Fragmentation of Urinary Calculi In Vitro by Burst Wave Lithotripsy

Adam D. Maxwell,* Bryan W. Cunitz, Wayne Kreider, Oleg A. Sapozhnikov, Ryan S. Hsi, Jonathan D. Harper, Michael R. Bailey and Mathew D. Sorensen

From the Department of Urology, School of Medicine (RSH, JDH, MDS) and Center for Industrial and Medical Ultrasound, Applied Physics Laboratory (BWC, WK, OAS, MRB), University of Washington (ADM) and Division of Urology, Department of Veteran Affairs Medical Center (MDS), Seattle, Washington, and Department of Acoustics, Physics Faculty, Moscow State University (OAS), Moscow, Russia

Abbreviations and Acronyms

BWL = burst wave lithotripsy

COM = calcium oxalate monohydrate

HIFU = high intensity focused ultrasound

p_f = focal pressure amplitude

SWL = shock wave lithotripsy

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* Correspondence: Department of Urology, University of Washington, 1013 Northeast 40th St., Seattle, Washington 98105 (telephone: 206-221-6530; FAX: 206-543-6785; e-mail: amax38@u.washington.edu).

Purpose: We developed a new method of lithotripsy that uses short, broadly focused bursts of ultrasound rather than shock waves to fragment stones. We investigated the characteristics of stone comminution by burst wave lithotripsy in vitro.

Materials and Methods: Artificial and natural stones (mean ± SD size 8.2 ± 3.0 mm, range 5 to 15) were treated with ultrasound bursts using a focused transducer in a water bath. Stones were exposed to bursts with focal pressure amplitude of 6.5 MPa or less at a 200 Hz burst repetition rate until completely fragmented. Ultrasound frequencies of 170, 285 and 800 kHz were applied using 3 transducers, respectively. Time to fragmentation for each stone type was recorded and fragment size distribution was measured by sieving.

Results: Stones exposed to ultrasound bursts were fragmented at focal pressure amplitudes of 2.8 MPa or greater at 170 kHz. Fractures appeared along the stone surface, resulting in fragments that separated at the surface nearest to the transducer until the stone was disintegrated. All natural and artificial stones were fragmented at the highest focal pressure of 6.5 MPa with a mean treatment duration of 36 seconds for uric acid stones to 14.7 minutes for cystine stones. At a frequency of 170 kHz the largest artificial stone fragments were less than 4 mm. Exposure at 285 and 800 kHz produced only fragments less than 2 mm and less than 1 mm, respectively.

Conclusions: Stone comminution with burst wave lithotripsy is feasible as a potential noninvasive treatment method for nephrolithiasis. Adjusting the fundamental ultrasound frequency allows for stone fragment size to be controlled.

Key Words: kidney, nephrolithiasis, lithotripsy, ultrasonic therapy, sound

SURGICAL management of urolithiasis has changed significantly since the introduction of SWL in the early 1980s.[1–4] This technology, along with the development of endoscopic techniques such as ureteroscopy[5] and percutaneous nephrolithotomy,[6,7] has almost completely replaced open surgery as a treatment option.[8,9] While minimally invasive methods continue to be refined, SWL remains the only extracorporeal procedure for stone disintegration.

Despite the discovery of shock wave induced stone fracture almost 40 years ago the acoustic output of

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lithotripters remains similar to that of the original implementation. Newer lithotripters have different focal dimensions and pressures but all systems deliver single shock waveforms at a rate of 1 to 2 Hz with a maximal dose of approximately 2,500 to 3,000 shocks. Several studies indicate that the HM3 (Dornier MedTech, Wessling, Germany), the first lithotripter used in clinical practice in the United States, is more effective than many of its newer counterparts.[10,11] These revelations in turn led to the production of several machines with specifications similar to those of the HM3, delivering broadly focused shocks with relatively low pressure amplitude.[12] Investigations into the physical mechanisms of lithotripsy also support that a broad focus, low pressure configuration is more effective in achieving stone comminution.[13–15] While there have been advancements toward achieving a more ideal lithotripter, the reported low effectiveness of many systems has led to a greater clinical preference for endoscopic techniques.[16]

Ultrasound based alternatives have been explored to expand the capabilities of SWL as extracorporeal treatment.[17,18] In previous studies HIFU pulses were focused strongly on the stone surface to generate a localized cloud of cavitation bubbles. Collapse of the associated bubble against the stone surface can erode the stone into fine dust. Heating the surrounding tissue, as observed in HIFU thermal therapy, is avoided by pulsing the ultrasound with a sufficiently low duty cycle.

