

Improving burst wave lithotripsy effectiveness for small stones and fragments by increasing frequency: theoretical modeling and *ex vivo* study

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Introduction and Objective: In clinical trial NCT03873259, a 2.6-mm lower pole stone was treated transcutaneously and *ex vivo* with 390-kHz burst wave lithotripsy (BWL) for 40 minutes and failed to break. The stone was subsequently fragmented with 650-kHz BWL after a 4-minute exposure. This study investigated how to fragment small stones and why varying BWL frequency may more effectively fragment stones to dust.

Methods: A linear elastic theoretical model was used to calculate the stress created inside stones from shock wave lithotripsy (SWL) and different BWL frequencies mimicking the stone's size, shape, lamellar structure, and composition. To test model predictions about the impact of BWL frequency, matched pairs of stones (1-5 mm) were treated at 1) 390 kHz, 2) 830 kHz, and 3) 390 kHz followed by 830 kHz. The mass of fragments greater than 1 and 2 mm was measured over 10 minutes of exposure.

Results: The linear elastic model predicts that the maximum principal stress inside a stone increases to more than 5.5 times the pressure applied by the ultrasound wave as frequency is increased, regardless of composition tested. The threshold frequency for stress amplification is proportionate to the wave speed divided by the stone diameter. Thus, smaller stones may be likely to fragment at higher frequency, but not lower frequency below a limit. Unlike with SWL, this amplification in BWL occurs consistently with spherical and irregularly shaped stones. In water tank experiments, stones smaller than the threshold size broke fastest at high frequency ($p=0.0003$), whereas larger stones broke equally well to sub-millimeter dust at high, low, or mixed frequency.

Conclusions: For small stones and fragments, increasing frequency of BWL may produce amplified stress in the stone causing the stone to break. Using the strategies outlined here, stones of all sizes may be turned to dust efficiently with BWL.

Introduction

We are developing an ultrasound-based burst wave lithotripsy (BWL) system for fragmenting stones in awake subjects.¹ Unlike shock wave lithotripsy (SWL), which uses a single broadband pulse of ultrasound to fragment stones, BWL employs narrowband pulses consisting of multiple cycles of ultrasound. The amplitude of the BWL pulse is lower than with SWL and has the potential to be used as an office-based procedure.

In a clinical trial, BWL is being used to fragment stones in anesthetized subjects during their standard-of-care ureteroscopy procedure to visualize the fragmentation.² Results from the first subject undergoing the BWL procedure were published,² and preliminary results for 19 subjects are in press.³ These results include a 2.6-mm stone, the smallest one targeted so far, that did not fragment. The stone was basket extracted intact and exposed for an additional 30-minutes to the same BWL settings in a water bath, with still no evidence of fragmentation. The stone was then exposed to a 650-kHz BWL pulse of the same number of cycles, pulse repetition frequency, and peak pressure. After 4 minutes, the stone broke into 4 fragments all ≤ 2 mm in largest dimension and ≤ 1 -mm fragments within 30 minutes. With this study, we sought to explain how the change in BWL frequency contributed to fragmentation success.

Studies have shown a decrease in SWL and BWL effectiveness to break a stone if the stone is larger than the beamwidth of the pulse.⁴⁻⁶ However, little has been discussed regarding a minimum stone size that can be broken. Theoretically, the smallest size fragments that can be generated using SWL are proportionate to the lithotripter pulse length. Achieving fragments smaller than the pulse length is thought to be a result of cavitation.⁷ Similarly, the largest fragments produced by BWL are proportionate to the BWL wavelength, which is the inverse of frequency.⁶ In other words, the higher the frequency, the smaller the fragment size, but potentially at the cost of a longer procedure in order to grow a denser web of cracks.

The question addressed in this paper is how the choice of frequency impacts not just the fragment size, but the size of stone that can be fragmented. The results include a calculation of the stress produced within a stone by the BWL pulse and an *ex vivo* study of

breaking stones of varying size using two different frequencies. The outcomes help explain why this particular (2.6 mm) stone did not break clinically and provide insight into optimizing BWL to break stones to sub-millimeter dust that will have a high likelihood of spontaneous asymptomatic passage.

Methods

Theoretical modeling.

The mechanical stresses generated by a BWL burst in a stone of size, structure, and composition similar to the clinically intact (2.6 mm) stone were estimated using a well-established linear elastic model used for investigating the fracture mechanism of SWL.⁹⁻¹² The primary plots show the stress over an initially 50 mm x 50 mm cross-section along the centerline of the stone. For this study the outputs include the maximum principal stress achieved within the stone, which corresponds to the maximum of all the stresses, the total strain energy in stone, and the damage potential evaluated by Tuler-Butcher criterion¹³ with a value of tensile strength of natural stone listed in Ref. 13. All are common metrics for predicting stone fracture.

