Published in final edited form as:

IEEE Trans Ultrason Ferroelectr Freq Control. 2013 February ; 60(2): 301–309. doi:10.1109/TUFFC.2013.2566.

Controlled Cavitation to Augment SWL Stone Comminution: Mechanistic Insights *In-Vitro*

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Abstract

Stone comminution in shock wave lithotripsy (SWL) has been documented to result from mechanical stresses conferred directly to the stone, as well as the activity of cavitation microbubbles. Studies have demonstrated that the presence of this cavitation activity is crucial for stone subdivision; however, its exact role in the comminution process remains somewhat weakly defined, in part due to the fact that it is difficult to isolate the cavitation component from the shock waves themselves. In this study, we further explored the importance of cavitation in SWL stone comminution through the use of histotripsy ultrasound therapy. Histotripsy was utilized to target model stones designed to mimic the mid-range tensile fracture strength of naturally occurring cystine calculi with controlled cavitation at strategic time points in the SWL comminution process. All SWL was applied at a peak-positive pressure (p+) of 34 MPa and a peak-negative pressure (p-) of 8 MPa; a shock rate of 1 Hz was used. Histotripsy pulses had a p- of 33 MPa and were applied at a pulse repetition frequency (PRF) of 100 Hz. Ten model stones were sonicated in-vitro with each of five different treatment schemes: A. 10 minutes SWL (600 shocks) with 0.7 seconds of histotripsy interleaved between successive shocks (totaling to 42,000 pulses); B. 10 minutes SWL (600 shocks) followed by 10 minutes histotripsy applied in 0.7 second bursts (1 burst per second, totaling to 42,000 pulses); C. 10 minutes histotripsy applied in 0.7 second bursts (42,000 pulses) followed by 10 minutes SWL (600 shocks); D. 10 minutes SWL-only (600 shocks); E. 10 minutes histotripsy-only applied in 0.7 second bursts (42,000 pulses). Following sonication, debris was collected and sieved through 8, 6, 4, and 2 mm filters. It was found that SWL-only generated a broad range of fragment sizes, with an average of $14.9 \pm 24.1\%$ of the original stone mass remaining >8 mm. Histotripsy-only eroded the surface of stones to tiny particulate debris that was small enough to pass through the finest filter used in this study (<2 mm), leaving behind a single primary stone piece (>8 mm) with mass $85.1 \pm 1.6\%$ of the original following truncated sonication. The combination of SWL and histotripsy (schemes A, B, and C) resulted in a shift in the size distribution toward smaller fragments and complete elimination of debris >8 mm. When histotripsy controlled cavitation was applied following SWL (B), the increase in exposed stone surface area afforded by shock wave stone subdivision led to enhanced cavitation erosion. When histotripsy controlled cavitation was applied prior to SWL (C), it is likely that stone surface defects induced by cavitation erosion provided sights for crack nucleation and accelerated shock wave stone subdivision. Both these effects are likely at play in the interleaved therapy (A), although shielding of shock waves by remnant histotripsy

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Author Disclosure

W. W. Roberts, C. A. Cain, and T. L. Hall have financial interests and/or other relationships with HistoSonics Inc.

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microbubble nuclei may have limited the efficacy of this scheme. Nevertheless, these results demonstrate the important role played by cavitation in the stone comminution process, and suggest that the application of controlled cavitation at strategic time points can provide an adjunct to traditional SWL therapy.

INTRODUCTION

Stone fragmentation in shock wave lithotripsy (SWL) is a dynamic process in which cracks initiate, grow, and coalesce within the stone matrix. It is well established that mechanical stresses induced directly by a lithotripter shock wave (LSW) play a critical role in this subdivision [1]–[10]. Mechanisms proposed to explain the contribution of these direct stresses include the superposition of longitudinal waves within the stone (spalling) [1]–[3], [5], [8], circumferential stresses generated by the portion of the LSW traveling in fluid adjacent to the stone boundary (squeezing) [6], and shear waves generated at stone corners that are reinforced by the squeezing wave (dynamic squeezing) [9].

