Published in final edited form as:
IEEE Int Ultrason Symp. 2014 September 3; 2014: 511–514. doi:10.1109/ULTSYM.2014.0126.

Ultrasonic propulsion of kidney stones: preliminary results of human feasibility study

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Abstract

One in 11 Americans has experienced kidney stones, with a 50% average recurrence rate within 5–10 years. Ultrasonic propulsion (UP) offers a potential method to expel small stones or residual fragments before they become a recurrent problem. Reported here are preliminary findings from the first investigational use of UP in humans. The device uses a Verasonics ultrasound engine and Philips HDI C5-2 probe to generate real-time B-mode imaging and targeted "push" pulses on demand. There are three arms of the study: *de novo* stones, post-lithotripsy fragments, and the preoperative setting. A pain questionnaire is completed prior to and following the study. Movement is classified based on extent. Patients are followed for 90 days. Ten subjects have been treated to date: three *de novo*, five post-lithotripsy, and two preoperative. None of the subjects reported pain associated with the treatment or a treatment related adverse event, beyond the normal discomfort of passing a stone. At least one stone was moved in all subjects. Three of five post-lithotripsy subjects passed a single or multiple stones within 1–2 weeks following treatment; one subject passed two (1–2 mm) fragments before leaving clinic. In the pre-operative studies we successfully moved 7 – 8 mm stones. In four subjects, UP revealed multiple stone fragments where the clinical image and initial ultrasound examination indicated a single large stone.

Keywords

kidney stone; clinical trial; ultrasound; ultrasonic propulsion; shock wave lithotripsy

I. Introduction

Current estimates are that 30 million (1 in 11) Americans will experience a kidney stone within their lifetime, and up to 50% of new stone formers will have a recurrence, within as early as 5 years [1,2]. Stone management carries an annual economic burden of $10B [3], and data suggest the incidence of kidney stones will continue to grow with our increasing obesity and diabetes rate, and even climate change [1].

Current minimally invasive treatment options for nephrolithiasis exist and are effective, but commonly leave behind residual stones [4]. These residual stones can grow and lead to symptomatic stone episodes, and up to 20% require further treatment procedures [5]. Lower pole stones are the most problematic with reported clearance rates as low as 35% (average 65%) [6]. In addition, approximately 10% of passable (< 5 mm) stones are treated surgically; these stone are symptomatic and do not pass on their own.

We have proposed using acoustic radiation force to reposition small stones and fragments, particularly lower pole calculi, to facilitate their natural passage. The technology, referred to as ultrasonic propulsion (UP), has been described previously [7–12]. This includes safety and efficacy evaluation in a porcine animal model. This paper reports on the current results from the first in human feasibility testing of UP.

II. Materials and Methods

A. Ultrasound System

The UP system (Fig. 1) is essentially a diagnostic ultrasound platform with a power supply capable of emitting longer, slightly higher amplitude focused pulses for short durations (VDAS, Verasonics Inc., Redmond, WA, USA). The unit has one 12-bit data acquisition board, permitting operation of 128 transmit channels and 64 receive channels simultaneously. The device is programmed and controlled through a host personal computer (HP Z820, Hewlett Packard, Palo Alto, CA, USA) using MATLAB (Mathworks, Waltham, MA, USA). A graphical user interface (GUI) is displayed on a touch screen monitor allowing easy control of the ultrasound system parameters. The ultrasound image is displayed on the same monitor. The system is programmed to work with the ATL HDI C5-2 (Philips Ultrasound, Andover, MA, USA).

B. Diagnostic Imaging Modes

1) B-mode—B-mode is achieved through a compound (flash) imaging sequence consisting of seven plane waves angled evenly from −12° to +12°. The excitation pulse for each wave is a single transmit cycle. The VDAS hardware receives on 64 channels simultaneously, so a synthetic aperture sequence is used to receive on all 128 elements of the probe.