Table 1 lists the properties used in the model including density ρ , longitudinal wave velocity c_l , and shear wave velocity c_s .¹⁴⁻¹⁶

The applied pressure field consisted of a plane wave characterized as a single cycle (mimicking SWL) or a tone-burst (BWL) waveform of 390-kHz or 650-kHz central frequency, 10-cycle pulse duration, and 6 MPa peak negative pressure. These models attempt to simulate aspects of the above-mentioned experiments with the 2.6-mm stone and show similar behavior for frequencies above a threshold value related to the stone size. The details of the waveform representation in the model were described previously by Sapozhnikov *et al*, 2020.¹⁰

Ex vivo experiments.

The rate of stone breakage by low (390 kHz) and high (830 kHz) frequency BWL in stones ranging in size of 1-3 mm (Set 1) and 3-5 mm (Set 2) was evaluated in water bath. The 830-kHz transducer was used because it had the same beamwidth (> 5 mm) of the 390-kHz

transducer to be effective on stones 5-mm and smaller and a frequency predicted to be effective on stones 1 mm and larger; the 650 kHz transducer used above had a narrower beamwidth only appropriate for the 2.6-mm stone. Each set of stones were matched by size and exposed to either the low frequency or high frequency burst. In addition, a third set of 3-5 mm stones was exposed to a combination of low frequency burst followed by a high frequency burst (Mixed Set).

Stones: All stones were predominately COM (>95% as measured by infrared spectroscopy), and all were hydrated for more than one week before the experiment. All stones were weighed wet before use. COM stones are the most common type, and other stone compositions were investigated in our companion paper by Sapozhnikov *et al.* 2021.¹²

Setup: The stone was held in a water-filled depression in a tissue mimicking phantom simulating a calyx (Fig. 1). The depression was cylindrical with a 5-mm diameter x 10-mm deep well with a pointed bottom that ensured stone and fragments stayed at the focus. The transducer pointed downward at the phantom in a water bath at 50% oxygen saturation.¹⁷ The conditions were chosen to mimic thresholds for cavitation *in vivo* as measured with the 390-kHz frequency, and exposure conditions for clinical trials with 390-kHz were chosen to avoid formation of a cavitation cloud. The inline ultrasound imaging is used to detect if a cavitation cloud forms, and treatment is then paused. No cavitation clouds were observed in the current experiment with either frequency.

Fragments were removed from the phantom every 2.5 minutes and passed through a 1-mm sieve. The remaining (residual) fragments that did not pass through the sieve were weighed and then passed through a 2-mm sieve. The residual fragments that did not pass through the 2-mm sieve were again weighed. All stones greater than 1 mm were returned to the phantom for more treatment.

Exposure parameters: The BWL therapy was delivered using two separate transducers for the different frequencies, but both had the same beamwidth, which was 6 mm and wider than the maximum dimension of all the stones. The exposure consisted of 6 MPa peak negative pressure, 20-cycle pulse duration, and 10 Hz pulse repetition frequency. This was

consistent with the clinical dose taking into consideration tissue attenuation. All stones were exposed for 10 minutes maximum. In the mixed frequency case, the first 2.5-minute exposure was at low frequency and the remaining 7.5-minute exposure was at high frequency.

Analysis: The residual masses were normalized to the initial mass and averaged at each time point for each exposure, sieve size, and stone (set) size. Large stones and small stones were analyzed separately. The rates of comminution were statistically compared in two approaches: interval censored time-to-event data and longitudinal data analysis based on the remaining percentages. Time-to-event data included two approaches - Generalized log-rank and a Cox proportional hazard model for interval censored data. The longitudinal data analysis approach was used to predict the probability outcome of complete comminution based on the remaining residual stone masses and were analyzed overall and at each time point. Linear mixed effects models were used with a random intercept for stone level, and another random intercept at the matching level. Time was treated as a categorical variable, for the time trend is nonlinear. The frequency effects were analyzed by comparing the longitudinal mean profiles across different frequencies. All duplicate measures agreed on statistical significance (p -value < 0.05), and the highest p -value is presented.

Results

The extracted stone was approximately spherical (Figure 2a). Micro computed tomography measured the stone as 2.6 x 2.5 x 1.8 mm. The stone had a calcium oxalate monohydrate (COM) core surrounded by a thin calcium oxalate dihydrate (COD) shell (Fig. 2b).¹⁸

Theoretical modeling.

Three stones were modelled: a 2.6-mm spherical COM only stone, a 2.6-mm spherical COM stone with a COD shell, and an asymmetric shape emulating the extracted stone. Figure 3 shows the maximum stress along the centerline of the stone. Except the last column which shows the stress, the maximum stress is normalized by the peak negative pressure of the BWL pulse to highlight the amplification of the stress within the stone. A single cycle pulse, like SWL, creates negligible amplification as does a 390-kHz BWL burst

for this size stone. However, the 650-kHz BWL burst creates a stress within the stone that is more than 5 times the pressure applied. The result is consistent even when including the COD shell on the stone and the irregular non-spherical shape of the stone as shown in Fig. 3.

