Renal Stone Management Technology Development and Clinical Validation Study

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Disclosure

I have equity in and consult for SonoMotion, Inc. which has licensed this technology from the University of Washington for commercialization.

Motivation

Test new ultrasound technology to mitigate

Risk of Renal Stones

using the Emergency Department as a space analog.

- Can operators locate the stones?
- Does the ultrasound therapy help?
- Can subjects tolerate the ultrasound therapy?
- What are the additional risks?

Risk of Renal Stones

Risk = Likelihood x Consequence (4 being the highest)

Risk Ratings and Dispositions per Design Reference Mission (DRM) Category

DRM Categories	Mission Duration	Operations		Long-Term Health	
		LxC	Risk Disposition *	LxC	Risk Disposition *
Low Earth Orbit	6 months	2x3	Accepted	3x3	Accepted
	1 year	2x3	Accepted	3x3	Accepted
Deep Space Sortie	1 month	2x3	Accepted	3x3	Accepted
Lunar Visit/ Habitation	1 year	2x3	Accepted	3x3	Accepted
Deep Space Journey/Habitation	1 year	2x4	Requires Mitigation	3x4	Requires Mitigation
Planetary	3 years	2x4	Requires Mitigation	3x4	Requires Mitigation

HRP Roadmap
https://humanresearchroadmap.nasa.gov/Risks/risk.aspx?i=81

Risk of Renal Stone

⊟ **Risk Statement**

Given changes in urinary biochemistry during space flight, there is a possibility that symptomatic renal stones may form, resulting in urinary calculi or urolithiasis, renal colic (pain), nausea, vomiting, hematuria, infection, hydronephrosis.

⊟ **Context**

Kidney stone formation and passage has the potential to greatly impact mission success and crewmember health for long duration missions. Alterations in hydration state (relative dehydration) and bone metabolism (increased calcium excretion) during space travel may increase the risk of kidney stone formation and it is unclear which mitigation strategy would be the most effective in the context of mission operations.

⊟ **Mitigation Strategy**

Historical spaceflight data have revealed both in-flight and post-flight instances of renal stones. While none have led to loss of crew life, there have been in flight medical conditions leading to either evacuation or early termination of mission. Renal stone formation in microgravity has been well studied and modeled. Recent results from simulations starting with the chemistry of renal stone formation and ending with associated risk have provided validated models quantifying the risk of clinically significant renal stones during exploration as a function of hydration, nutritional countermeasures, and gravitational environment. Current research efforts are aimed at 1) integrating in-flight strategies to reduce stone formation into exploration medical system designs, 2) progressively autonomous ultrasound monitoring and biochemical diagnostics for early detection of stones, and 3) treatment interventions, such as moving renal stones through the application of ultrasound waves.

⊟ **Gaps (9)**

⊞ Renal-101: We do not have the capability to mitigate renal stones in spaceflight.

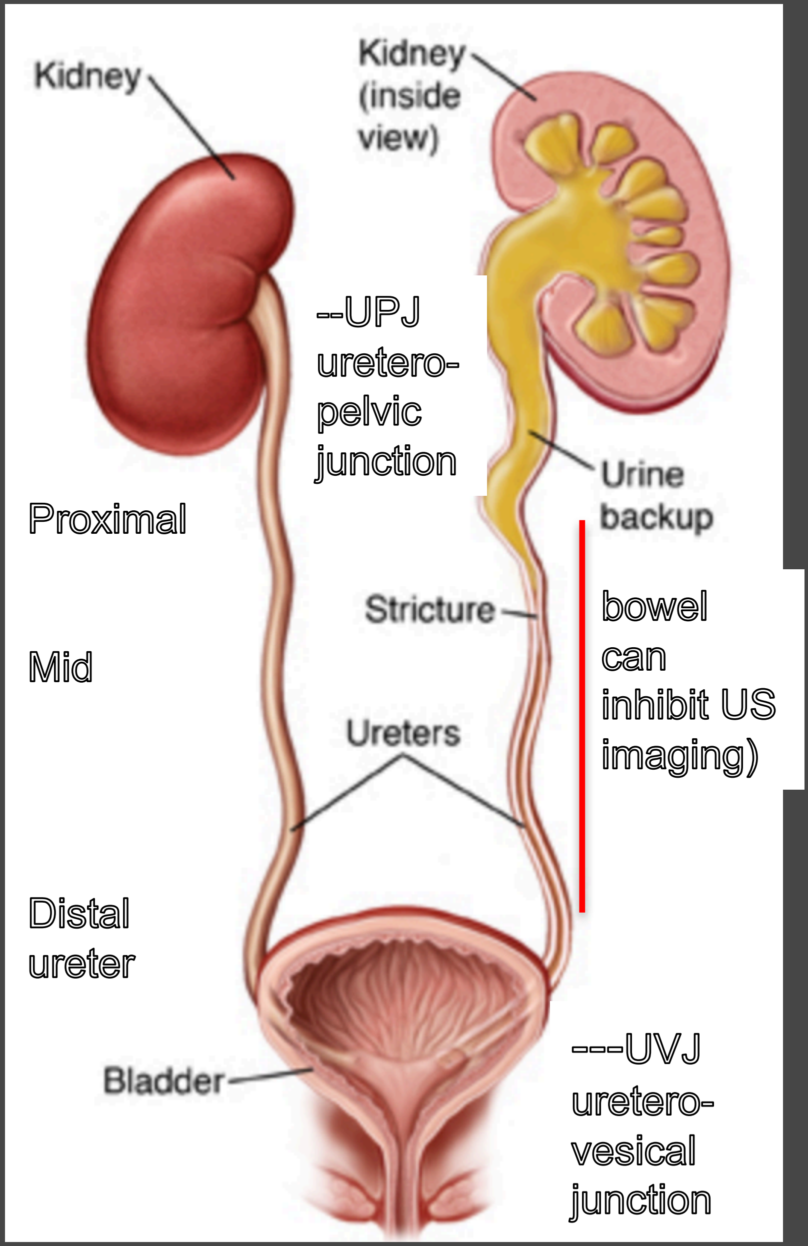
Risk of Renal Stones

One in 11 Americans will have stones[1]

Risk is obstruction by a stone
in the ureter (cramping, backpressure).