These direct stress mechanisms do not act in isolation, however, and there is a great deal of evidence suggesting that cavitation produced by the trailing tensile tail of the LSW is a crucial component of the stone comminution process [7]–[21]. Studies in which the cavitation component of LSWs was suppressed through shock wave modification [11], viscous fluids [7], [8], [12], or static overpressure [13], [14] have yielded a drastic reduction in stone fragmentation. Conversely, Xi and Zhong demonstrated that an auxiliary shock wave timed such as to intensify the collapse of LSW-induced bubbles can markedly enhance comminution [15]. The damage conferred by cavitation activity is typified by numerous minute pittings on the stone surface, which are likely the result of localized stress created by the impact of fluid jets or secondary shock waves produced by bubble collapse [15]–[17], [19]–[21]. Additionally, the work of Sass, *et al.* suggests that cavitation may act to facilitate the growth of fissures in the stone material induced by the direct stress wave component of LSWs [10].

In contrast to these studies demonstrating the vital role played by cavitation in stone subdivision, additional work has established that the persistence of cavitation microbubbles from one LSW to the next can hinder the comminution process. Enhanced stone subdivision with decreasing rate of LSW delivery has been demonstrated both *in vitro* [22], [23] and *in vivo* [24]. These studies are corroborated by clinical trials in which higher success rates were observed for patients treated with LSWs at a rate of 1 Hz in comparison to those at 2 Hz [25]. Such outcomes are demonstrative of the “shielding” phenomenon commonly associated with SWL, in which a population of prefocal cavitation nuclei—here, remnant bubbles created by the preceding LSWs—act to attenuate the tensile component of the waveform and reduce the efficacy of cavitation at the stone surface [26], [27]. Treatment strategies to minimize the degree of this undesirable cavitation and maximize stone fragmentation have been the subject of recent investigative work [28], [29].

In this study, we aim to further explore the role of cavitation in SWL by applying controlled cavitation at strategic time points in the stone comminution process. This was accomplished using histotripsy, a technique originally developed for the mechanical fractionation of tissue structures in which focused ultrasound pulses are utilized to control the activity of a cavitation bubble cloud. Typical histotripsy pulse sequences are very short (<50 cycles), have high peak negative pressure (>6 MPa), and are delivered at low duty cycles (0.1 to 5%). In contrast to HIFU, the low duty cycle used in histotripsy results in damage being mechanical rather than thermal. Previous work with histotripsy has demonstrated the feasibility of mechanical tissue fractionation via controlled cavitation [30]–[33], as well as the ability of histotripsy to readily erode model stones [34], [35]. It was found that

application of histotripsy therapy to stone phantoms results in erosion of the surface to fine particulate debris, all of which was measured to be $<100\ \mu\text{m}$ in size. Our ultimate goal is to investigate how cavitationally-based histotripsy stone erosion can be synchronized with LSWs to augment the stone comminution process.

METHODS

A. Preparation of Model Urinary Stones

Composite stone phantoms formulated to mimic the mid-range tensile fracture strength of naturally occurring cystine calculi were cast from a mixture of BegoStone plaster (BEGO USA, Smithfield, RI), albumin (Carolina Biological Supply Company, Burlington, NC), and tap water. Following the procedures detailed by Simmons, *et al.* [36] the constituents were mixed rigorously by hand for 4 minutes; a mass ratio of 73% BegoStone, 24.5% water, and 2.5% albumin was used to achieve the desired stone properties. Subsequently, 0.6 mL aliquots of the slurry were distributed into the 1 cm diameter cylindrical wells of a Delrin plastic mold and allowed to cure overnight. Following this initial setting, stone phantoms were removed from the mold and slowly heated to 90°C in a low temperature oven (Model 10GC, Quincy Lab Inc., Chicago, IL). Stones were held at this temperature for 12 hours to permit albumin polymerization, then removed and allowed to cool to room temperature before being submersed in a beaker of tap water to hydrate. Prior to treatment, phantoms in the hydrated state were degassed in a vacuum desiccator (Bel-Art Products, Wayne, NJ) overnight to minimize any air trapped in the stone material. The end result of this process was the production of cylindrical model stones measuring 1 cm in diameter and having a hydrated mass of $1.03 \pm 0.03\text{ g}$ (mean $\pm$ SD, $n = 50$).