Figure 4 shows the amplification of the stress at the center of a COM spherical stone over the applied acoustic pressure for a 10-cycle, 6 MPa BWL pulse at the same two frequencies (390 kHz and 650 kHz) for two stone sizes. At 390-kHz the pressure within the 2.6 mm stone more than doubled to 17 MPa. For a larger (4.5 mm) stone the amplification was more than 5.5 times to 34 MPa. Alternatively, the amplification was 5.5 times to 34 MPa for both the 2.6 mm and 4.5 mm stones at the higher frequency. Thus, selection of the frequency increased the stress in the stone by a factor of five and a half to a level sufficient to break the stone. This is consistent with the result that 390-kHz BWL did not break the 2.6-mm stone, but 650-kHz BWL did.

Figure 5a shows the time history of the peak strain energy and damage potential inside the 2.6-mm asymmetric stone at the end of a 1-cycle or 10-cycle, 6-MPa (peak negative pressure) lithotripsy pulse for each frequency. Both indicators support that fragmentation is less effective at 390 kHz compared with 650 kHz. Similar to the results for the principal stress, the peak strain energy requires at least approximately 4 cycles before amplification is observed, which is why the amplification is not seen with the single cycle lithotripsy (i.e., SWL) pulse.

Ex vivo experiments.

Twenty stones were included within each test population for a total of 100 stones fragmented. Figure 6 (upper) shows the average mass fraction of small stone (1-3 mm) fragments greater than 1 mm remaining at each time point (a) and the probability of the stone being completely broken to < 1 mm fragments (b) based on the remaining fragments at each time point. The stones exposed to the higher (830 kHz) frequency broke the small stones faster and more completely. For all three statistical models, the fragmentation of 1-3 mm to < 1 mm size at 830-kHz is statistically better than at 390-kHz ($p=0.0003$). Because a fraction of the stones within this group start smaller than the 2 mm sieve, those data are not presented.

Figure 6 (lower) shows the mass fraction of large stone (3-5 mm) fragments over 2 mm (c) and over 1 mm (d) remaining at each time point for high, low, and mixed frequency. There are no statistical differences ($p=0.2055$). For this size range (3-5 mm) at these frequencies for equal beamwidths greater than the stone size, there was no detriment to using high frequency, which breaks smaller stones better, to also break larger stones. Although not statistically significant, there is a trend of improved comminution effectiveness with the mix frequencies. The statistical results for the fraction of stones are consistent with the longitudinal data analysis. Only one time point (at 5 minutes) was found to be significant, but significance was lost when the model was adjusted for multiplicity.

Discussion and Conclusions

Theoretical modeling and *ex vivo* experiment showed a statistically significant benefit of fragmenting small, < 3 mm, stones using multiple cycles at a higher frequency relative to a lower frequency capable of breaking a 3-5 mm stone. This concept potentially contributed to the lack of fragmentation of a small, 2.6-mm stone clinically at 390 kHz. The increase in fragmentation effectiveness correlates with an amplification of the incident pressure within the stone. The threshold frequency at which amplification initiates is approximately the ultrasound wave speed divided by stone size. Above the threshold frequency, the pressure of the applied BWL in the simulation was amplified five and a half times. Amplification was consistent for the stone shape, structure, and composition. Ultimately on average 87% of the stone mass of 1-3 mm stones and 30% of the stone mass of 3-5 mm stones was broken to submillimeter dust in 10 minutes. For the conditions tested we suspect particularly a beamwidth larger than the stone, the high frequency was not slower than low frequency at breaking the larger stones, and the one method of mixing frequencies that was tested might indicate mixing frequencies may accelerate comminution to dust.

Although 4-mm residual fragments have historically been considered insignificant, modern ureteroscopy techniques often aim to dust the stone to 1-mm fragments or smaller, and as such the clinical implications of this work are twofold. One, a potential application for BWL is the fragmentation of small symptomatic or asymptomatic stones or residual

fragments before they require surgical intervention. We are embarking on a new randomized controlled trial (NCT04796792) to test BWL and ultrasonic propulsion¹⁹ together to facilitate clearance of small kidney stones; this work provides guidance toward selecting a frequency effective for small stones. Two, changing BWL frequency as the stone breaks has potential to more efficiently break even large stones to dust. In this case, by starting with lower frequency to rapidly generate fragments and then transitioning to higher frequency to turn the fragments to fine dust.