Mid ureter 1% and UVJ 61%
of Emergency Dept (ED) presentations[2]

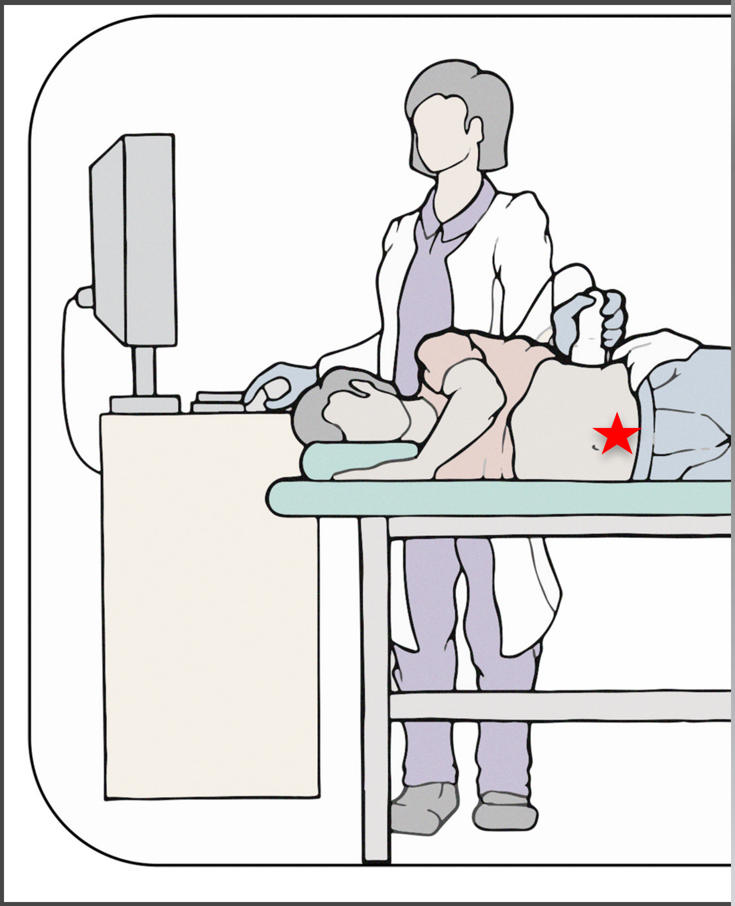
Generally OK once in bladder.

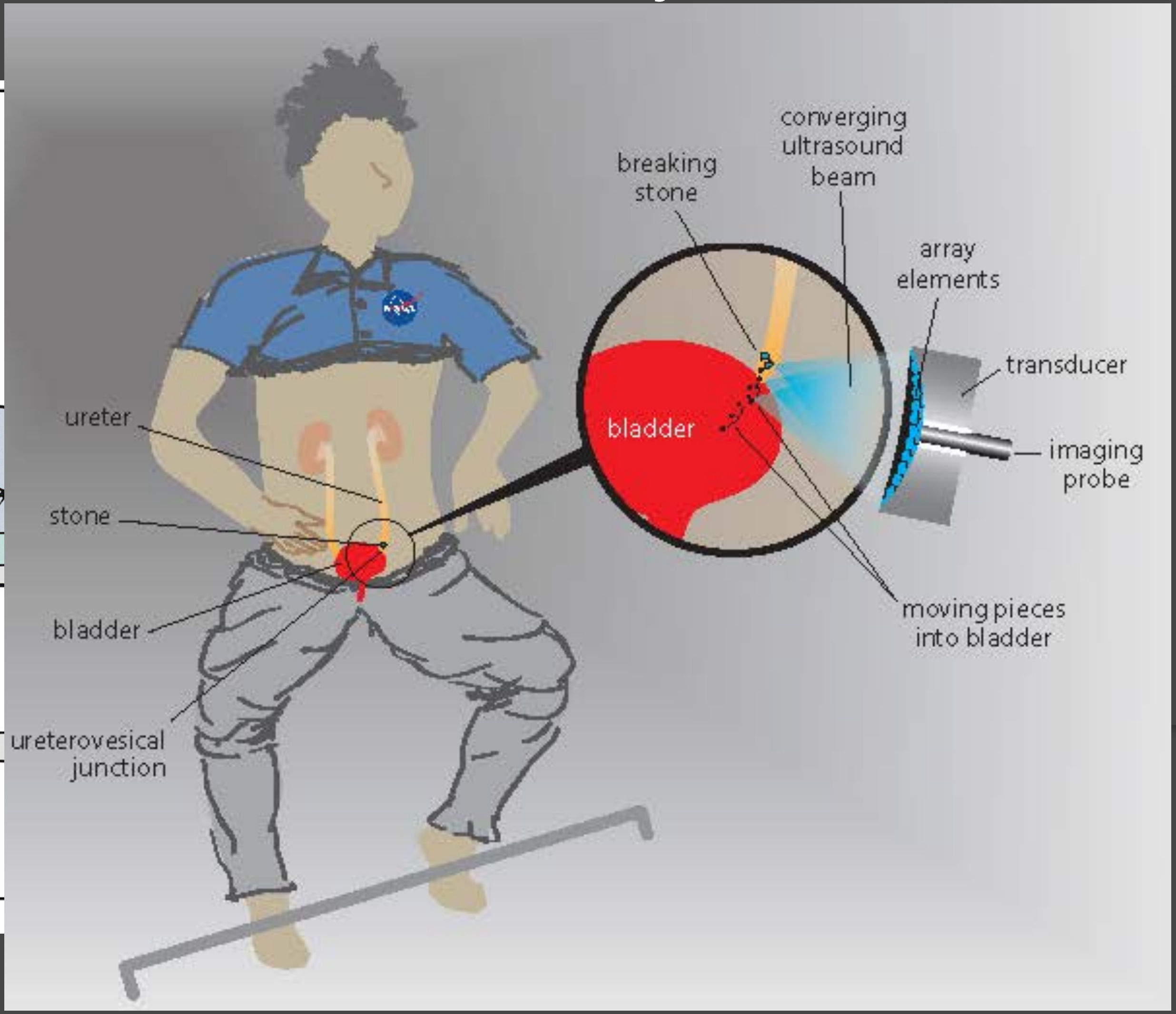


1. Scales, Jr. CD, Eur. Urol., 2012, 62:160-165.
2. Eisner BH, J Urol. 2009 Jul;182(1):165-8

Technology

Handheld ultrasound to target, detach, break, and expel stones and stone fragments from the urinary space to facilitate natural clearance in awake subjects.