B. Experimental Setup

The experimental setup used for the treatment of composite stone phantoms is displayed in Fig. 1. During sonication stones were held within a channel in an optically transparent 1% agarose hydrogel (Sigma Type VII, Sigma-Aldrich Co., St. Louis, Missouri), the construction of which is detailed in Fig. 2. Briefly, this gel-holder is composed of an Accura-60 plastic bottom that was fabricated on a stereolithography machine. A concave “basket” containing 2 mm holes extends up from the bottom and serves as the surface on which the stone sample was ultimately placed [Fig. 2(a)]. Next, the agarose gel was cast surrounding this basket, creating a channel measuring 15 mm in diameter and 40 mm in height [Fig. 2(b)]. Stone fragments were free to move about within this channel during sonication, with debris reduced to sub-2 mm size able to pass through the basket into a collecting dish placed below [Fig. 2(c)]. The entire gel-holder assembly was positioned within a treatment tank measuring $58 \times 43 \times 45\text{ cm}$ (L $\times$ W $\times$ H) that was filled with deionized water at room temperature degassed to a dissolved oxygen content of $77\% \pm 2\%$ ($n = 10$) to mimic that of urine [37]. These levels were measured at the beginning and end of each treatment day using a Traceable Digital Oxygen Meter (Control Company, Friendswood, TX). Additionally, sodium chloride was added to the treatment tank in order to achieve a water conductivity of $600\ \mu\text{S}/\text{cm}$, which is a typical value used for electrohydraulic shock wave sources such as the one used in this study. Both the LSW source and the histotripsy therapy transducer were positioned at the top of the tank focused downward. Alignment of the therapy focus to the stone was maintained on an inter-trial basis via two lasers laterally positioned at the known geometric focal location.

C. Ultrasound Generation and Treatment

Stones were sonicated using a system built in-house that is capable of delivering both electrohydraulic SWL and histotripsy therapy in a confocal manner (Fig. 3). The electrohydraulic SWL portion of the system has been described previously [38], and is based

on prior research lithotripters designed to simulate the acoustic field generated by the Dornier HM3 [39], [40]. Briefly, a high voltage capacitor charging power supply (TDK-Lambda Americas, Inc., Neptune, NJ) is used to charge an 80 nF high voltage capacitor (General Atomics Energy Products, San Diego, CA), which is subsequently triggered to discharge across an underwater spark electrode via optical input to a solid state switch (Applied Pulsed Power, Inc., Freeville, NY). Consistent with traditional electrohydraulic SWL design, this spark electrode is positioned at one of the foci of an ellipsoidal reflector; upon firing, acoustic energy is focused by the ellipse to the distal focus at which the target sample is positioned. The capacitor charging power supply utilized here is a current drive system that produces a series of voltage ramps, and as such must be coupled to an additional 100 nF high voltage filter capacitor (Maxwell Laboratories, Inc., San Diego, CA) to smooth the output voltage. Finally, a resistor bank composed of fifteen 25 k Ω , 225 W resistors (Vishay Intertechnology, Inc., Shelton, CT) is incorporated at the power supply output for isolation and prevention of internal damage to the supply when the output becomes negative. All SWL treatments were conducted at a shock rate of 1 Hz and charging voltage of 20 kV. This generates an acoustic shock wave having a peak positive pressure (p_+) of 34 MPa and a peak negative pressure (p_-) of 8 MPa, as calibrated by an optical hydrophone constructed in our lab [41], [42]. Prior to treatment, electrohydraulic SWL electrodes were preconditioned with 200 shocks; each electrode was replaced after the generation of 2,000 shocks.

The histotripsy portion of the system consists of an annular array of 11 PZT-8 disc elements (Channel Industries, Santa Barbara, CA), each measuring 2 in diameter and having a center frequency of 500 kHz. Water-tight housings designed to hold the individual elements were fabricated from Accura-60 plastic using a stereolithography machine. The front face of each housing contains an acoustic lens with a focal length of 15 cm; PZT-8 elements were matched to this lens using a mixture of tungsten powder (74MR-0005, Inframat Advanced Materials, Farmington, CT) and epoxy adhesive (Hysol E-120HP, Loctite Corporation, Rocky Hill, CT). Individual housing/lens assemblies were aligned such that their geometric focus was coincident with that of the lithotripter. This was accomplished using a stereolithography-fabricated scaffold surrounding the lithotripter's ellipsoidal reflector. In this case, Accura Peak plastic was utilized due to the fact that it has excellent moisture resistance and is therefore less likely to deform under the weight of the housings over time.

