms a dark spot in the shadowgraphs or a negative spike in the light transmission signal temporarily (3’) [31]. However, the tensile wave cannot be picked up. Because the bubbles block the light transmission, negative changes (4’) in the light signal correspond to the whole process of expansion and collapse of SW-induced cavitation in the focal region (see Fig. 2b). Bubble collapse times measured by these two methods are 166.7±34.8 μs and 167.8±37.6 μs, respectively, without significant difference ($p > 0.05$). The absolute value of 3’ and integral area of 4’ beginning at the end of the spike 3’ (arrow in Fig. 2b) present the compressive component of LSW and SW-induced cavitation, respectively, and are used to evaluate the field of ESWL.

Cavitation induced by 20 SWs (energy flux of 1.05 mJ/mm^2) alone or in combination with LIPUS (2 W/cm^2 and pulse duration of 500 ms) at PRF of 1 Hz and trigger delay of 300 ms was measured and compared with each other (see Fig. 3). Since the trigger delay is positive (LIPUS being delivered after SW), the first cavitation event is attributed to SW only. With the progress of SW delivery, both the negative peak and integral area of cavitation in the light transmission signal decreased **rapidly** (from 2.84±0.30 V to 1.68±0.10 V and from 135.6±71.0 V·μs to 7.1±4.5 V·μs, respectively), which shows more reduction of cavitation than the compressive pressure and **is** due to the bubble shielding effect hindering the delivery of acoustic energy. In comparison, although no difference was found initially using the combined wave scheme, improvement showed up after the 5th pulse and began to enhance afterwards. At the end of the 20-pulse exposure, the negative peak and integral area of cavitation in the light transmission signal were 2.47±0.29 V and 73.5±46.2 V·μs, corresponding to 87% and 54% of initial values or 1.5 and 10.4 folds increase from SW alone, respectively, which suggests suppression of the bubble shielding effect and restoration of the stress wave and cavitation in stone comminution.

3.2. Effect of Parameters

In order to understand the phenomenon of shielding bubble suppression better and optimize the operation (maintenance of cavitation at the focus for consequent SWL efficiency), working parameters of SW and LIPUS were varied. Negative peak and integral area in the light transmission signal at the 1st, 5th, 10th, and 20th pulse were used to evaluate the improvement with the progress of treatment. Firstly, interval delay time varied from -500 ms (negative means that LIPUS is delivered before SW) to 300 ms (see Fig. 4). There is no statistical difference between the measurement data ($p > 0.05$), which means that the improvement effect of combining LIPUS is independent on the delivery time with respect to SW.

Secondly, the pulse duration of LIPUS was varied from 100 ms to 500 ms (see Fig. 5). Variation in the negative peak increases almost linearly with the pulse duration, while the relationship of the integral area with pulse duration seems to be more complicated, which is due to the increase in both bubble expansion size and collapse time. It means that the improvement effect becomes more significant for longer LIPUS.

Thirdly, acoustic intensity of LIPUS was varied from 1.0 W/cm^2 to 2.0 W/cm^2 (see Fig. 6). The additional LIPUS enhanced both stress wave and cavitation, and the enhancement increased with the LIPUS intensity. At the end of the 20-pulse exposure, the increases in the negative peak and integral area are 1.07, 1.22, 1.47 folds and 3.6, 6.5, 10.4 folds, respectively. Therefore, it is possible that with the higher LIPUS intensity the cavitation may be able to resume the initial value (the 1st pulse).

Fourthly, PRF was varied from 4 Hz to 0.1 Hz (see Fig. 7). It is found that the negative peak and integral area in the light transmission signal increase by decreasing the PRF of SW alone, which is the strategy used clinically to enhance the cavitation effect [23-25]. However, such improvement seems to decrease from the 5th pulse to the 10th one and then become saturated afterwards, suggesting that even lower PRF may be used to minimize the accumulative bubble shielding effect with the progress of treatment because of longer dissolution time for large remnant bubble cloud. In comparison, enhancement by combining LIPUS grows with the number of SWs delivered after the 5th one (see Fig. 3). Using the proposed wave scheme leads to significantly higher negative peak (1.97±0.22 V) and integral area (16.9±7.9 V·µs) at the 20th pulse at PRF of 4 Hz than SW alone at PRF of 1 Hz (1.68±0.10 V and 7.1±4.5 V·µs, $p < 0.05$), which could not only enhance the performance but also reduce the treatment duration of SWL.