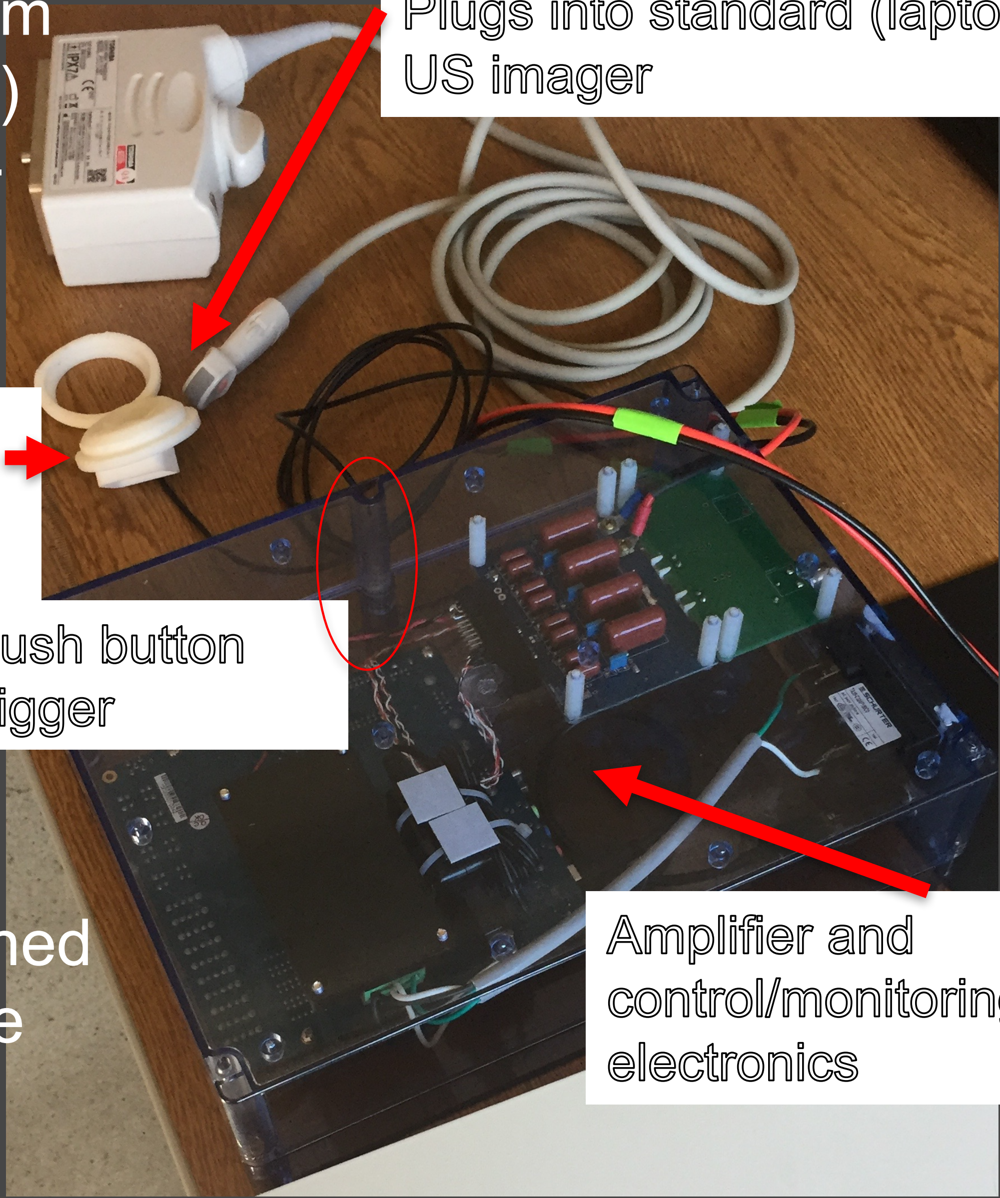




Technology- Hardware

Implemented on

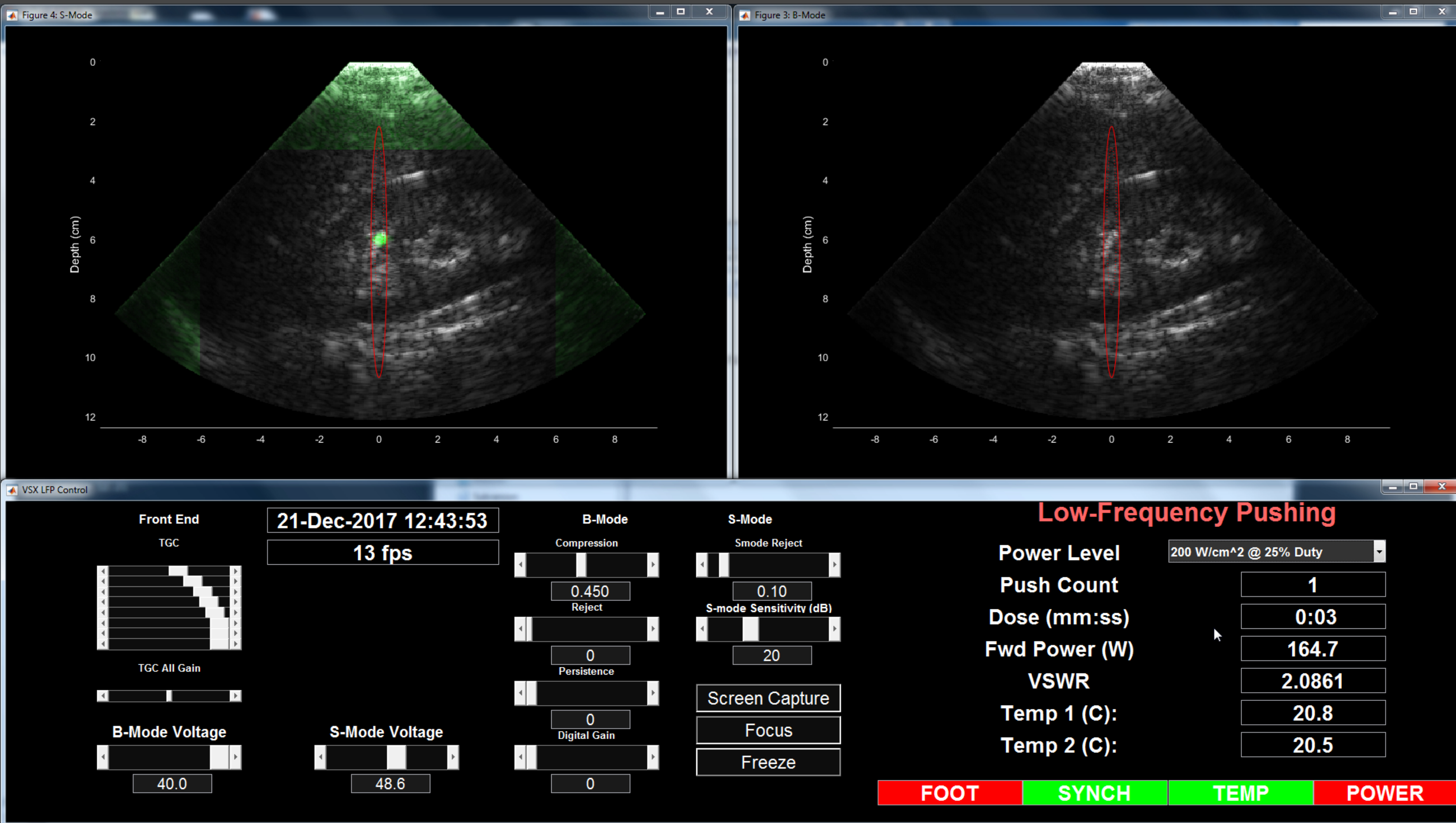
- Univ. of Washington (UW) system
- NASA Flexible Ultrasound (FUS)
- SonoMotion commercial-off-the-Shelf (COTS) product