The histotripsy array was driven using a pulse amplifier developed in our lab. All histotripsy treatments were conducted at a pulse repetition frequency (PRF) of 100 Hz and a power setting such that the peak-peak voltage applied to the PZT-8 elements was roughly 2900 V. This corresponds to a p_- of 33 MPa based on calibration with a fiber optic hydrophone developed in-house [43]. An example acoustic output from the system is displayed in Fig. 4. This waveform was acquired at a lower peak-peak driving voltage of approximately 1700 V, due to the fact that higher intensities resulted in cavitation damage to the fiber tip after only several pulses and prevented us from obtaining a clean averaged waveform. The p_- of 33 MPa at our therapy intensity was determined via linear extrapolation on the basis of the observation that the p_- of the waveform increases extremely linearly with driving voltage. The lateral and axial -6-dB beamwidths were measured on the p_- and p_+ pressure profiles at p_-/p_+ of 10/11 MPa. It was found that the lateral -6-dB beamwidths for p_- and p_+ were 2.2 and 2.1 mm, respectively, while the corresponding values in the axial direction were 16.0 and 12.3 mm. Again, an intensity well below that used for stone treatments was utilized for these scans in order to prevent cavitation damage to the hydrophone tip. For comparison, it has been previously reported that the -6-dB beamwidth of the lateral field of an HM3-mimicking research lithotripter is approximately 10 mm, while the -6-dB length of the axial field is approximately 60 mm [40].

Model stones were sonicated with one of five treatment schemes, as summarized in Table I. In scheme **A**, stones were exposed to 10 minutes of SWL (600 LSWs) with 0.7 seconds of histotripsy (70 pulses) interleaved between successive LSWs (totaling to 42,000 pulses). The duration of interleaved histotripsy was selected based on a preliminary investigation to minimize the shielding effects of remnant histotripsy nuclei on subsequent LSWs. Additionally, a delay of 1 ms was imposed between the arrival time of a LSW and the first histotripsy pulse of a burst. This ensured that histotripsy pulses did not arrive prior to the collapse of LSW-induced cavitation bubbles surrounding the stone, as determined by high speed imaging. A representation of this pulse scheme is displayed in the top panel of Fig. 5. In scheme **B**, stones received 10 minutes of SWL followed by 10 minutes of histotripsy. Consistent with the interleaved scheme, histotripsy was delivered in 70 pulse bursts (PRF= 100 Hz), with one burst applied per second. The middle and bottom panels of Fig. 5 display the timing utilized for SWL and histotripsy, respectively. In scheme **C**, stones were sonicated with 10 minutes of histotripsy followed by 10 minutes of lithotripsy; pulse timing in this case was again consistent with the representations presented in the lower-most panels of Fig. 5. Treatment schemes **D** and **E** acted as controls, with stones receiving 10 minutes of SWL only or 10 minutes of histotripsy only, respectively. Ten model stones were treated with each respective scheme.

D. Evaluation of Fragment Size

Following sonication, stone fragments remaining in the treatment channel were collected and sequentially sieved through 8, 6, 4, and 2 mm filters. The hydrated mass of stone debris trapped on each respective filter was measured immediately following sieving, with care taken to gently blot any standing water off the surface of the fragments with tissue paper. The mass of stone debris <2 mm in size was calculated by subtracting the sum of the debris trapped on the filters from the initial mass of the hydrated stone (measured prior to treatment). Quantification of debris size distributions utilized the metric of ‘stone mass fraction,’ which was calculated as the hydrated mass of debris trapped on a given filter divided by the initial mass of the hydrated stone.