We also explored focused ultrasound to break stones. However, we used a beam that was broadly focused to a width similar to or greater than the stone to excite elastic waves in the stone to produce discrete fragments rather than dust-like particles. This technique applies sinusoidal ultrasound bursts with relatively low pressure amplitudes rather than shock waves to prevent the accumulation of cavitation bubbles, which shield acoustic waves from propagating into the stone and causing fracture (fig. 1).[19] Similar to SWL, BWL uses a focused source to generate pressure pulses that can be administered transcutaneously. In this study we examined the feasibility of stone fracture by BWL applied to artificial and natural calculi in vitro.

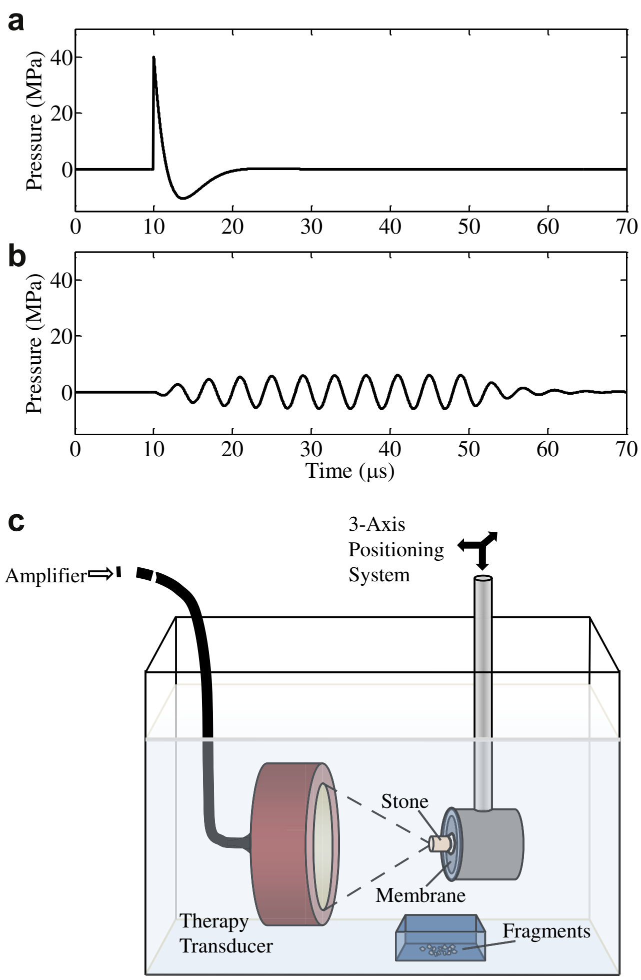

Figure 1. Modeled focal pressure waveforms of lithotripsy shock wave (*a*), approximating HM3 lithotripter shock, and ultrasound burst wave (*b*) wave, corresponding to highest pressure amplitude of 6.5 MPa applied in study. In experimental setup (*c*) to expose stones to burst waves focused ultrasound transducer was placed in water tank and stone was aligned with focus using motorized 3-axis positioning system. Transducer was driven by amplifier to expose stone to ultrasound bursts. Fragments were collected in small container positioned below stone.