Our modelling calculations were limited here to COM stones with no attenuation and uniform composition. The mechanism of action described here is the reverberation of sound within the stone allows for focusing and constructive interference of waves and reflections. The attenuation of stones is known within a range considered with our model in a physics-centered companion paper.¹² Were attenuation much greater than that range then the waves would be too quickly absorbed to reverberate and obtain the stress amplifications reported here. Likewise, linear elastic models are used to predict the stress with the highest stresses having the highest probability of growing cracks. The cracks or other heterogeneities other than irregular shapes and lamellar structures were not considered here. However, cracks like surface features related to irregular shapes concentrate the stress that created them, and tone-burst reflections from cracks can also further add to regions of high stress throughout the stone.¹⁶ The companion paper shows the amplification occurs for stones of different homogeneous compositions and a range of parameters suitable for heterogeneous stones and can be greater than the amplification seen for COM stones.¹² COM stones appear to have the highest threshold frequency; thus, selecting an operational frequency for a COM stone should also be effective for stones of the same size but different composition.¹²

The primary limitation of the current study is small stones were studied to work in the range of stone sizes where higher than the current clinical frequencies were beneficial. Although no stones larger than 5 mm were broken here, it was shown stones up to 5 mm could be broken to dust and hinted that the process might be accelerated by using a lower followed by higher frequency. It appears the fragments created from a larger stone are slightly smaller than the threshold size for a small stone to be broken at the same

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frequency, indicating that this threshold may also be related to the size of fragments generated from a large stone. This paper neglects cavitation and focuses on elastic waves, as these have been demonstrated to correlate with the location and presence of fractures. Although cavitation which is neglected in the model and surface waves which are included in the model are thought to contribute to stone erosion and may initiate fracture, stones and fragments do not appear to erode significantly in BWL, particularly hard stones such as COM, but rather fracture into fragments as seen in this study.^{6,12, 16, 20} In addition, cavitation would be expected to have the opposite effect to that measured: cavitation decreases with frequency yet here fragmentation increased with frequency.

The practical limitation to clinical application is the transducer. An encouraging conclusion of this study is the frequency does not have to be tuned for a specific stone, only selected to be above a threshold value to achieve higher stress. However, it is easier to make a broad beam at lower frequency, and all transducers are limited to isolated or limited ranges of frequencies and cannot be used at all frequencies of potential interest.²¹ Nevertheless, techniques exist to make the BWL beam broader.²¹ Also, nonlinear acoustics can be used to generate waves that contain several harmonic frequencies, and transducers often work at their fundamental frequency and a frequency three times higher, providing ways of obtaining low and high frequencies without changing transducers. In addition, higher frequency is more readily attenuated by tissue but even for a large skin-to-stone distance with ultrasound (10 cm), the energy loss is 7% at 390 kHz and 13% at 830 kHz.²²

In conclusion, a small stone did not break after a 40-minute BWL exposure at one frequency but then broke completely after a 4-minute exposure to a higher frequency with the same pulse duration, pulse repetition frequency, and incident pressure level. The result is consistent with theoretical elastic wave modeling that shows amplification of stone stress beyond the applied acoustic pressure in the stone above a threshold frequency for a given stone size. In the simulation presented here, the amplification was greater than five times the applied pressure and occurred for stones of different compositions, structures, and shapes. Overall, the work supports that adjusting BWL frequency can accelerate stone comminution and enhance fragmentation to sub-millimeter fragments.

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Author Disclosure Statement

MB, AM, BC, and MS have equity in, and consulting agreements with, SonoMotion, Inc., which licensed the reported technology from the University of Washington for commercialization.

Author Contribution Statement

All authors contributed to concept and design of the study, acquisition of data, analysis and interpretation of data, drafting the article or revising it critically for intellectual content, and final approval of the version to be published.

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Abbreviations

AUA American Urological Association

BWL Burst Wave Lithotripsy

SWL Shock Wave Lithotripsy

Table 1: Properties Used in the Simulation to Model Renal Calculi Composition

MATERIAL*	ρ , kg/m ³	c_l , m/s	c_t , m/s
Water	1000	1500	0
COM	1823	4476	2247
COD	1875	2687	1344