2) Doppler—The Doppler transmit is a plane wave at an angle of 12° from the probe axis. The excitation is a 14 pulse ensemble where each pulse contains three transmit cycles. The received Doppler data is processed with color-flow, power, or custom algorithms designed to enhance the “twinkling artifact” commonly seen when viewing kidney stones with Doppler ultrasound [13–15].

C. Therapy Mode

The custom derived Push sequence was developed and optimized to work with conventional imaging probes and provide enough force to move a stone from the lower pole to the urinary pelvic junction. The burst is constructed from of a series of pulses (Figs. 2). Each pulse consists of 450 μs of on time followed by 165 μs of off time (73% duty cycle). This is repeated 81 times for a total burst duration of 50 ms.

The total length of the Push sequence was established as a balance between utilizing all the energy stored in the power supply capacitor, but of short enough duration to fit between two imaging frames. On-time was fixed at 450 μs due to a hard-wired limit within the VDAS on the maximum number of transmit pulses. The delay of 165 μs was established through optimization of the pulse intensity integral, assuming this correlates with the acoustic force delivered to the stone.

Acoustic power and intensity were calculated based upon a burst average intensity model. Spatial peak pulse average intensity, spatial peak temporal average intensity and thermal index were all below the FDA limits for diagnostic ultrasound devices. The peak rarefactional pressure was approximately 6 MPa, resulting in a mechanical index near 2.2.

D. System Operation

The same probe is used to both image the kidney and stone, and generate the acoustic radiation force to push the stone. A typical treatment involves placing the probe in contact with the patient's skin to image the stone following standard ultrasound imaging procedure. The operator identifies the stone location and then targets the stone with the screen cursor using either a mouse or by touching directly on the screen. A single Push is activated by the push of a mouse button or touch of the screen. The Push sequence is short enough in duration that it occurs between two B-mode imaging frames without affecting frame rate, giving real-time imaging feedback of stone motion. The Push can be applied to any location and any depth within the image, though the effective force varies as a function of target location and the force vector is always in the direction of the ultrasound beam axis. A screen video capture is occurring over the entire treatment and a 10 frame IQ acquisition is occurring with each Push transmit. To prevent overheating of the probe surface, a programmed delay occurs after each Push sequence.

E. Human Feasibility Study

This is a 15 subject human feasibility study approved by the FDA through an investigational device exemption.

1) Study Population—Three populations were incorporated into the study. A) Subjects with *de novo*, i.e. newly formed, stones < 5 mm. This tests our ability to move stones that were potentially attached to the kidney tissue. B) Post lithotripsy patients with stone fragments < 5 mm. This tests our ability to manipulate individual loose stone fragments and clusters of loose debri. C) Subjects with stones > 5 mm and scheduled for lithotripsy. This tests our ability to move large stones. These subjects were treated just prior to their surgery to avoid potential complications.

2) Study Protocol—Subjects are screened with B-mode prior to the UP treatment to ensure the stone is identifiable, at an appropriate angle for pushing, and no other unforseen complications exist. The subject is asked to fill out a pain questionairre before and after the therapy treatment. A maximum of 40 Push attempts are administered at 50 V_p or 90 V_p (maximum) electrical drive voltage. Subjects are asked after each of the first three Pushes if they experienced any sensations. Subjects are contacted once a week for three weeks following treatment for the occurrence of any adverse events and stone passage. Subjects receive a follow-up imaging examination 4–6 weeks after treatment and a final check of their medical charts is made 90 days after treatment for any treatment related events beyond the first three weeks.

III. Results

To date 15 subjects have been consented and ten subjects have undergone the UP study. Results are summarized in Table 1.

A. Efficacy

Efficacy is measured by stone movement. This was graded as 1–no movement, 2–shift in position < 3 mm or rollback into the same position or 3–displacement to a new location. A detailed breakdown for each subject is provided in Table 2. At least one stone was moved in all subjects. The greatest number and extent of movement was from the post-lithotripsy group. An example is shown in Fig. 1, where a stone fragment was moved along the lower pole infundibulum (a) and out of the calyx (b).