Repositioning has been accomplished using the imaging probe without the therapy probe.

Harper, J Urol, 2016 195:4;956–64

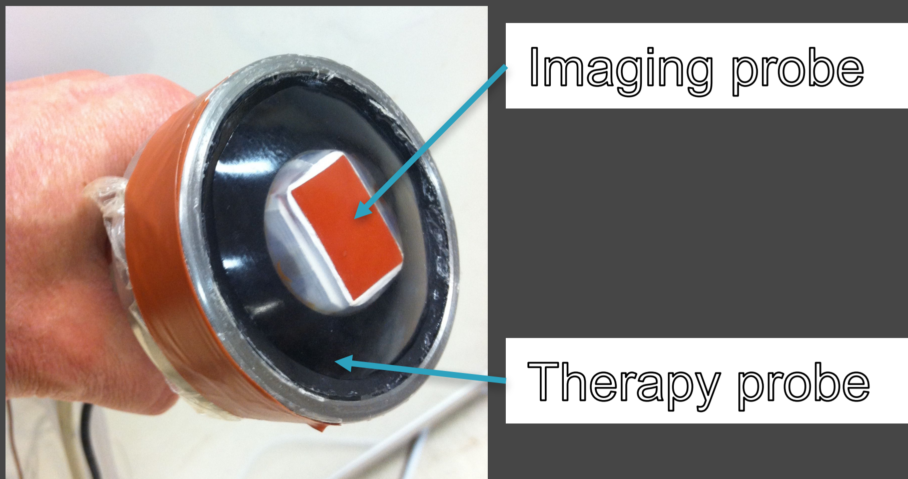
Technology-Software



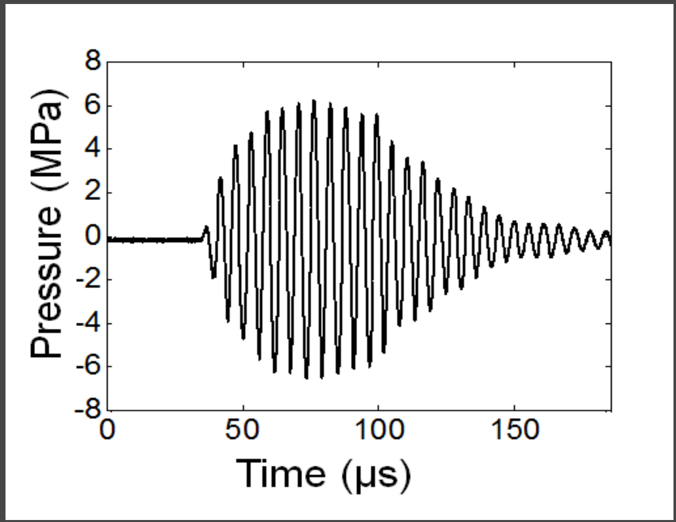
Software-based, on-screen control with real-time imaging.
Doppler twinkling artifact highlights the the stone in green on the left screen.

Technology – Therapy Dose

UW Transducer Embodiment



Example Dislodging Burst (Propulsion bursts are lower amplitude and longer duration.)



Subjects treated with bursts of ultrasonic propulsion alone, or a combination of propulsion and dislodging bursts

Ultrasound Therapy	Peak Negative Pressure	Pulse Duration	Pulse Repetition Rate	Burst Duration	Total Exposure
Propulsion	2.4 MPa	25 ms	20 Hz	≤ 3 s	10 min
Dislodging	6 MPa	0.1 ms	17 Hz	≤ 30 s	

Methods – Approvals

Study approved by the UW IRB.

Clinicaltrials.gov number: NCT02028559

FDA Investigational Device Exemption: G130085

Methods - Procedures

1. Protocol to identify potential subjects in the ED or clinic.
   - All received a clinical CT before research
   - All had a urinalysis and if appropriate a pregnancy test.
2. Consent based on Inclusion/Exclusion summarized as
   - Subjects with a proximal or distal ureter stone
   - Subjects able to consent & without co-morbidities/conditions of greater risk.
3. Pain assessment (0-10)
4. Image with research device to see if stone is targetable.
5. Image for hydronephrosis. Pain assessment (0-10)
6. Attempt to move UPJ stone to the kidney and distal ureter stones retrograde or into the bladder.
7. Image for hydronephrosis. Pain assessment (0-10)
8. Follow phone calls 1 once per week for 3 weeks to assess stone passage and time, and occurrence of any Adverse Events (AEs). (Several subjects texted when the stone passed.)
9. Follow up ultrasound within 120 days for safety regarding stone status

Methods – Study Endpoints

Primary Effectiveness Endpoint

- Stone Motion

Secondary Effectiveness Endpoints

- Stone passage
- Reduction in pain level
- Reduction in hydronephrosis

Primary Safety Endpoint

- Occurrence of Adverse Events

Secondary Safety Endpoint

- Pain/discomfort associated with the procedure
- Occurrence of further intervention

Results - Enrollment

# Subjects Enrolled	# Subjects undergoing Investigational Procedure	# Subjects lost to Follow-up
42	23	1

Reason for Screen Exclusions

Stone Location	Stone not visible on US	Stone Moved (to)	Stone too deep for available probe	Instrument Unavailable
distal ureter	4	2 (bladder)	6	1
Proximal ureter	1	4 (mid ureter) 1 (lower pole)	0	0

88% (36 of 41) of stones seen with the investigational device

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Success! MK Hall. JACEP Open 2020;1:252–256.