* COM = calcium oxalate monohydrate; COD = calcium oxalate dihydrate

Figure Captions

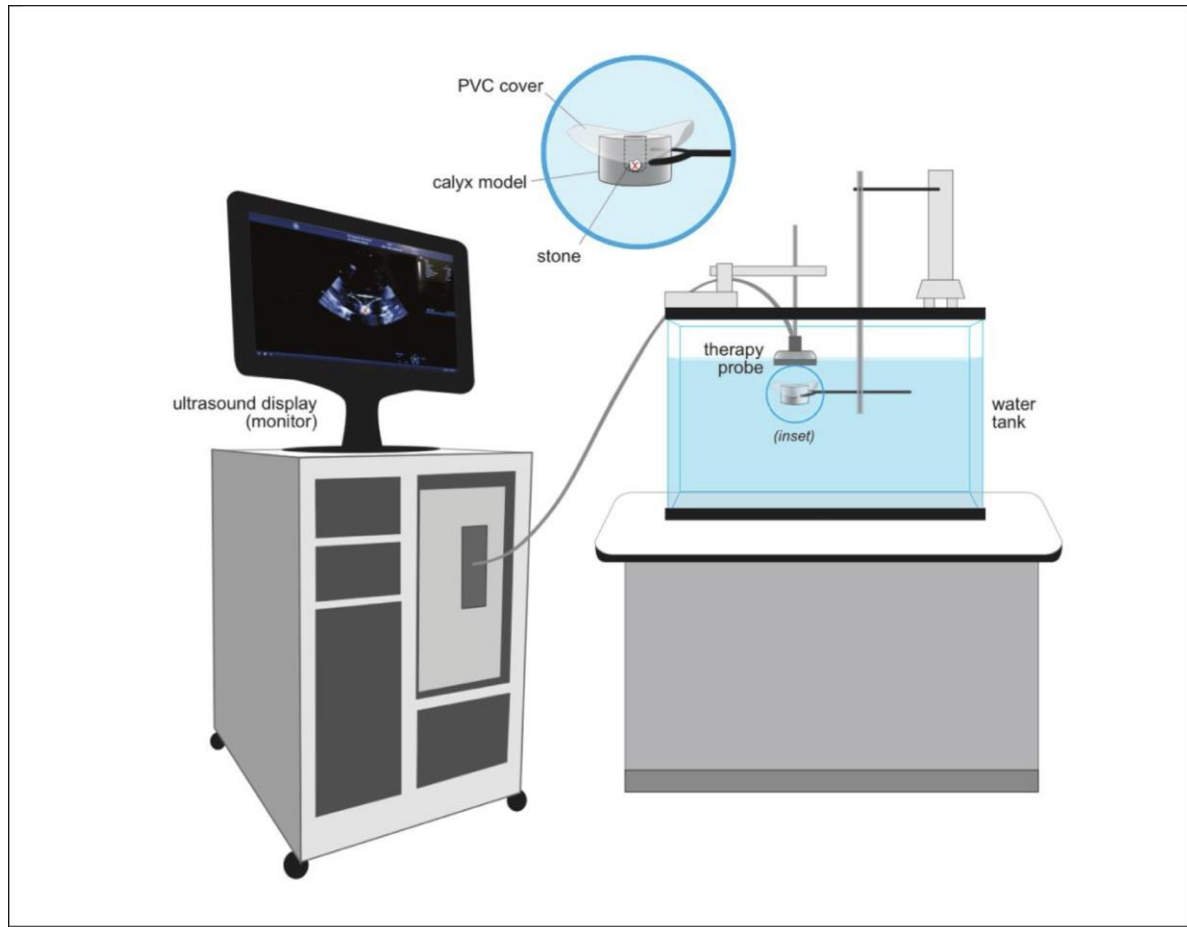


Figure 1. Experimental set up.

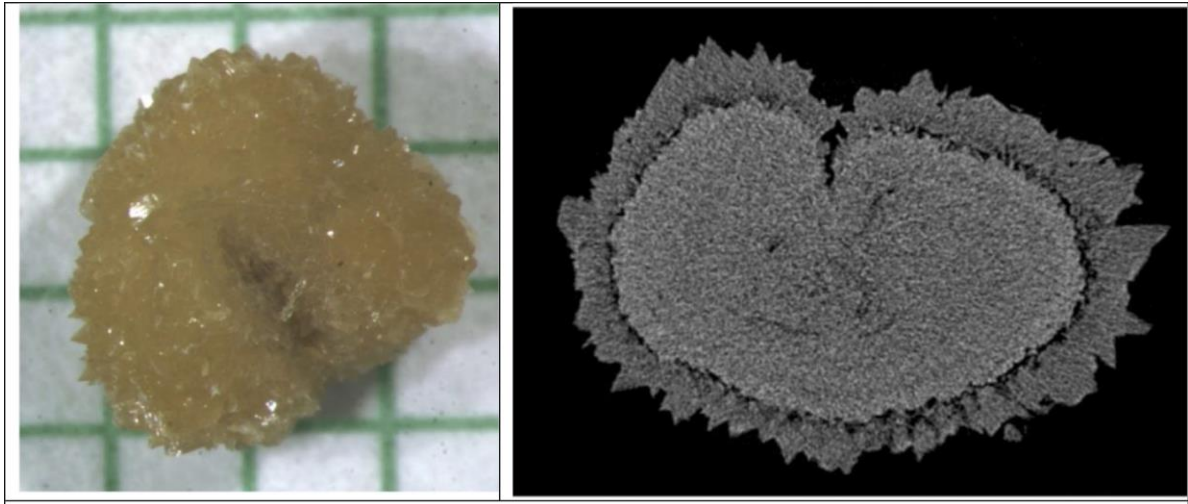


Figure 2: (a) Photograph of the extracted stone on 1-mm graph paper, and (b) slice of a volume image of the stone made by micro computed tomography after the *in vivo* exposure to BWL. The inner material is COM and the outer COD. The fissure at the top of the stone appears to be naturally present and not caused by BWL.