Finally, SW output was varied from 60% to 100% of its maximum energy flux (see Fig. 8). The bubble shielding effect has more influence on the cavitation than the compressive wave. At the end of 20-pulse exposure, negative peak values in the light transmission signal still increase with output power of SW but smaller in comparison to the first pulse, which suggests certain pass of the compressive wave (69.5%, 57.8%, and 40.2% reduction at 60%, 80% and 100% SW output, respectively). In contrast, integral areas after 10 pulses are almost the same and independent on the SW output. The reductions of the integral area after 20-pulse exposure are 90.8%, 93.5%, and 94.7% for 60%, 80% and 100% SW output, respectively. Using the combined wave scheme, the enhancements in both compressive wave and cavitation increase with the SW energy despite of more significance in the cavitation. At the end of exposure, the negative peaks and the integral areas are 87.6%, 89.1%, 88.1% and 22.2%, 30.4%, 54.7% of those of the first pulse at the SW intensities of 60%, 80%, and 100%, respectively. In addition, the compressive wave and cavitation using the combined wave scheme at SW energies of 60% and 80% are no less or even more than that using SW alone at the intensities of 80% and 100%, respectively, which suggests the use of lower SW energy without compromising its outcome.

3.3. High-Speed Photography

In order to observe the cavitation directly and illustrate the mechanism of cavitation enhancement by using the combined wave scheme, high-speed photography was taken at continuous pulse delivery at PRF of 1 Hz, and representative sequences in the focal region of SW in water are shown in Fig. 9. 33 μs after the arrival of the 1st SW, bubble nuclei in the water began to expand, reached the maximum size at about 100 μs, merged with the neighbors, and then shrank to collapse at 167 μs (see Fig. 9a). Afterwards, the remaining and fragmented bubble nuclei had some afterbounces. If no coalescence occurs, the bubble collapse time is much shorter than merged large bubble although the coalescence into a single spherical bubble may not be completed during the LSW interval. No visible bubble was found after 300 μs. Bubble collapse time is in good agreement with the measurement results using PCD and light transmission method. It is interesting to find that some bubbles with a sharp and conical tip may not be the high-speed microject formed by the asymmetric collapse due to the surrounding SW propagating through it, but the wall distortion from neighboring bubble (diamond arrow in Fig. 9a). Therefore, they will not disappear immediately as bubble collapse, and may continue the expansion and coalescence. At the 10th SW, much fewer bubbles could be produced and their maximum size is much smaller than that of the 1st pulse (see Fig. 9b). Bubble density seems higher in the pre-focal region. In comparison, it is clear to observe the recovery of cavitation using the combined wave scheme although the bubble density and maximum expansion size are smaller than those of the initial pulse, which agrees with the results of light transmission.

Furthermore, bubble activities near a solid surface (i.e., stone phantom) were also investigated (see Fig. 10). The high speed camera was triggered at the same time as SW. At the 10th pulse, cavitation bubbles induced by SW accumulated at two sites, on the proximal surface of the stone and about 5 mm close to the SW source. Bubbles on the stone surface began to collapse around 233 μs, almost twice as that in the free field, which is similar to our observation in an electrohydraulic lithotripter field [31]. However, because of the convex surface bubbles would not merge together into a single large one to cover the whole proximal surface as for the flat cylindrical stone [15, 31]. No or much less coalescence may occur away from the axis on the stone surface (arrow in Fig. 10). Subsequently, the corresponding collapse time was a little shorter. After the collapse on the stone surface, tiny fragments came out of the collapse site (arrow head in Fig. 10). However, the bubble cloud in the pre-focal region coalesced into a big one with the size of 1.7 mm and had the collapse time of about 400 μs. When LIPUS was applied during the interval of SWs, the consequent cavitation has several differences. First, fewer bubbles were found in the pre-focal region with no consequent coalescence and collapse. Second, although the bubble density in water is smaller, there was no significant difference in bubble activities on the stone surface. Third, the cavitation induced the stone fragmentation from the stone surface was more significant (t = 1.6 ms in Fig. 10b).