Results - Demographics

Patient Demographics

Mean Age ± SD (years)	Mean BMI ± SD (kg/m^2)	Sex		Ethnicity		First Time Stone Former	Race			
		Male	Female	Hispanic	Non-Hispanic		White	African American	Asian	American Indian / Native Alaskan
46 ± 17	25.4 ± 4.5	16	7	4	19	16	19	1	2	1

BMI = body mass index; SD = standard deviation

Stone Demographics

Stone Size (mm)	Time since Onset		Side		Location		
	Acute ≤10 days	Chronic > 10 days	Left	Right	UPJ	UVJ	Distal Ureter
3 - 18	18	5	12	11	3	15	5

UPJ = ureteropelvic junction; UVJ = ureterovesical junction; distal ureter = > 1 cm proximal to UVJ

Broad demographics that encompass those expected for astronauts.

Results – Effectiveness: Stone Passage

Treatment Group	Time since Onset	# of Subjects	Mean Stone Size ± SD (mm)	Percent Passage	Time to Passage
Data for untreated ureter stones from published meta-analyses of 27* and 16 studies.**					
AUA guidelines[1] & Cui et al.[2]	mixed	1205*	<10	**54.4%**	**N/A**
Singh et al.[3]	acute	292*	5.6	**54%**	**7.4 days**
Results of ultrasound treatment in the current study					
All results	acute	15†	4.4 ± 1.3	**93%**	**3.6 days**
Propulsion alone	acute	9	4.0 ± 1.1	**89%**	**1.5 days**
Propulsion + Dislodging	chronic	3	5.0 ± 1.4	67%¥	<1 day, <11 days

† One subject lost to follow-up.

¥ Subjects passed fragments but continued to previously scheduled surgery after 2 and 14 days.

Improved passage rate and time by ~2-4x compared to literature.

Comparable to rates for medical expulsive therapy (77%), shock wave lithotripsy (74%), and ureteroscopy (94%).[1]

[1]Assimos, J Urol. 2016;196:1161-9. [2]Cui, J Urol 2019 201:950-5. [3]Singh, Ann Emerg Med 2007;50:552-63.

Results – Effectiveness Endpoints

Report of Percent and Number of Subjects

Any Level of Stone Motion	Stone Displaced (> 3 mm)	Resolution of Hydronephrosis	Decrease in Pain Level	Mean Pain Score	
				Before	After
74% (17 of 23)	26% (6 of 23)	0%: (0 of 16)* during procedure 100% (16 of 16) on follow-up imaging	43% (10 of 23)	2 ± 2.4	1.5 ± 1.7

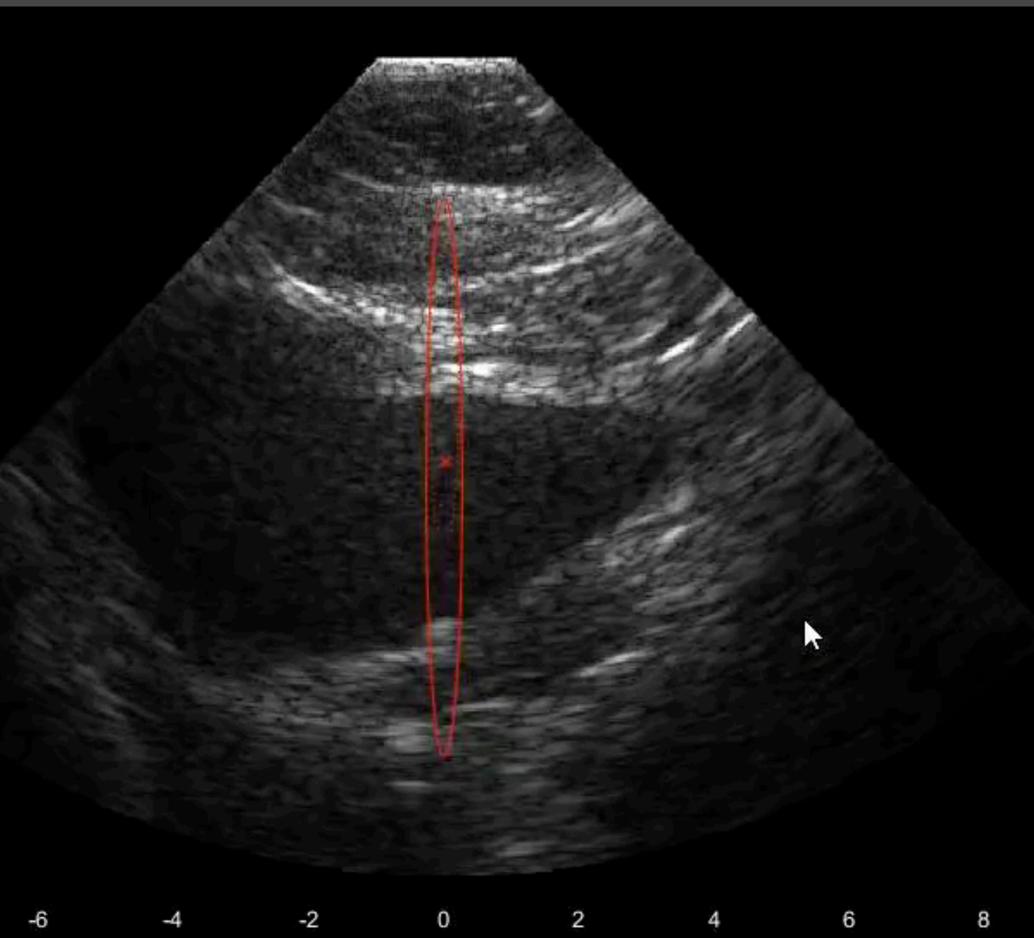
* Hydronephrosis was only reported for 16 of the 23 subjects.