MATERIALS AND METHODS

Artificial and Natural Stone Preparation

Artificial stones were created using the model developed by Liu and Zhong.[20] Such artificial stones have acoustic properties similar to those of natural COM stones. BegoStone plaster powder (BEGO USA, Lincoln, Rhode Island) was mixed with deionized, degassed water at a ratio of 5:1 by weight. Mixture aliquots were pipetted into an acetal plastic mold to form cylindrical stones 6 mm in diameter and 10 to 12 mm long. The mold was placed in a water bath 30 minutes after pipetting and allowed to set further for at least 12 hours. The stones were removed from the mold and placed in deionized water until use in experiments.

Human stones with a primary composition of uric acid, magnesium ammonium phosphate (struvite), COM and cystine were also obtained for experiments. Primary composition was defined as greater than 90% on spectroscopic analysis. The largest mean ± SD dimension of each stone was 8.2 ± 3.0 mm (range 5 to 15). Stones were submerged in deionized water at least 72 hours before experiments.

BWL System

Exposure was done using 3 piezoelectric focused ultrasound transducers with an operating frequency of 170, 285 and 800 kHz, respectively. Transducers were driven by a high voltage radiofrequency amplifier[21] controlled by a DE1 field programmable gate array board (Altera, San Jose, California). Each transducer was calibrated using a FOPH2000 fiber optic hydrophone (RP Acoustics, Leutenbach, Germany) to measure pressure waveforms in the focal region and effective beam width in a degassed water bath. The focus of each ultrasound transducer was defined by an ellipsoidal region of high pressure amplitude. The table lists the aperture, focal length and focal beam dimensions of the 3 transducers. Because focal dimensions of the transducers differed significantly, stones were aligned in a prefocal position when using the 285 and 800 kHz transducers to match the beam width of the 170 kHz transducer. The pressure output of each transducer was then adjusted so that the peak pressure amplitude in the plane aligned with the stone center was virtually the same for all 3 devices. This was done to facilitate even comparison among frequencies by treating stones using the same beam width and burst pressure amplitude at all 3 frequencies.

Stone Exposure

The transducer was positioned in a bath of filtered water degassed to approximately 20% O_2 saturation (fig. 1, *c*). A small amount of cyanoacrylate adhesive was used to affix the stone to a 25 μm thick, acoustically transparent polyester membrane attached over a polyvinyl chloride plastic hoop. This apparatus held the stone in a stable position during treatment to observe the progression of fragmentation and minimize reflections from the holder. The stone and holder were attached to a motorized, 3-axis positioning system (Velmex, Bloomfield, New York), which allowed for precise alignment of the stone with the focus. A digital camera was used to record images of stones and fragments before, during and after acoustic exposure.

Stones were exposed to ultrasound bursts for a duration of 10 cycles and a p_f of 6.5 MPa or less. The number of bursts administered per second (the burst repetition rate) was fixed at 200 Hz. The burst repetition rate is a parameter separate from ultrasound frequency that determines the oscillation rate in a single burst. After treatment the stone fragments that dropped in a basket were collected and allowed to dry. They were then photographed and passed through a series of sieves to determine the fragment size distribution.

Geometric characteristics and −6 dB focal pressure beam width of 3 study transducers

	Transducer		
	1	2	3
Center frequency (kHz)	170	285	800
Aperture (mm)	80	100	147
Focal length (mm)	54	75	140
Beam width (mm):			
Axial	32.4	42.0	17.0
Lateral	7.6	5.6	2.6

Several experiments were performed to evaluate the in vitro characteristics of stone fragmentation by BWL (see Appendix). 1) To determine the pressure threshold for stone fragmentation artificial stones were treated for 5 minutes each at different pressure amplitudes (3 per amplitude, p_f 1.2 to 6.5 MPa) at 170 kHz. 2) To determine the effect of stone composition on stone fragmentation 3 natural stones per composition and 12 artificial stones were exposed to the highest pressure amplitude (p_f 6.5 MPa). Resulting exposure times and fragment size distributions were compared. 3) To evaluate the effect of ultrasound frequency on fragment size artificial stones were exposed to an ultrasound frequency of 170, 285 and 800 kHz, respectively.