The filter pore sizes utilized in this study were selected based on clinical literature describing the fate of residual stone fragments following SWL treatment. It has been documented that residual fragments >4 mm carry a statistically higher risk for causing complication and becoming clinically significant during follow-up [44]. Contrastingly, those 4 mm are expected to pass spontaneously without further treatment and are referred to as clinically insignificant residual fragments (CIRF). It is certainly possible that, in some cases, even these CIRF may be retained and seed recurrent stone growth [45]. For this reason it is preferable to minimize the size of such residual debris; indeed, study has shown that the probability of eliminating residual lithiasis is significantly greater in patients with “dust” in comparison to those with significant residual fragments [46]. With respect to this study, it is important to remember that all treatments are truncated and designed for the sole purpose of investigating comminution mechanism rather than achieving a complete clinical outcome. Nevertheless, the authors feel it is important that the reader have a basic understanding regarding the clinical perspective of fragment size in order to frame the context of our results.

E. High Speed Imaging

A potential limitation to interleaving histotripsy pulses between successive LSWs is shielding. It is possible that remnant microbubbles that persist following the collapse of the histotripsy bubble cloud may reduce the efficacy of subsequent shock waves. The interleaved pulse scheme utilized in this study was selected based on a preliminary investigation to minimize these shielding effects; however, it is quite possible that some

degree of shielding is still present in comparison to the LSWs in isolation (scheme **D**). To further investigate this phenomenon, high speed images were acquired during schemes **A** and **D** using a Phantom v210 camera (Vision Research, Inc., Wayne, NJ). In each case, a single image with 2- μ s exposure time was taken 20- μ s following the arrival of the LSW at the stone surface. Backlighting was used to produce a projection of the cavitation activity in the axial-lateral plane of the lithotripter. The extent of bubble excitation induced by LSWs with and without histotripsy pulses interleaved was compared.

RESULTS

A. Stone Fragment Size Distributions

The stone fragment size distributions resulting from each respective treatment scheme are displayed in Fig. 6. Application of 600 LSWs (scheme **D**) resulted in stone subdivision to a broad range of fragment sizes, with an average of $14.9 \pm 24.1\%$ of the original stone mass remaining >8 mm. In contrast, sonication with histotripsy (scheme **E**) only eroded the surface of stones to tiny particulate debris that was small enough to pass through the finest filter used in this study (<2 mm). Following the truncated histotripsy sonication session, an average of $14.9 \pm 1.6\%$ of the original stone mass was eroded from the surface, leaving behind a single primary stone piece (>8 mm) with mass $85.1 \pm 1.6\%$ of the original.

The combination of SWL and histotripsy (schemes **A**, **B**, and **C**) resulted in a shift in the size distributions toward smaller fragments and complete elimination of all debris >8 mm. The highest degree of stone comminution was achieved using SWL followed by histotripsy (scheme **B**), in which $71.1 \pm 16.0\%$ of the original stone mass was reduced to fragments <2 mm in size. This represents a statistically significant increase in sub-2 mm fragments in comparison to all other treatment schemes (t -test, $P < 0.01$). Correspondingly, the mass fraction of fragments falling in the 2–8 mm range showed a statistically significant decrease in comparison to treatment schemes **A**, **C**, and **D** (t -test, $P < 0.01$). Visually, during the SWL phase of scheme **B** the stone was subdivided to a range of fragment sizes, consistent with the results of the SWL-only therapy. During the subsequent histotripsy phase no further subdivision of the fragments was observed; rather, their surfaces were eroded to fine particulate debris <2 mm in size. Histotripsy cavitation erosion of these subdivided stones displayed an increase in efficacy relative to histotripsy erosion of whole stones (scheme **E**). This is a result of the subdivided stones having a greater exposed surface area, providing the cavitation bubble cloud with more material over which to erode. Correspondingly, the final treatment outcome in scheme **B** was highly dependent on the degree of stone subdivision achieved during the initial SWL phase.