Any level of observed motion appears effective but not required consistent with previous propulsion studies.[1]

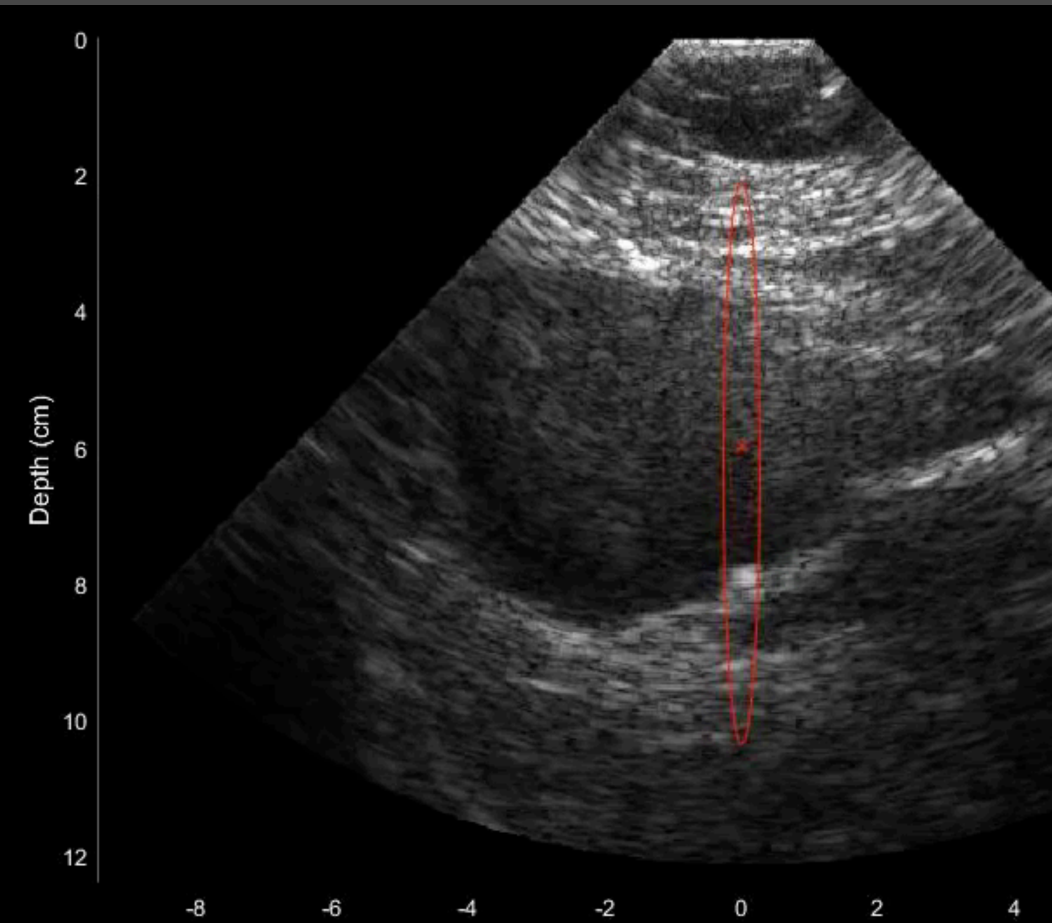
[1]Dai ,J Endourol 2019;33:850-7

Results – Mechanism: Motion

Stone motion retrograde in UVJ



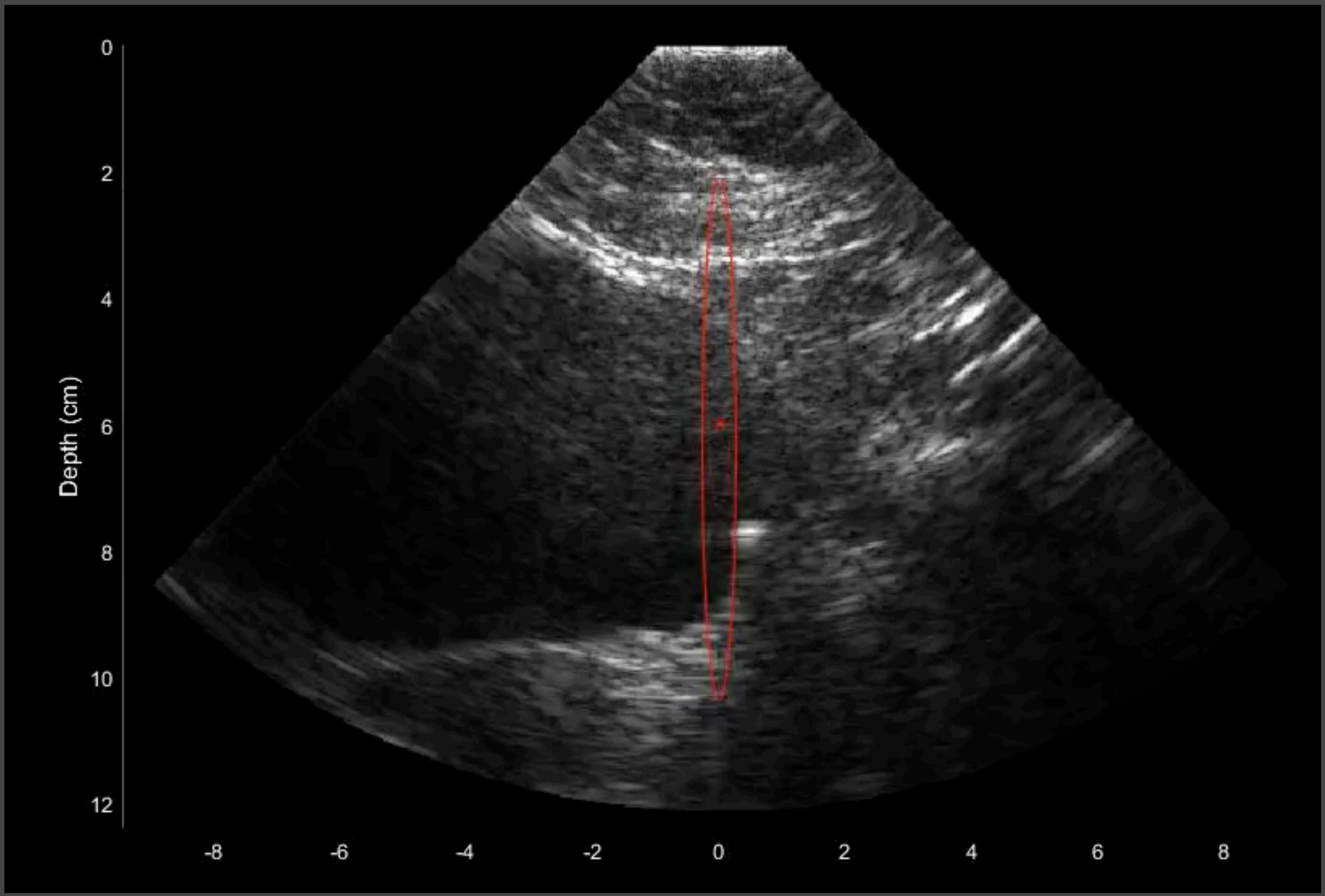
Stone motion forward into bladder



Example of propulsion moving the stone backward in the ureter and then forward into the bladder.
The subject felt immediate relief.