RESULTS

Erosion and multiple fractures were observed in stones treated at 170 kHz for a p_f of 2.8 MPa or greater (fig. 2). At the next lowest pressure amplitude (p_f 2.3 MPa) and below no change was visible in stones during the 5-minute exposure duration (60,000 bursts). Above a p_f of 2.3 MPa fine dust was emitted from the stone and fracture lines were observed on the surface, predominantly aligned along the circumferential and longitudinal directions of the cylindrical stone. Subsequently fragments separated from the stone with fragment geometry resulting from the location of these fractures. Fragmentation was generally initiated at the surface of the stone nearest the transducer and proceeded distal.

In the second series of experiments all of the artificial stones and the natural stones of 4 compositions were exposed to 170 kHz bursts at the highest pressure amplitude (p_f 6.5 MPa) and

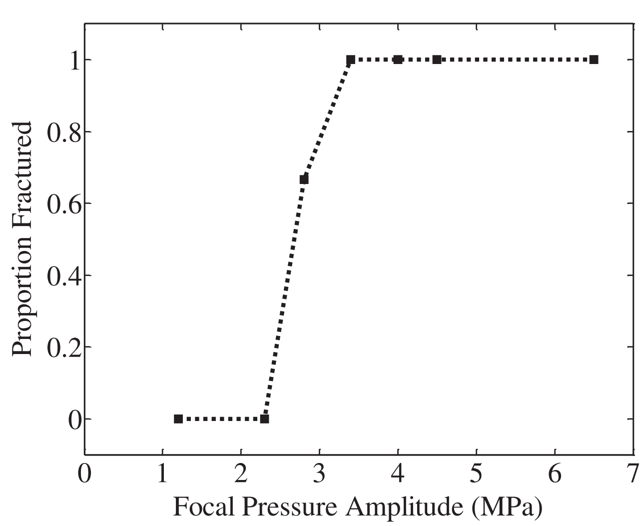

Figure 2. Proportion of 3 artificial stones per pressure level containing fractures after exposure to 60,000 bursts as function of focal pressure amplitude.

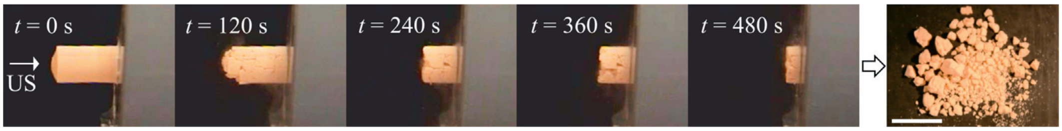

Figure 3. Photographic sequence shows artificial stone during exposure to 170 kHz bursts (p_f 6.5 MPa) during 8 minutes. Ultrasound (*US*) burst waves were incident on stone from left side (white arrow). *t*, time. *s*, seconds. Open arrow indicates fragments generated after 8-minute exposure. Scale bar indicates 1 cm.

successfully fragmented (figs. 3 and 4). In these trials the entire stone was disintegrated except a small portion that adhered directly to the membrane (fig. 3). The 12 artificial stones treated at a p_f of 6.5 MPa required a mean of 9.7 ± 2.8 minutes to achieve complete fragmentation.

The progression of treatment and resulting fragmentation of natural stones proceeded similar to that observed in the artificial stones. However, the time required to achieve fragmentation varied greatly by stone type. For instance, a 7 mm struvite stone could be fragmented in 4 seconds (800 bursts) while a cystine stone of similar size required 10.3 minutes (123,600 bursts). The range of treatment time was 0.17 to 1.40 minutes for uric acid, 0.07 to 2.02 for struvite, 8.0 to 18.1 for COM and 10.3 to 21.3 for cystine stones.

The size of fragments produced by each treatment was consistent among stones of the same composition. Figure 5 shows the distribution of collected fragments as a proportion of the total mass, which was obtained by sequential sieving. While variations in the distribution of fragment sizes were noted among stone types, the largest fragments produced for each type were similar in size. No treatment produced fragments greater than 4 mm. The largest fragments were 3 to 4 mm for COM, uric acid and artificial stones, and 2 to 3 mm for struvite and cystine stones. Most of the fragment mass was less than 3 mm for COM and uric acid stones, less than 2 mm for artificial stones and less than 1 mm for struvite and cystine stones.