Three of the five subjects in the post lithotripsy group passed a stone within 1–2 weeks following treatment. One subject passed 2 fragments before leaving clinic (Fig. 2a) and 14 additional granule size fragments within 1–2 days following clinic (Fig. 2b). A second subject passed over 10 granular fragments within few days following treatment and the third subject passed at least one, 1–2 mm fragment within 1–2 weeks following treatment. None of these subjects had passed a stone within two weeks prior to the treatment. A fourth post lithotripsy subject experienced discomfort commonly associated with passing a stone over the first few days post treatment, but did not observe a stone being passed.

We had moderate success moving *de novo* stones and stones > 5 mm. For the *de novo* subjects, there was no means to identify if the stones were attached. The physician did report that there was one strongly attached stone in the preoperative case, believed to be the one stone we could not move. In four subjects, Pushing revealed a distribution of stone fragments where the clinical image and initial ultrasound examination indicated a single large stone (Fig. 2). This has potential diagnostic implications for stone management.

B. Safety

None of the subjects reported pain associated with the treatment, just a mild warming of the transducer at the peak output power. There have been no unanticipated adverse effects and no device related adverse events.

IV. Conclusion

This is a preliminary report for the ultrasonic propulsion of kidney stones in humans. This study has demonstrated the ability to manipulate stones transcutaneously with this technology. The therapy treatment for three subjects is potentially clinically significant, as it promoted the passage of multiple stone fragments that may have grown into future symptomatic stone events. A diagnostic benefit was evident for differentiating several passable stones from a single large stone requiring surgery. There have been no reported unanticipated adverse events and no device related adverse events. Modification to the technology may be need for detaching and moving *de novo* stones and for moving large stones.

Acknowledgments

The clinical trial is supported by a grant from the National Space Biomedical Research Institute through NASA NCC 9-58. Research and development were supported by NIH NIDDK grants DK43881 & DK092197.

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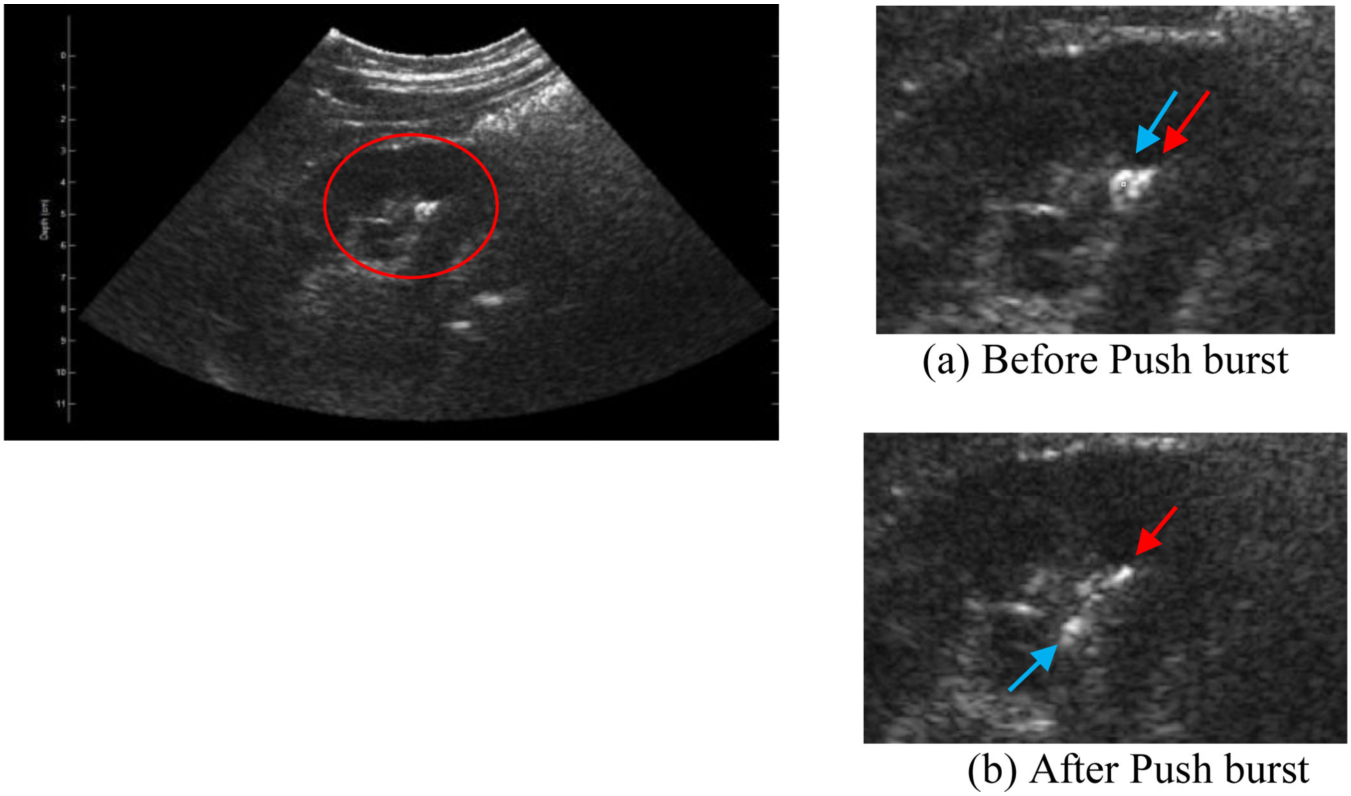