Histotripsy followed by SWL (scheme **C**) and the interleaved therapy (scheme **A**) also produced an increase in sub-2 mm debris relative to SWL or histotripsy in isolation (t -test, $P < 0.01$), with $45.6 \pm 9.6\%$ and $44.9 \pm 8.1\%$ of the original stone mass passing through the 2 mm filter, respectively. Although these sub-2 mm mass fractions are not statistically different from one another (t -test, $P = 0.87$), histotripsy followed by SWL appears to achieve a higher degree of comminution in comparison to the interleaved therapy; examining fragments 6–8 mm in size, histotripsy followed by SWL achieved a reduced mass fraction of $6.8 \pm 11.3\%$ in comparison to the $19.3 \pm 13.0\%$ of the interleaved scheme. This represents a statistically significant reduction in debris of this size (t -test, $P = 0.03$). Visually, following the histotripsy phase of scheme **C** extensive pitting was induced on the stone surface (Fig. 7), and during the subsequent SWL phase the onset of stone subdivision was observed to require a reduced number of LSWs in comparison to SWL-only (scheme **D**). Conversely, during the interleaved therapy the onset of stone subdivision was observed to require a greater number of LSWs relative to SWL-only. This suggests that remnant cavitation

nuclei from the histotripsy burst may indeed be acting to shield the stone from subsequent LSWs. Fig. 8 displays five representative images captured 20 μ s after LSW arrival for the interleaved and SWL-only pulse schemes. A higher degree of LSW-induced bubble excitation is apparent for the interleaved case.

DISCUSSION

The importance of cavitation in SWL stone comminution has been documented in numerous studies. Work in which the cavitation component of LSWs was suppressed has resulted in drastically reduced fragmentation [7], [8], [11]–[14], while actively intensifying the collapse of LSW-induced bubbles has been shown to enhance the comminution process [15]. The physical mechanisms underlying the role of cavitation in SWL remain somewhat weakly defined, however, in part due to the fact that it is difficult to isolate the cavitation component of LSWs. In this study we utilized histotripsy ultrasound therapy to temporally and spatially direct the activity of a cavitation bubble cloud, allowing us to further explore the relationship between cavitation and LSW stone comminution in a way that was not previously possible. Through the application of controlled cavitation at specific time points relative to LSWs, we aimed to further elucidate the role of cavitation in SWL and demonstrate the ability of histotripsy to provide an adjunct to the SWL stone comminution process.

The highest degree of stone comminution in this study was achieved using pulse scheme **B**, in which histotripsy controlled cavitation was applied following SWL (Fig. 6). This treatment demonstrates a major point of synergy between SWL stone subdivision and histotripsy cavitation erosion: when a minimal number of LSWs are first used to subdivide a stone into multiple pieces, the efficacy of cavitation erosion is enhanced as a result of an increase in exposed stone surface area. Further adding to this synergistic interaction is the fact that the direct stress (spalling) mechanism of LSW stone subdivision displays an inherent size limitation in the fragments it generates [7], [9]. Zhu, *et al.* found that both model and natural kidney stones immersed in castor oil cannot be fragmented into passable pieces, and it was concluded that while stone subdivision via stress waves is important for the initial fragmentation of a stone, cavitation is essential for the production of fine passable debris [7]. This suggests that SWL stone comminution may be viewed as a two-phase process. During the first phase, the direct stress wave component of LSWs dominates to produce the initial subdivision of a stone. As these fragments are further comminuted to smaller and smaller size, the efficacy of the stress waves attenuates and the cavitation component of the LSW becomes the primary means of fragment reduction. Thus, the application of controlled cavitation at this point in the comminution process should be expected to provide an adjunct to SWL therapy, as was observed in treatment scheme **B**.

Application of histotripsy cavitation erosion prior to SWL (scheme **C**) was also found to increase the degree of stone comminution relative to the control (SWL-only) case (Fig. 6). This suggests that sonicating a stone with histotripsy preconditions it for LSW subdivision. As displayed in Fig. 7, following the histotripsy phase of the therapy extensive pitting was produced on the stone surface. Such pitting is commonly associated with cavitation damage, and is attributed to localized stress created by the impact of fluid jets or secondary shock waves produced by bubble collapse [15]–[17], [19]–[21]. It is likely that these surface defects provide sites for crack initiation and propagation during the subsequent SWL phase of this treatment scheme—a concept that has been suggested previously in SWL literature. Zhu, *et al.* showed that when the cavitation component of LSWs is isolated by positioning stone phantoms off the shock wave axis, the resulting damage is primarily surface erosion that is likely to weaken the surface structure and increase susceptibility to LSWs [7]. Cleveland and van Cauweleart used computed tomography to demonstrate that when model