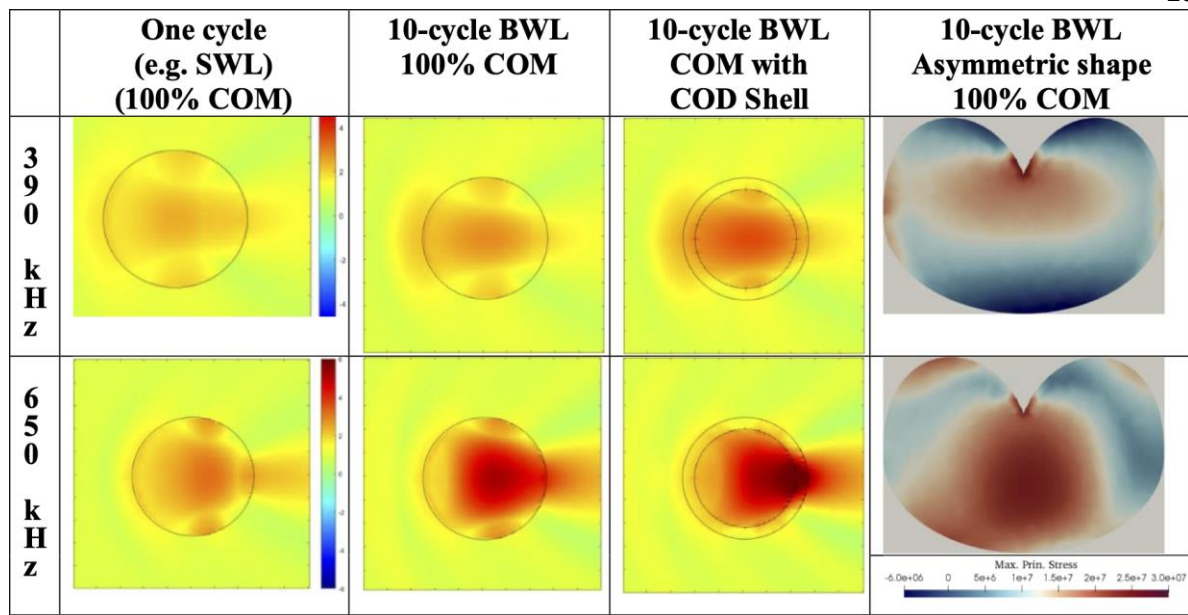


Figure 3. Simulated image of the peak maximum principal stress along the centerline of the stone. The upper column shows stress induced by 390-kHz lithotripsy burst and the lower shows stress induced by a 650-kHz lithotripsy burst. The scale (-6 to 6) is maximum stress divided by the incident pressure and represents the amplification of the applied pressure. A single cycle, similar to the shape of an SWL pulse, produces little stress and negligible amplification in the 2.6 mm diameter spherical stone regardless of the frequency. The second column shows the results from a 10-cycle BWL pulse, where the lower frequency produces little stress in the stone, but the higher frequency yields 5.5 times the applied pressure within the stone. Adding a COD shell (column 3) increases the stress within the stone slightly, because of COD's slower sound speed; however, significant amplification of the incident pressure within the stone is still only achieved at 650 kHz. The trend is similar for the irregularly shaped stone. (Scale in this column is stress not amplification).