In order to illustrate the mechanism of suppressing bubble shielding effect, high-speed images were captured during the LIPUS exposure (see Fig. 11). Here the time zero was set as the trigger of LIPUS. After the arrival of LIPUS, some bubbles close to each other may coalesce during the motion to achieve high speed (~0.6 m/s, red solid circle) while some may interact with each other with corresponding low speed (~0.2 m/s, blue dash circle). However, bubbles close to the stone surface (arrow in Fig. 11) had more resistance of motion under LIPUS exposure (i.e., only 0.02 m/s motion speed), which is due to no-slip condition for the flow near a rigid boundary.

3.4. Stone Comminution

The result of stone comminution by 1,000 pulses of SW alone and combination of SW (100% power output) and LIPUS (acoustic intensity of 2 W/cm^2 and pulse duration 500 ms) with trigger delay of 300 ms and PRF of 1 Hz were shown in Figure 12. Because of the suppression of the bubble shielding effect by the wave combination strategy as shown previously, stone phantom can be broken into smaller fragments with fewer large pieces left (2 cases had complete fragmentation). There is a 2.6-fold increase from 30.8±6.0% to 80.5±25.4% in the stone comminution efficiency (weight percentage of fragments less than 2 mm in size) with the addition of LIPUS ($p < 0.05$). If only LIPUS was delivered, the stone was almost intact, which suggests that the enhancement is not due to the additional acoustic energy to the stone phantom but the control of cavitation in the focal region. This promising performance will further be investigated *in vivo*.

4. Discussion

Cavitation is an important mechanism in ESWL. In order to suppress the bubble shielding effect, SWs were combined with LIPUS and the corresponding bubble activities were monitored using both light transmission and high-speed photography in this study. It is found that the combined wave scheme began to restore the compressive wave and cavitation from the 5^{th} SW and gradually increase the improvement effects afterwards. Suppression of bubble shielding effects is independent on the trigger delay between SWs and LIPUS, but increases with the acoustic intensity and pulse duration of LIPUS as well as the energy flux of SWs, which allows easy operation without careful parameter determination. There is a 2.6-fold increase in the stone comminution after 1,000 pulses delivered at PRF of 1 Hz. Remnant bubble coalescence and motion in response to the acoustic radiation force from LIPUS may be the major reason for the performance improvement as illustrated in the high-speed photographs. Using our strategy, SWs could be delivered at a lower energy flux and a higher PRF without compromising their outcome. Skin pains at the wave entry site are almost proportional to the energy flux of SWs [48]. Low power output of lithotripter may result in less or no use of anesthesia or sedative in the ESWL. Higher PRF will reduce the treatment duration. More investigation will be performed to further evaluate this technology *in vivo*, where the nucleation environment, cavitation threshold, and bubble dynamics in the acoustical field would be different from those in water. Because both ESWL and LIPUS have already been approved by FDA, combination of them may be translated into clinics quickly. Besides ESWL, it may also be used in the rehabilitation and orthopedic treatment of musculoskeletal diseases.

In the acoustic field, transported momentum by the beam to an absorbing medium causes the movement of medium along the propagation direction [49]. The acoustic radiation force is proportional to the attenuation and effective acoustic intensity (product of delivered acoustic intensity and duty cycle). Thus, it increases with the acoustic intensity and duration of LIPUS and the bubble size. Insonified microbubbles have radial oscillations as well as translation due to radiation force and the drag imposed by the fluid, which has significant moving distances shown in both theoretical simulation (modified Rayleigh-Plesset equation) and experiments using high-speed photography [50]. The average motion velocity of a 1.5 μm ultrasound contrast agent (UCA) at the frequency of 2.25 MHz and acoustic pressure of 380 kPa is about 0.5 m/s, translating over 5 μm during a single 20-cycle pulse, which is in the same order in our study (LIPUS at acoustic intensity of 2 W/cm^2 or pressure of 245 kPa). Microbubble translation is maximized when the center frequency matches it fundamental or harmonic resonance frequencies. 6.6 μm air bubble has the resonant frequency of 1 MHz. However, the size distribution of remaining bubble nuclei in ESWL is unknown. When the bubbles are close to each other, the secondary Bjerknes forces determine the consequent interaction. If the bubbles lay on the same side of resonance, either both larger or both smaller than the resonance size of sonication frequency, an attractive force will be applied to them for coalescence. The merged bubble will have larger acoustic radiation force applied to it because of increased size than the individual one. In comparison, if laying on opposite sides of resonance, the bubbles will experience a repulsive force and lead to a smaller motion speed, which has been illustrated in our high-speed photography (see Fig. 11).