In experiment 3 we compared artificial stones treated with exposure to 3 frequencies. At 170 kHz circumferential fractures in the stone appeared evenly spaced at approximately 3 mm apart along the cylinder length and did not appear to change in density with pressure amplitude. Exposure at 285 and 800 kHz produced more closely spaced fractures in the stone and resulted in smaller fragments compared with treatment at 170 kHz (figs. 5 and 6). At 285 kHz no fragments larger than 2 mm were generated and at 800 kHz no fragments larger than 1 mm were generated.

DISCUSSION

For more than 30 years SWL has been the only extracorporeal therapy for renal stones. While the physical mechanisms of shock wave induced stone fracture were not fully understood during its clinical introduction, subsequent research identified 2 particularly important effects, including elastic waves in the stone and cavitation at the stone surface.[14,15,22] 1) Elastic shear waves appear to be a dominant mechanism when using a focus broader

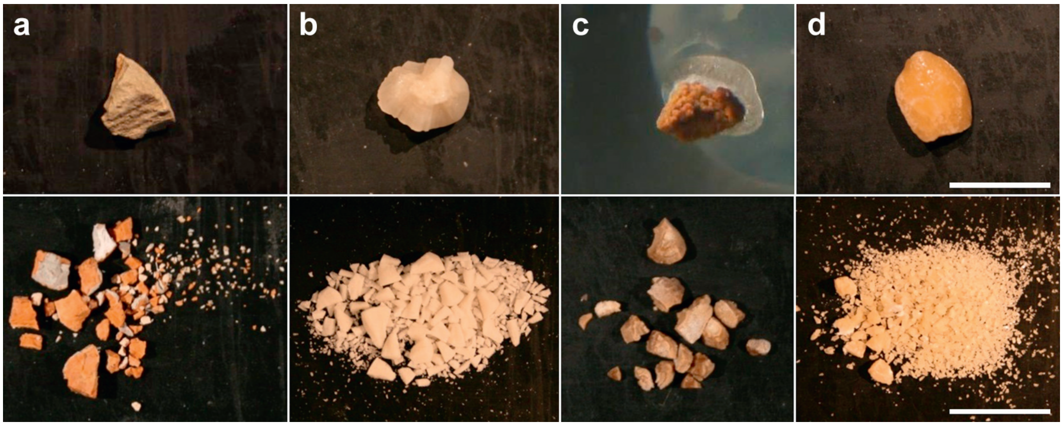

Figure 4. Uric acid (*a*), struvite (*b*), COM (*c*) and cystine (*d*) stones before 170 kHz burst wave exposure and after treatment. Scale bars indicate 1 cm.