Figure 1.

Ultrasound image of a kidney and two stones, approximately 2–3 mm, in the lower pole (left panel). The two panels on the right show the position of two stones before the application of a Push (a), and immediately following the Push (b). One stone (red arrow) is moved up the infundibulum.

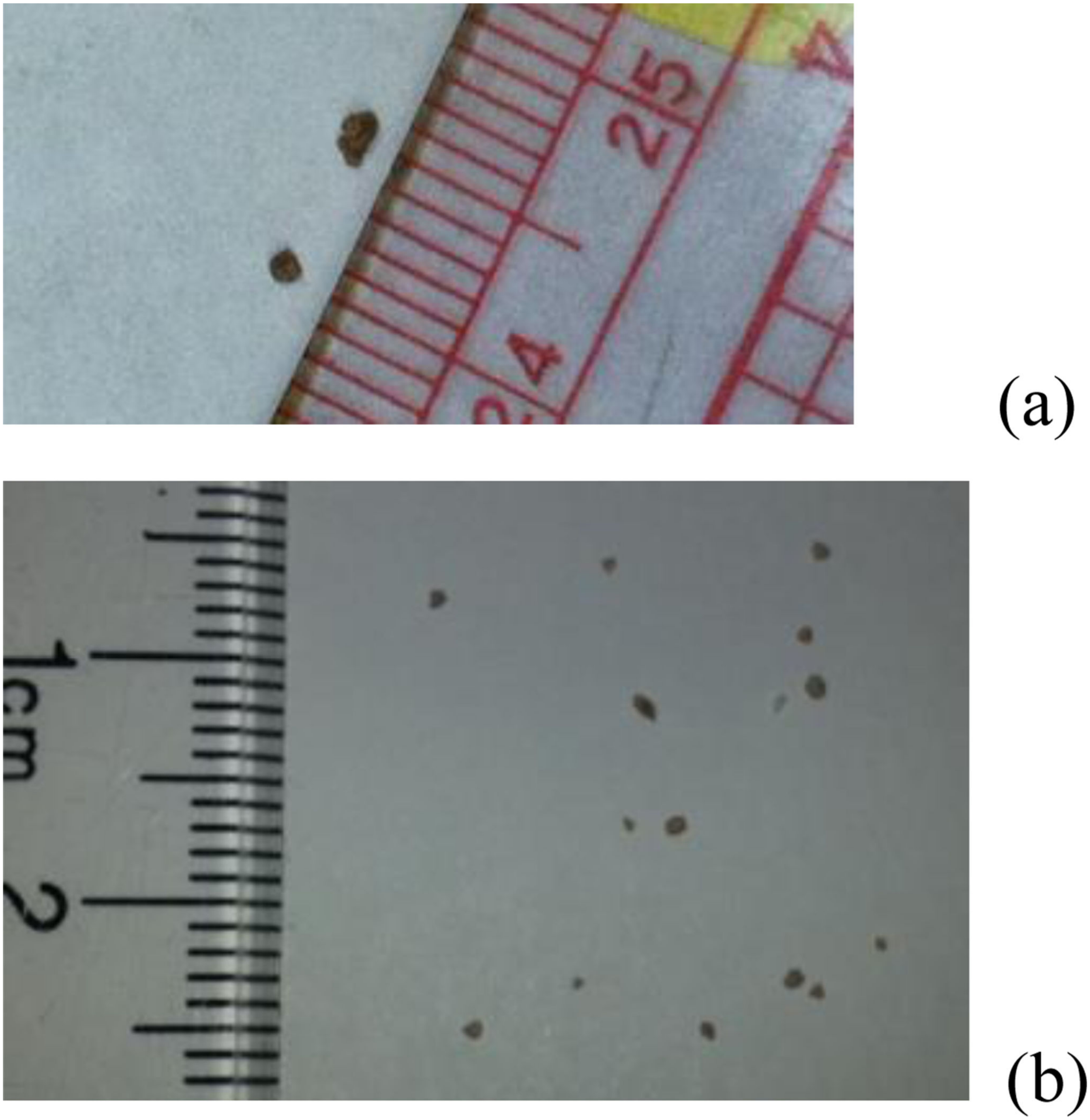

Figure 2.
(a) Two stone fragments passed by a post lithotripsy subject in clinic after the UP treatment. (b) 14 fragments passed by a post lithotripsy subject within 1–2 days following UP treatment.