Bubble activities, rectified diffusion or inertial cavitation (IC), in the acoustic field are dependent on the initial bubble size and the acoustic pressure field [51].

However, the process of rectified diffusion requires a much longer time (i.e., seconds) than that of IC (i.e, microseconds) [52]. Therefore, smaller bubbles (around 6 μm in size) will undergo IC while larger ones will reach their stabilized size by either rectified diffusion or gradual dissolution at the acoustic pressure of 250 kPa according to the theoretical calculation. These stabilized bubbles will oscillate continuously throughout the sonication while tiny bubble nuclei with the size less than about 1 μm will gradually dissolve. Due to the limited magnification of lens and **the** number of image pixels used in this study, only large bubbles in the viewing field were observed. They have a long dissolution time and a high threshold of IC (no collapse was found in Fig. 11). At low frequency and high acoustic pressure, these residual bubbles have high potential of IC [29], which is another effective way of suppressing bubble shielding effect.

The bubble shielding effects exist in not only SWL but also the other therapeutic ultrasound technologies. The presence of a single 2.4-mm air bubble 5 mm pre-focally on high-intensity focused ultrasound (HIFU) axis reduced the focal intensity by 50% and increased the beam width by 50% in both numerical simulation and experimental measurement [53]. A bubbly layer can work as a filter for the coming HIFU pulses, a mechanical band-stop filter in the transmission and a band-pass filter in the reflection, whose characteristics depends on the bubble size, the bubble density, the number of layers, and the acoustic intensity of the HIFU pulses [54]. Remanent bubbles occurred in a tissue-fluid interface in histotripsy with an extremely high pulsing rate (> 10 kHz) lead to the production of inhomogeneous tissue fractionation [55]. Longer interval time (i.e., $\Delta t \geq 100$ ms) allows the removal of the cavitation memory and results in complete and homogeneous tissue fractionation, which is similar to slowing PRF in ESWL. In addition, a weak preconditioning pulse delivered 30 μs before histotripsy pulse can effectively suppress cavitation in the periphery of the target without affecting that in the center in order to sharpen the fractionation in the active focal zone [56]. Therefore, suppressing the bubble shielding effect in an acoustic field is of important for the practice of ultrasound therapy.

5. Conclusion

The bubble shielding effect is a common phenomenon in the acoustic cavitation field induced by acoustic pulses. The accumulative bubble shield effect has more influence on the cavitation than compressive component of LSW in the focal region as shown in the light transmission signals. In order to suppress it, SWs and LIPUS were combined for ESWL in this study. Suppression effect was found due to moving the remnant bubble in the pre-focal region away by the acoustic radiation force from LIPUS. As a result, stone comminution efficiency could be improved by 2.6-folds. Easy setting of LIPUS parameters and the existing approval by FDA may allow quick translation into clinics to benefit all stone patients.

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Table 1. Variations of SW and LIPUS parameter in the experiment. The maximum energy flux of SW (Output 100%) is 1.05 mJ/mm^2.

SW Output (%)	60, 80, 100
SW pulse repetition frequency (Hz)	0.1, 1, 4
LIPUS Intensity (W/cm^2)	1.0, 1.5, 2.0
LIPUS Length (ms)	100, 200, 300, 500
Trigger Delay (ms)	-500, -300, -100, 20, 100, 300

Figure Legends

Figure 1. Schematic diagram of experimental setup. LIPUS was aiming at the focus of SW transducer. Laser generator, optical lens set, and photo detector were replaced by the illuminating light source and the high-speed camera when the imaging study was conducted. Shock wave lithotripter, LIPUS, and PCD transducers are aligned orthogonally to each other.

Figure 2. Representative SW-induced cavitation signals measured by (a) PCD and (b) light transmission technique in a free field. The first peaks (1' and 3') in both figures, which correspond to the arrival of SW to the focal point, were shifted to time zero for easy comparison. Arrow is the end of the negative change in the light transmission signal due to the compressive component of lithotripter shock wave.

Figure 3. (a) Negative peak and (b) integral area of light transmission signals during twenty continuous pulses of SW alone and in combination of SW and LIPUS. Ten samples were recorded in each condition for statistical analysis. *: $p < 0.05$.