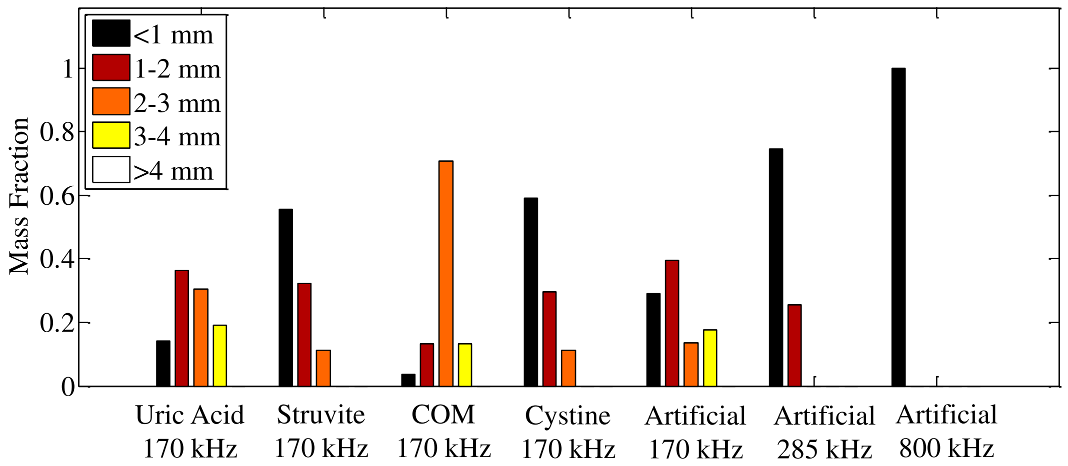

Figure 5. Mean size of post-exposure fragments measured by serial sieving. Natural uric acid, struvite, COM and cystine stones were treated with 170 kHz bursts. Artificial stones were treated with 170, 285 and 800 kHz bursts.

than the stone, causing tension that leads to the growth of fractures and fragmentation.[15,23] 2) Shock induced cavitation at the stone surface can initiate these fractures.[13,16] At the same time proliferation of cavitation clouds caused by delivering shocks at too great a rate tends to decrease their effectiveness[19] and can lead to tissue damage.[24]

In the current study we used bursts that were broadly focused to generate shear. We also sought to avoid cavitation clouds by using relatively low pressure pulses that could be delivered at a fast repetition rate to maximize the energy transferred to the stone. A shocked waveform is not required to produce comminution provided that such bursts produce the necessary tension in the stone to generate and propagate fractures.

Another technique using focused ultrasound was also reported that takes an alternate approach, relying only on acoustic cavitation.[17,18] While the cloud of bubbles likely decreases the propagation of acoustic energy into the stone, cavitation collapses against its surface can reduce it to fine dust through surface erosion without generating the deep fractures that we observed. While to our knowledge this technique has not yet been demonstrated in vivo, it may also represent a noninvasive therapeutic alternative to SWL.

Our results revealed that broadly focused burst waves are capable of fracturing stones of varying compositions, including some considered to be resistant to SWL such as cystine.[25,26] While we did not measure the threshold to fragment natural

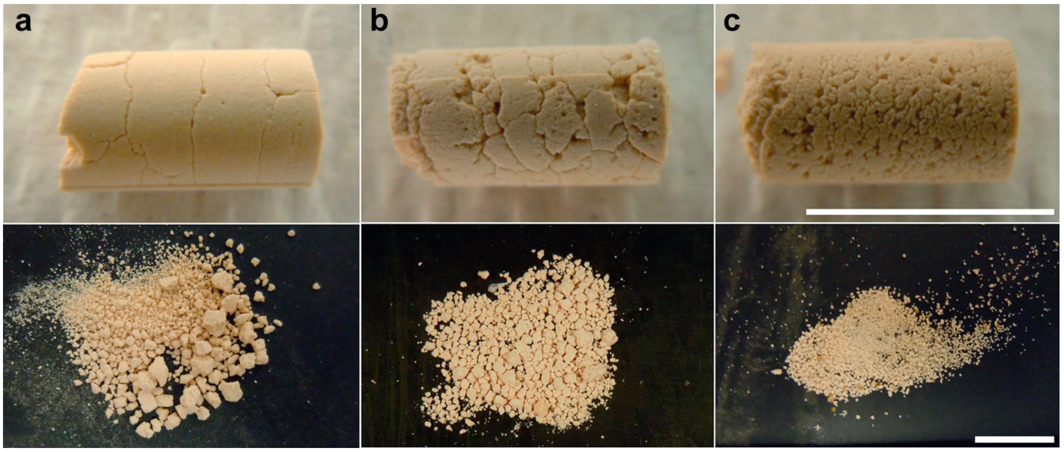

Figure 6. Photographs show fractures and fragments generated from stones treated with 170 (*a*), 285 (*b*) and 800 kHz (*c*) bursts with similar peak pressure amplitude applied. Increased ultrasound frequency resulted in stone surface fractures closer together and decreased fragment size. Bursts were incident from left side of stone in each photograph. Scale bars indicate 1 cm.