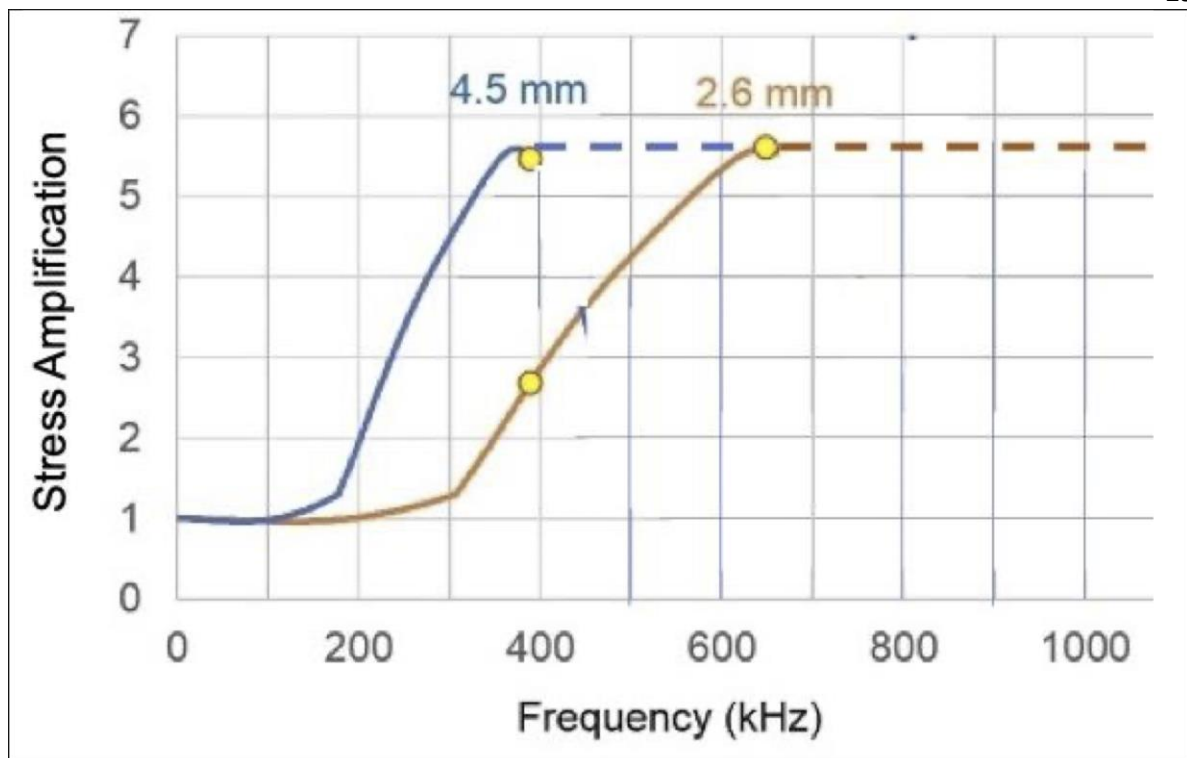


Figure 4. Peak maximum principal stress within a COM stone normalized to the peak pressure of the applied BWL pulse vs. BWL frequency for two stone sizes. For the 4.5 mm stone (blue line), the pressure amplification is more than 5.5 at both 350 kHz and 650 kHz. However, for the smaller 2.6-mm stone (orange line), the amplification is 2.8 at 390 kHz but 5.5 at 650 kHz. A dashed line is shown to the right of the peak to reflect that the amplification remains consistent, but there is a shift off-center and variations with specific resonances that are not shown but are discussed further in the paper by Sapozhnikov *et al.*, 2021.¹² The plots show a threshold in minimum frequency that must be used to achieve the maximum pressure amplification for a certain stone diameter.

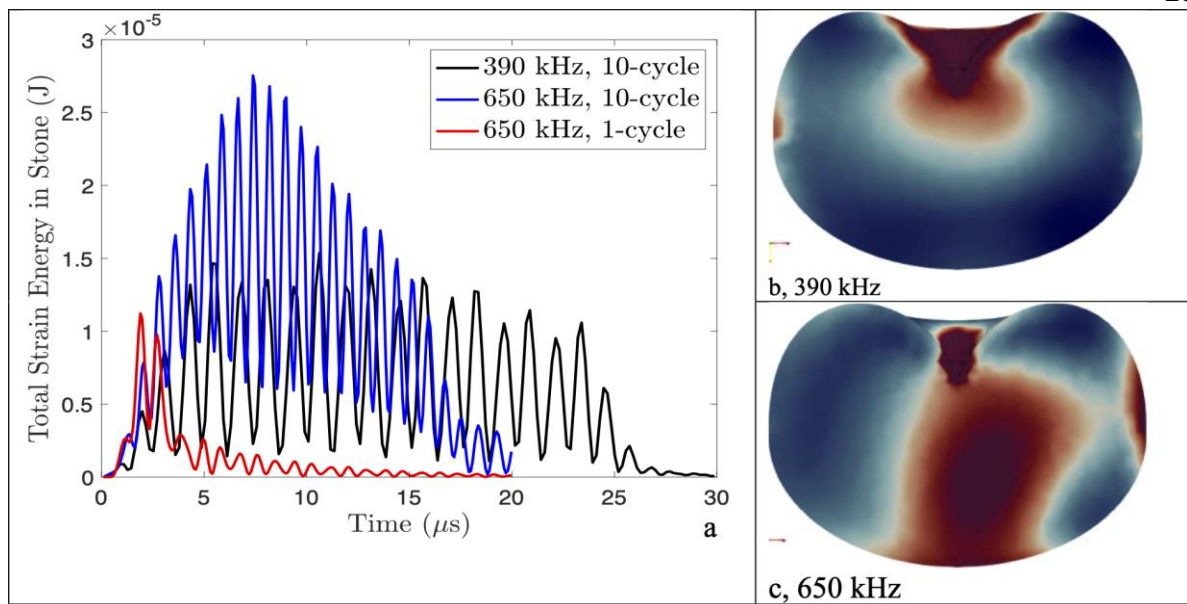


Figure 5. Time history of the total strain energy (a) and damage potential with BWL at 390 kHz (b) and 650 kHz (c) inside the 2.6-mm asymmetric stone. Multiple cycles are required to reach the maximum strain energy for a given a frequency. The total stain energy is nearly double for the higher frequency in this small stone. In addition, 650-kHz BWL produces a potential damage throughout the full width of the stone; whereas 390-kHz only yields damage potential at the stress concentrating surface feature.