stones are exposed to LSWs, fractures first form at the surface and then grow inward [47]. It has been postulated that following the generation of such crevices, liquid enters the stone material and is cavitated upon the application of subsequent LSWs [10]. Crack propagation is then likely to result as enormous stresses are generated within the fissure [13], [48]. Sapozhnikov, *et al.* found that model stones could only be fractured in a cavitation suppressing medium when they contained an etched band to simulate cavitation damage, suggesting that cavitation-induced surface cracks play an important role in stone subdivision [9]. These studies corroborate the idea that the application of histotripsy cavitation erosion prior to SWL increases the susceptibility of a stone to LSW subdivision.

During the interleaved treatment (scheme **A**), one would expect both the aforementioned phenomena to be at play. In the initial stages, surface defects induced by histotripsy cavitation erosion are likely to facilitate the formation and growth of cracks within the stone matrix. Following primary stone subdivision, the increase in exposed surface area should augment histotripsy therapy and enhance the cavitation erosion process. However, the degree of stone comminution resulting from this interleaved treatment was reduced in comparison to schemes in which histotripsy and SWL were applied in isolation subsequent to one another (**B** and **C**, see Fig. 6). Furthermore, it was visually observed that the onset of stone subdivision required a greater number of LSWs during this interleaved scheme in comparison to SWL-only. We hypothesize that this outcome is a result of shielding caused by remnant bubble nuclei that persist following a histotripsy burst. The phenomenon of shielding is well established in SWL, in which a population of prefocal cavitation nuclei generated by a LSW act to attenuate the tensile component of subsequent LSWs and reduce the efficacy of cavitation at the stone surface [26], [27]. This effect can be passively mitigated by increasing the time between successive LSWs, and enhanced stone subdivision with decreasing shock rate has been demonstrated both *in vitro* [22], [23] and *in vivo* [24]. Additionally, clinical trials have yielded higher success rates for patients treated with SWL at a rate of 1 Hz in comparison to those at 2 Hz [25].

The interleaved pulse scheme utilized in this study was selected based on preliminary investigation to minimize the shielding effects of remnant histotripsy nuclei on subsequent LSWs. However, regardless of the timing, generation of a cavitation bubble cloud between successive LSWs is likely to amplify the extent of shielding to some degree. This can be seen in Fig. 8, in which it is apparent that LSW-induced bubble activity increases when LSWs are preceded by a histotripsy burst. The interleaved therapy then becomes an optimization problem in which the added benefit of histotripsy cavitation erosion must be considered against the propensity for remnant cavitation nuclei to induce shielding. As suggested by previous SWL studies, passively increasing the wait-time between a histotripsy burst and subsequent LSW can afford residual nuclei with sufficient time to dissolve and mitigate the extent of shielding. However, we would like to interleave a maximal amount of histotripsy therapy between successive LSWs in order to accentuate the positive effects of cavitation erosion in a minimal amount of time. For this reason, one of the primary aims of our future work is to explore the possibility of developing a pulse sequence for actively mitigating this shielding effect. Finally, it should be noted that for the purpose of this study, histotripsy therapy was used solely to explore the *trends* associated with the interaction between cavitation and LSW stone comminution. The histotripsy parameters utilized in this study were selected following a coarse preliminary investigation, and a full parametric optimization remains for future work.

CONCLUSION

In this study, histotripsy ultrasound therapy was used to explore the role of cavitation in the SWL stone comminution process. When applied prior to SWL, histotripsy cavitation erosion