Results – Mechanism: Motion

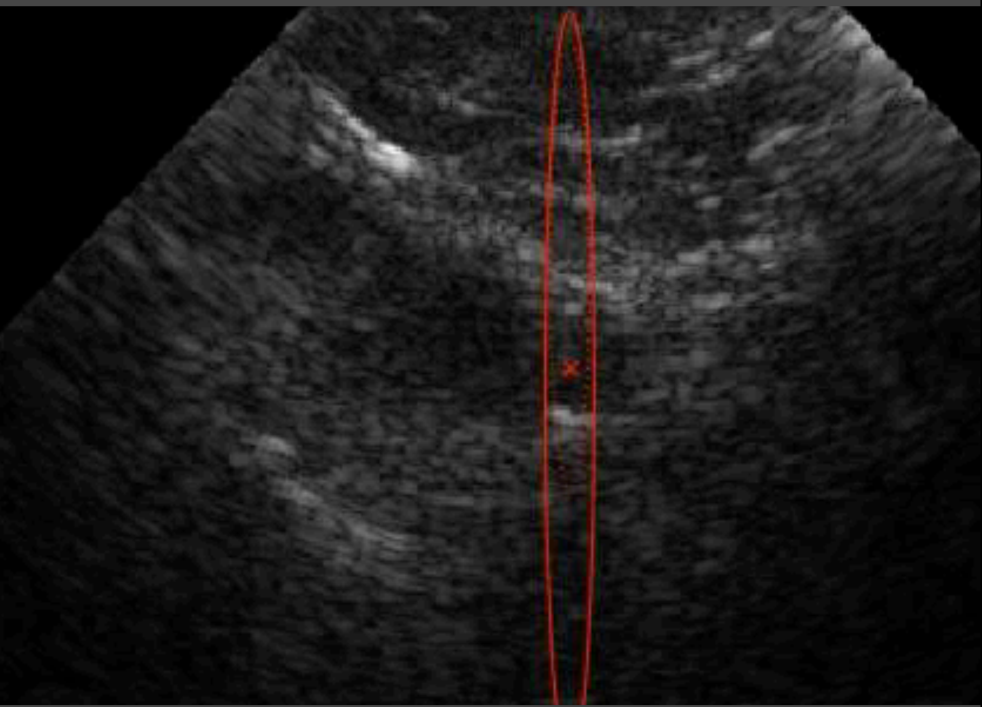
Forward motion and partially gravity-induced roll-back in the bladder



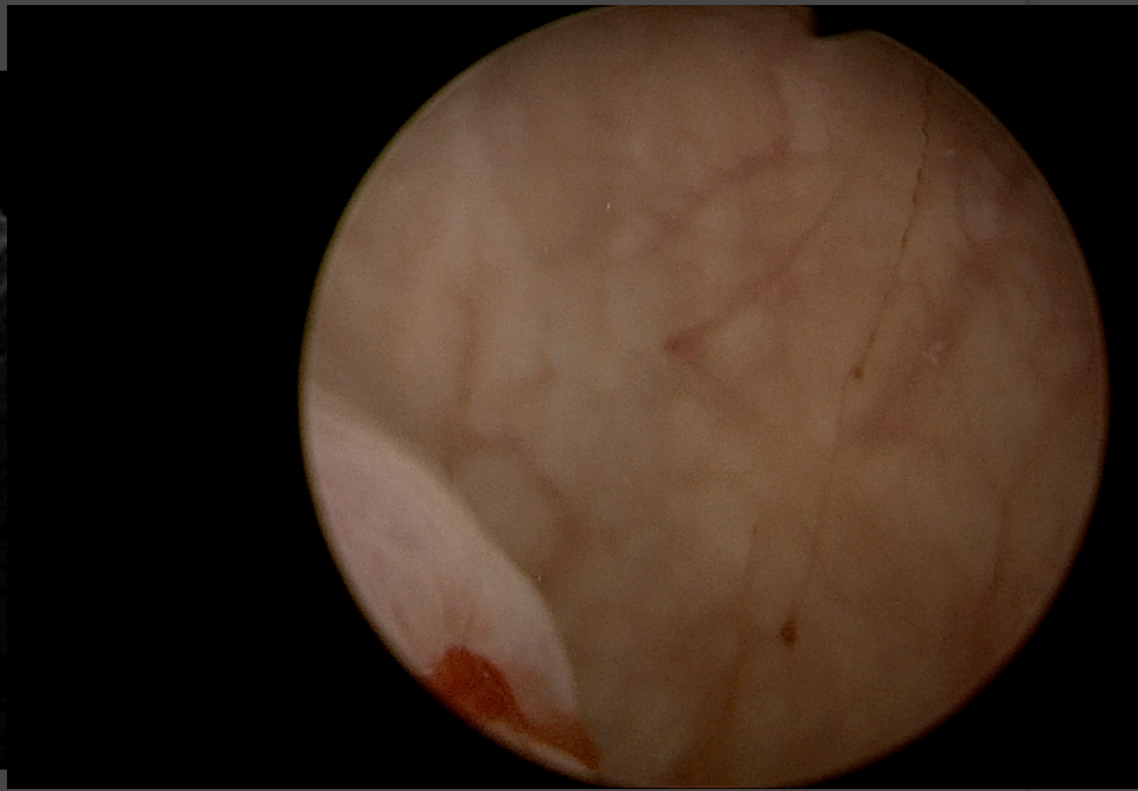
Gravity is a force affecting motion in the current study.