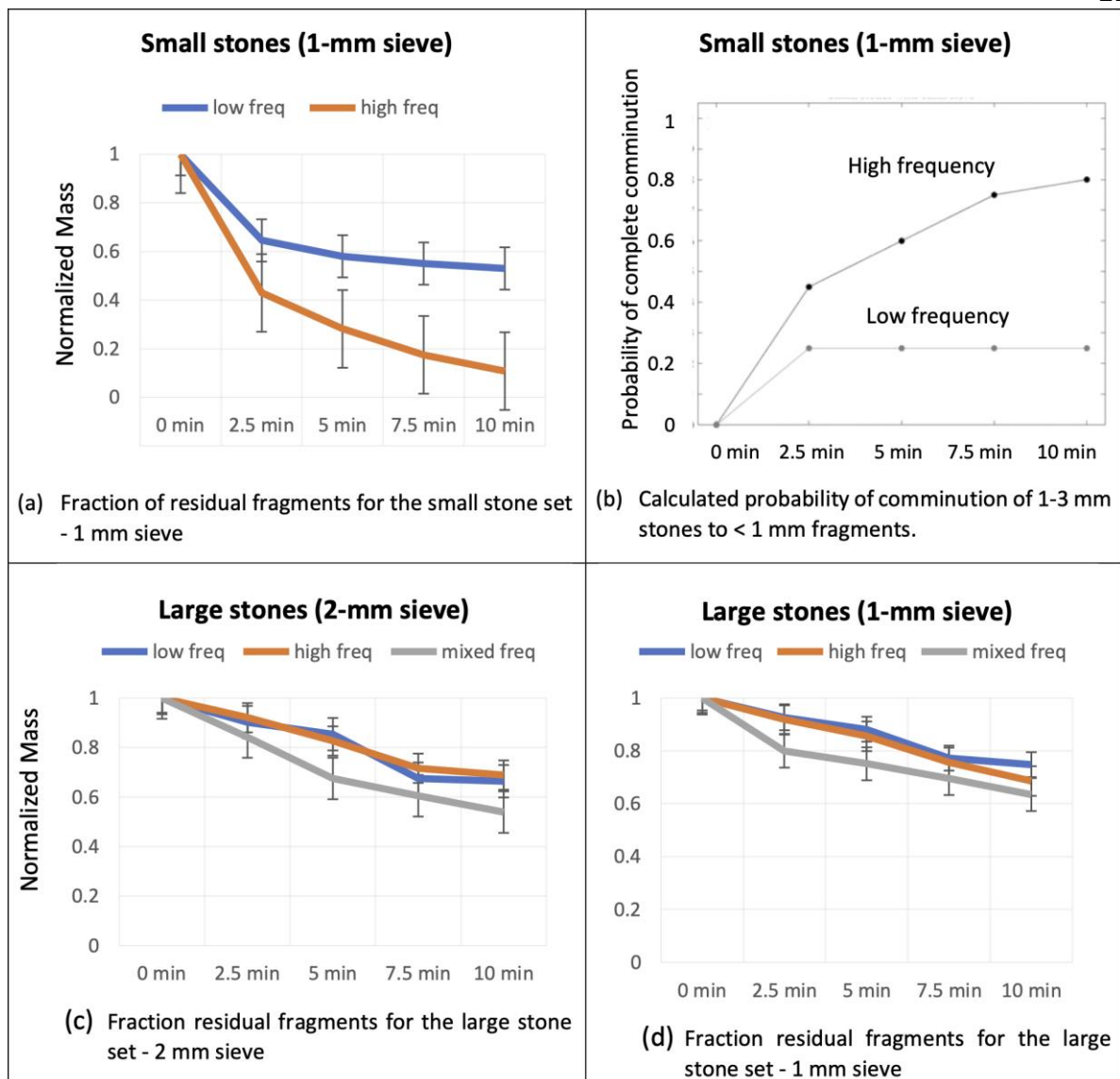


Figure 6 (upper) The average normalized mass fraction of initially small stone (1-3 mm) fragments greater than 1 mm remaining at each time point (a) and the probability of the stone being completely broken to < 1mm fragments (b). Under both conditions the stones exposed to the higher frequency (830-kHz) BWL burst broke COM stones in the 1-3 mm size range faster and more completely than when exposed to the lower frequency (390-kHz) BWL burst ($p=0.0003$). The calculated probability curve for the 390-kHz frequency flattened after 2.5 minutes, indicating the stones were not breaking further with additional exposure. (lower) The average normalized mass fraction of initially large stone (3-5 mm) fragments greater than 2 mm (c) and 1 mm (d) remaining at each time point. There are no statistical differences in rate of fragmentation between large stones exposed to low

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frequency (390 kHz) BWL, high frequency (830 kHz) BWL, or low frequency (2.5 minutes) followed by high frequency (mixed) ($p=0.2055$). The results suggest though it may not be possible to break a small stone at low frequency, it may be possible to use higher frequency over a broad range of stone sizes (1-5 mm) without a loss of fragmentation effectiveness.