produced extensive pitting on the stone surface. It is likely that this damage acts to precondition stones for LSW subdivision by providing sites from which cracks can nucleate. The application of histotripsy cavitation erosion following SWL resulted in the greatest degree of stone comminution. This treatment scheme takes advantage of a major point of synergy between LSW stone subdivision and cavitation erosion: whereas the direct stress wave (spalling) component of LSWs has an intrinsic size limitation to the fragments it can produce, the efficacy of cavitation erosion increases as a stone is comminuted and has a greater exposed surface area. When histotripsy pulses are interleaved between successive LSWs, we would expect both the aforementioned effects to contribute to stone comminution. At the onset of treatment, histotripsy-induced pitting on the stone surface should accelerate LSW fragmentation; following primary stone subdivision, the increase in exposed surface area should enhance the cavitation erosion process. However, the degree of stone comminution produced by the interleaved treatment was reduced in comparison to applying SWL and histotripsy separately and subsequent to one another. We expect that this is a result of shielding induced by remnant histotripsy bubble nuclei, and plan to explore bubble deleting pulse sequences to mitigate this effect. Nevertheless, this study confirms that cavitation plays a critical role in kidney stone comminution, and demonstrates the fact that application of controlled cavitation at strategic points in the fragmentation process can provide an adjunct to SWL therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research reported in this publication was supported by The National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under award number R01DK091267. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Fig. 1.

Experimental setup used for the treatment of composite stone phantoms. Stones were held within a channel in an agarose hydrogel, while ultrasound was delivered from the electrohydraulic lithotripter and/or histotripsy transducer positioned above.

Fig. 2.

Gel-holder assembly used to position composite stone phantoms during sonication. (A) The bottom portion of the holder (not pictured in its entirety) was fabricated from Accura-60 plastic. It contains a concave basket with 2 mm holes that served as the surface on which model stones were ultimately placed. (B) 1% agarose hydrogel was cast surrounding the basket, creating a channel in which stone fragments were free to move. (C) During treatment, debris reduced to sub-2 mm size was able to pass through the basket into a collecting dish placed below (not pictured).

Fig. 3. Research system capable of delivering electrohydraulic SWL and histotripsy therapy confocally (driving electronics not pictured). The histotripsy transducer consists of an array of eleven 500 kHz PZT-8 discs sealed in water-tight housing/lens assemblies. Individual housings are geometrically aligned by a scaffold that surrounds the ellipsoidal reflector of the electrohydraulic lithotripter.

Fig. 4.

Example histotripsy pressure waveform as recorded by a fiber optic hydrophone. The signal shown has been averaged over 300 pulses and was taken at a sub-therapy driving voltage of 1700 V_{pk-pk} to prevent cavitation damage to the fiber tip. It can be seen that the histotripsy pulse amplifier produces relatively short pulses, roughly 2 cycles in length.

Fig. 5.

Pulse timing schemes for the interleaved therapy, SWL, and histotripsy. A one-second duration is shown for each. SWL was applied at a shock rate of 1 Hz, while histotripsy was administered in 70 pulse bursts at a PRF of 100 Hz. The five treatment schemes investigated in this study were composed of combinations of these three therapies, as describe in both the text and Table I.

Fig. 6.

Stone fragment size distributions. Following sonication, stone debris remaining in the treatment channel was sequentially sieved through 8, 6, 4, and 2 mm filters. It was found that SWL alone produced a broad range of fragment sizes, while histotripsy only eroded the stone surface to fine particulate debris (<2 mm). The combination of SWL and histotripsy (A, B, and C) resulted in a shift in the distributions toward smaller fragments and complete elimination of all debris >8 mm.

Fig. 7. Representative model stones prior to treatment (left) and following sonication with histotripsy (right). Histotripsy cavitation erosion was observed to produce extensive pitting on the surface of the stone.

Fig. 8.

High speed images showing LSW-induced cavitation surrounding the stone. The direction of ultrasound propagation is top-bottom in each image, and the stone was free to move within the treatment channel (as described previously). A single image was captured 20 μ s after the arrival of each LSW. The top panel presents five representative images for the interleaved treatment (scheme A), while the bottom panel displays representative images for the SWL only treatment (scheme D). An increase in bubble excitation is observable in the former case.

TABLE I

Treatment Scheme Summary

Treatment Scheme	Description	Shock Wave Total	Histotripsy Pulse Total	Treatment Time (min)
A	Interleaved	600	42,000	10
B	SWL followed by Histotripsy	600	42,000	20
C	Histotripsy followed by SWL	600	42,000	20
D	SWL Only	600	0	10
E	Histotripsy Only	0	42,000	10