calculi, artificial stones could be treated at focal pressures as low as 2.8 MPa. This level is at least an order of magnitude lower than shock amplitudes for SWL in practice (30 to 100 MPa). However, Eisenmenger reported that artificial stones can be fractured by shock amplitudes as low as 11 MPa.[27] Although lower pressure amplitudes were applied in our study, bursts were administered at a much greater rate than a typical SWL pulse repetition rate (200 vs 1 to 2 Hz). The result of this rapid delivery of energy to the stone was particularly evident in stones of softer composition (uric acid and struvite), which underwent fragmentation in only a few seconds in some experiments. COM and cystine stones required longer exposures but all treatments achieved complete comminution of stones into clinically passable fragments of 4 mm or less. In current practice a fairly consistent dose of shock waves (2,000 to 3,000 per session) is applied but these results suggest that different stone types require greatly varying energy to disintegrate. Feedback on treatment progression could be valuable to efficiently achieve a therapeutic end point.

A notable advantage of this type of therapy over SWL may be the ability to control fragment size. This is clinically relevant to produce stone fragments with a high likelihood of spontaneous passage through the urinary tract. Treatment with a 170 kHz transducer produced fragments of similar size for different stone types with a maximum fragment size of approximately 3 mm. Studies in which stones were exposed to 3 frequencies suggest that higher frequencies generate more densely spaced fractures, resulting in smaller fragments. Our preliminary simulations and experiments suggest that bursts between 400 and 500 kHz would generate fragments approximately 1 mm in maximum size, which might be clinically ideal.

While optimizing stone fragmentation may be achievable by such experimentation, it must also be carefully weighed against the effect of the particular burst parameters on the surrounding kidney tissue. SWL causes parenchymal injury to kidney tissue,[24,28] and lesion type and severity can vary for different lithotripters.[29,30] It is possible that mechanical hemorrhagic injury could result from cavitation in BWL when the pressure amplitude or pulse repetition frequency is too high, similar to SWL. Heating due to ultrasound is minimized because of the low frequency and low spatial-peak temporal-average intensity of approximately 15 W/cm^2. Thus, it is not expected that thermal injury such as that due to HIFU thermal therapy would result using the parameters applied in this study. We did not evaluate kidney injury. BWL requires a separate investigation in an in vivo model to accurately assess the acute and long-term effects of the exposures.

In addition to injury evaluation, further tests are needed to assess the characteristics of stone fragmentation under clinically relevant conditions. The in vitro experimental setup that we used provided exposure on fixed stones in a specific orientation. While this allowed us to examine the repeatable characteristics of stone fracture, a free stone would more accurately simulate a physiological situation. Fragments did not remain in the focus for the duration of treatment but rather fell out after separation from the stone. It could be argued that these fragments would be further reduced in size had they remained in or near the focus for the treatment duration. Another limitation of this preliminary study was that several burst parameters were necessarily fixed. Future studies should explore the effects of changing parameters such as burst length, burst repetition rate and amplitude as guided by theoretical and experimental analysis of the physical mechanisms.

CONCLUSIONS

This study demonstrates the feasibility of fragmenting urinary calculi using broadly focused ultrasound bursts. Bursts produced fractures in artificial and human calculi that led to the fragmentation of all stone types. The duration of exposure required to reduce stones to passable fragments varied by stone type. The size of the resultant stone fragments could be controlled by adjusting ultrasound frequency. These characteristics suggest that BWL may represent a potentially viable noninvasive alternative to SWL.

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APPENDIX

Study Experiments

	Experiment Description	Stone Type	Variable	Measurements
1	Determine pressure threshold for stone fracture by bursts	Artificial	Pressure amplitude	Stone fracture (yes/no)
2	Determine effect of stone composition on fragmentation	Artificial + natural	Stone composition	Time to fragment + fragment size distribution
3	Determine effect of ultrasound frequency on fragmentation	Artificial	Ultrasound frequency	Fragment size distribution

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