Results – Mechanism: Stimulation

US video: jet correlated with propulsion



Ureteroscope video: ureteral jet

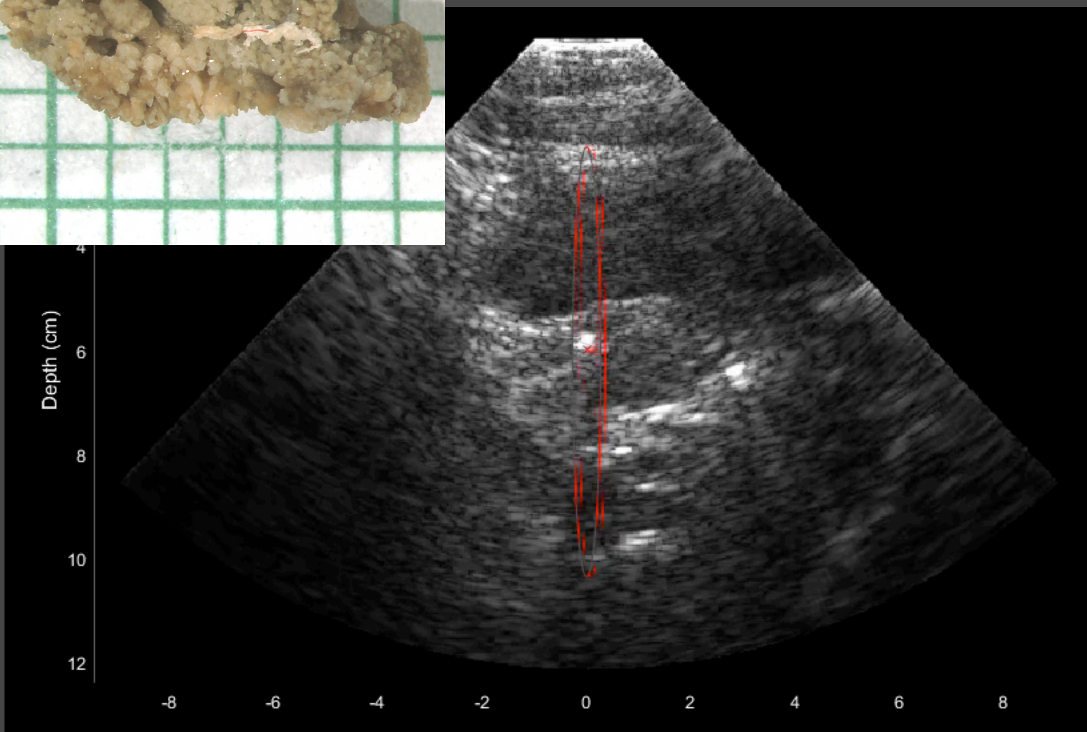


In 9 of 20 subjects with a distal ureter/UVJ stone, urinary jets and ureteral peristalsis were observed and correlated with the ultrasound therapy bursts.

Ultrasonic propulsion appears to stimulate or activate the body's natural mechanism to clear stones.

Results – Mechanism: Fragmentation

Appearance of cracks in stone passed by subject (left). In another case, CT imaging 11 days post procedure showed reduction in stone size (not presented).



Appearance of fragmentation with real-time US imaging

On ureteroscopic inspection 2 days post-procedure stone is fragmented.

Dislodging Bursts fragmented stones

and are now being used in Burst Wave Lithotripsy (BWL).[1]

[1]Metzler, J Endo (epub). http://doi.org/10.1089/end.2020.0725

Results – Safety – Adverse Events

AE* (Total N = 35)	Propulsion Only (n = 12, 1 pending)	Propulsion + Dislodging (n = 7, 3 pending)
During Procedure		
Skin redness at treatment site	1 (8%)	3 (43%)
Skin bruising at treatment site	0 (0%)	0 (0%)
Discomfort/pain with procedure	1 (8%)	3 (43%)
During Follow-up		
Discomfort / Pain during follow-up	0 (0%)	0 (0%)
Gross hematuria	0 (0%)	2 (29%)
Changes in urinary frequency / urgency	0 (0%)	0 (0%)
Diarrhea / constipation	0 (0%)	0 (0%)
Nausea / vomiting	0 (0%)	0 (0%)
UTI	0 (0%)	0 (0%)

Adverse Events (AEs) related to the device / procedure were all mild and self limiting.

Results – Safety – Adverse Events

Example of skin redness at treatment site

Example of gross hematuria (transient) associated with dislodging

Results – Safety – During Procedure

Sensations experienced during the procedure

Warming of the Probe	Focal Sensation (vibration)	Referred Sensation	Discomfort / Pain
13 of 23	3 of 23	13 of 23	4 of 23

- Warming of the probe was associated with propulsion bursts only, primarily at highest setting.
- Some subjects reported feeling a sensation locally (e.g. at the kidney or ureter) with the therapy burst, like a vibration or electrical stimulus. This was not considered painful.
- Some subjects reported a referred sensation (e.g. stimulating the urge to urinate) with the therapy burst; this was not considered painful.
- Discomfort / pain experienced during the procedure included a momentary increase in pain level, which lasted no longer than the 1-3 s burst (n = 3). This was described in two cases like a pin prick (pain level 1) and was reported in only 3 of 619 bursts. One initially asymptomatic subject reported discomfort from the pressure of the probe immediately after treatment (pain level 2, n = 1).

Results – Total Dose

Ultrasound Therapy	Average Dose Exposure
Propulsion Only	29 bursts (each burst 1-3 s long)
Propulsion + Dislodging	9.3 minutes

The maximum outputs were not always used or needed.
The most effective settings are still to be determined.
Not a time consuming addition to US imaging for stone diagnosis.

Study Limitations

- Our study contained no control group but there is extensive literature on the passage of distal ureter stones.
- Consistent with the literature, our study included a broad range of stone sizes, depths, and locations. This showed the therapy is robust, but future grouping by more narrowly defined medical conditions may be needed to optimize the therapy settings and protocols (i.e., large stone may benefit from breaking while small stones might not; and we have no idea of the pulses that best stimulate ureter peristalsis).
- Our study design did not include daily or even hourly follow up on stone passage which would measured stone passage within an even shorter time resolution.
- It is possible to perform repeated treatments, this was generally not needed but was not investigated.
- We did not withhold standard of care. These subjects had just been in the greatest pain of their lives. Pain scores around imaging act as a control for pain scores around therapy.

Conclusions

In this study we tested new ultrasound technologies to mitigate Risk of Renal Stones using the Emergency Department as a space analog.

Our Results Showed:

- A broad range of operators successfully performed the therapy, including: EM physicians, urologists, urology fellows, and sonographers
- Benefits were measured and all study outcomes and more were met, including: stone movement, stone passage, stone fragmentation, a reduction in subject pain, and resolution of hydronephrosis.
- The procedure was well tolerated and showed minimal risk to the subjects.
- There is a minimal time commitment to moving stones.

Our results establish an effect size for future trials.
NASA has used the results to request to downgrade the risk from ”requires mitigation” to “accepted risk disposition.”

Study supported by NASA HRP ExMC MTL ID 1265
and system development by NIH NIDDK P01 DK043881 and NSBRI.

More information available at: apl.uw.edu/pushingstones

Future Work

- Longitudinal monitoring and countermeasures for Sarcopenia.
- Automatic continuous monitoring of pneumonia.
- Continued kidney stone related basic science, clinical trials, and device development, including Acoustic Forceps (below).

Model stone lifted and moved in a circle by transcutaneous ultrasound in the bladder of a living animal model.

Ghanem PNAS 2020 117:16848–55