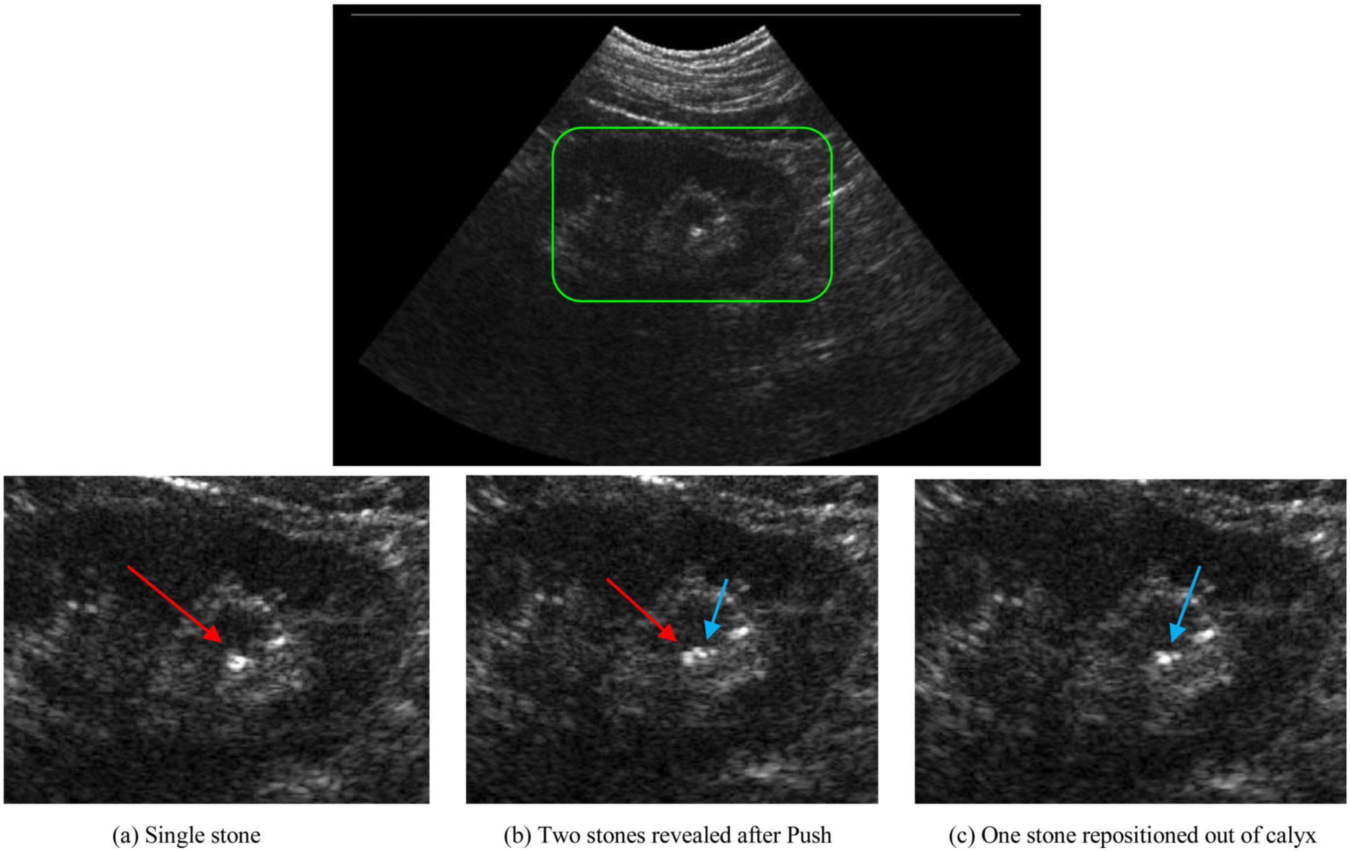

Figure 3.

Ultrasound image of a kidney and stone (Top). The three panels highlight the section surrounding the stone (green box). A single stone observed on ultrasound (a) is seen to be multiple stones after delivery of a Push pulse (b). The stone on the left was then pushed out of the calyx on subsequent pulses (c).

TABLE I

Preliminary Summary Results for Ultrasonic Propulsion of Kidney Stones

Population Group	Total # Stones	# Stones Moved		Stones Passed
		Grade 2	Grade 3	
De novo	10	5	1	0
Post lithotripsy*	14	12	10	3 (1–2 mm) 20 (< 1 mm)
Pre-operative	3	2	1	N/A

*Difficult to establish the total number of fragments pushed as they often occurred in clumps of granules.

TABLE II

Detailed Preliminary Results for Ultrasonic Propulsion of Kidney Stones

Arm	Subject	Number of stones	Stone size (mm)	Motion Grading			Total Push Bursts	Passed Stones
				1	***2***	***3***		
De- Novo Stones	1	3	2 – 3	20	5	0	25	N
	2	5	2 – 3	16	17	4	37	N
	4	2	2 – 3	20	1	0	21	N
	13	1	3 – 4	1	1	0	2	N
*Post-Lithotripsy**	6	Multiple	< 2	9	23	5	36	• 2 fragments (1–2 mm) before leaving clinic • > 14 granules (1 mm)
	7	5	< 2	16	23	1	40	• > 10 granules (1 mm)
	8	Cluster	< 2	22	12	5	39	• 1 fragment (1–2 mm)
	9	Cluster	2 – 5	14	6	19	39	N
	13	1	3 – 4	15	21	2	38	N
Pre-operative	12	2	7	20	7	0	27	N/A
	15	1	8 – 9	11	6	0	17	N/A

*Difficult to establish the total number of fragments pushed as they often occurred in clumps of granules.