Figure 4. Comparison of (a) negative peak and (b) integral area at the 1st, 5th, 10th, and 20th pulse during continuous exposures of SW alone (energy flux of 1.05 mJ/mm^2) and in combination with LIPUS (2 W/cm^2 and pulse duration of 500 ms) at PRF of 1 Hz but varied trigger delay from -500 ms to 300 ms.

Figure 5. Comparison of (a) negative peak and (b) integral area at the 1st, 5th, 10th, and 20th pulse during continuous exposures of SW alone (energy flux of 1.05 mJ/mm^2) and in combination with LIPUS (2 W/cm^2 and varied pulse duration from 100 ms to 500 ms) at PRF of 1 Hz and trigger delay of 300 ms.

Figure 6. Comparison of (a) negative peak and (b) integral area at the 1st, 5th, 10th, and 20th pulse during continuous exposures of SW alone (energy flux of 1.05 mJ/mm^2) and in combination with LIPUS (1-2 W/cm^2 and pulse duration of 500 ms) at PRF of 1 Hz and trigger delay of 300 ms.

Figure 7. Comparison of (a) negative peak and (b) integral area at the 5th, 10th, and 20th pulse during continuous exposures of SW alone (energy flux of 1.05 mJ/mm^2) and in combination with LIPUS (2 W/cm^2 and pulse duration of 200 ms) at PRF of 0.1, 1, and 4 Hz and trigger delay of 20 ms.

Figure 8. Comparison of (a) negative peak and (b) integral area at the 1st, 5th, 10th, and 20th pulse during continuous exposures of SW alone (60%-100% of energy flux of 1.05 mJ/mm^2) and in combination with LIPUS (2 W/cm^2 and pulse duration of 500 ms) at PRF of 1 Hz and trigger delay of 300 ms.

Figure 9. Representative high-speed images of bubble cavitation produced by (a) the 1st pulse, the 10th pulses of (b) SW (energy flux of 1.05 mJ/mm^2) alone and (c) combination of SW and LIPUS (acoustic intensity of 2 W/cm^2, duration of 500 ms, and trigger delay of 300 ms) during continuous exposures at PRF of 1 Hz in the focal region of a free field. The number above each frame is the time delay in μs after the arrival of SW to the focus. SW and LIPUS were coming from the top and the right, respectively. Red ⊙ denotes the focus of SW. Red triangles show bubbles with complete coalescence while arrow are those with incomplete coalescence. Arrow with diamond head illustrates microjet-looking bubble that may be formed by the distortion from neighboring bubbles. Each frame has the size of 7×7 mm.

Figure 10. Representative high-speed images of bubble cavitation produced at the 10th pulses of (a) SW (energy flux of 1.05 mJ/mm^2) alone and (b) in combination

of SW and LIPUS (acoustic intensity of 2 W/cm^2, duration of 500 ms, and trigger delay of 300 ms) during continuous exposures at PRF of 1 Hz in the focal region near a solid surface. The number above each frame is the time delay in μs after the arrival of SW to the focus. SW and LIPUS were coming from the top and the right, respectively. The focus of SW was aiming the center of the stone surface. Arrow shows bubble on the stone surface but away from the axis; arrowhead illustrates the diffusion of fine stone fragments after the bubble collapse. Each frame has the size of 7×7 mm.

Figure 11. Representative images of bubble motion at the tenth combined pulses (SW energy flux of 1.05 mJ/mm^2, LIPUS intensity of 2 W/cm^2, duration of 500 ms, and trigger delay of 300 ms) during continuous exposures near a solid surface at PRF of 1 Hz (a) 0 ms, (b) 1.6 ms and (c) 3.0 ms after the delivery LIPUS, and (d) the corresponding motion vectors using particle image velocimetry method. LIPUS was coming from the right. Red solid circle: merged bubbles; blue dash circle: repulsive bubbles; arrow: bubble close to the stone surface with negligible motion during LIPUS sonication. (The video clip can be found at http://www3.ntu.edu.sg/home/yfzhou/LIPUS.mp4)

Figure 12. Representative photos of stone fragments following 1,000 pulses of (a) SW alone and (b) in combination of SW and LIPUS at PRF of 1 Hz, and (c) the corresponding stone fragmentation efficiencies, which are the percentages of stone fragments less than 2 mm in size (p = 0.04 and n = 6).