Fiscal Year:	FY 2015	**Task Last Updated:**	FY 07/07/2015
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Project Title:	Prevention of Renal Stone Complications in Space Exploration		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Smart Medical Systems and Technology Team		
Joint Agency Name:		**TechPort:**	Yes
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Human Research Program Risks:	(1) **Medical**:Risk of Adverse Health Outcomes & Decrements in Performance due to Inflight Medical Conditions (IRP Rev I) (2) **Renal**:Risk of Renal Stone Formation		
Space Biology Element:	None		
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Space Biology Special Category:	None		
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Zip Code:	98105-6698	**Congressional District:**	7
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No. of Bachelor's Candidates:	5	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
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Flight Program:			
Flight Assignment:	NOTE: Extended to 12/31/2016 per NSBRI (Ed., 3/11/16)		
Key Personnel Changes/Previous PI:			
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Task Description:

1. Specific aims
We will refine and validate probes to integrate with the NASA Flexible Ultrasound System to address Exploration Medical Capability (ExMC) Gap 4.02 Nephrolithiasis. [Ed. note 9/22/2016: This Gap was merged into the following Gap: Med13: We do not have the capability to implement medical resources that enhance operational innovation for medical needs]

AIM 1. Refine ultrasound probes to detect, reposition, and fragment kidney stones. AIM 2. Validate probes to visualize, reposition, and fragment stones. AIM 3. Refine and validate imaging to guide therapy.

2. Key Findings

Technology developed in this research has been licensed to a spin-off company SonoMotion Inc. Three articles are cited that independently review our technology. The first human trial of repositioning kidney stones was completed. A report was presented to National Space Biomedical Institute (NSBRI), FDA (Food and Drug Administration), NASA, and OMB (Office of Management and Budget). A manuscript has been submitted to the Journal of Clinical Investigation. The trial was successful. Two patients reported skin discomfort and sensation at depth with a few pushes. Otherwise, there was no pain or adverse effects associated with the treatment. Stones were localized with the system and repositioned in 14 of 15 subjects. In total, the system targeted and repositioned stones from all parts of the kidney and ureteropelvic juncture (UPJ, kidney outflow tract) including the lower pole (20 targets), midpole (10 targets), upper pole (6 targets), and renal pelvis/UPJ (7 targets). Stones were imaged and repositioned at depths as great as 11 cm. Stones were repositioned to a new location in all 6 post-lithotripsy patients, while 4 of the 6 passed over 30 stone fragments within a few days of treatment. One passed two 2 mm fragments immediately after the completion of treatment. De novo stones and stones as large as 8 mm were repositioned in awake patients and during URS, although movement was not as great as seen with residual fragments. In four of the 15 subjects, what was noted in clinical imaging as a single, potentially unpassable stone was shown to be several passable stones upon repositioning with ultrasound. One subject with a potentially obstructing UPJ stone felt relief. FDA has granted 15 more subjects for the next clinical trial. We have developed and tested new probes and systems to continue to improve and validate performance of ultrasonic propulsion. We have participated in several meetings with GE (General Electric) and ExMC about NASA's flexible ultrasound system (FUS), and have recently received the GE probe used on the FUS. We have started integrating our ultrasonic propulsion onto the GE probe. A new stone specific imaging mode was developed and reported, and a patent application was submitted. In the first step the system automatically identifies the location of stones in the image and highlights them with color during real-time scanning. In the second step, the system automatically determines the size of the kidney stone. In a series of publications, we showed that stone size could be determined more accurately by measuring the shadow width not directly the stone width in the ultrasound image. The first paper on Burst Wave Lithotripsy (BWL) was published in the Journal of Urology and reviewed in Nature Reviews Urology. Progress has been made in measuring effectiveness and safety and on image guidance. We have used preclinical data generated with NSBRI funds to obtain funding from NIH (National Institute of Health) to pursue additional clinical trials to investigate the benefit of expelling small asymptomatic kidney stones, stone clearance with repositioning, obstructing stone displacement, and stone detachment. We continue to present demonstrations of ultrasonic propulsion and BWL. We presented at the American Urological Association in 2012, 2013, 2014, and 2015 and at NSBRI's Congressional demonstration in 2014.

3. Impact

We have invented a technology to reposition kidney stones and demonstrated it works in people. In four of the cases, what appeared as one large stone on x-ray was two or three small passable stones. This had direct diagnostic benefit to these subjects and changed their course of treatment. In four other subjects, we moved stones out of the kidney, which they passed. This result was a direct therapeutic benefit to these subjects. One subject felt relief from a painful obstructing stone. We have shown we can produce a working prototype, develop sufficiently high-quality imaging to guide treatment, train new users, and conduct a successful clinical trial. This opens the path to refine the system and repeat, to commercialize the system, to add refined imaging as a software upgrade, and to repeat the process with BWL to demonstrate an improved way to comminute stones in humans. Specifically, we have now implemented our technologies with different probes making it efficient to add the probes NASA selects or to continue to refine the probes we could provide. Our software continues to be refined and validated. The preclinical work funded by NSBRI enables us to pursue demonstration in humans to assess where best this technology fits into care in the clinic and in space exploration. Our new stone sizing technique can be used on any imager by any user to improve the accuracy of stone size determination with ultrasound. Overestimated stone size leads to unnecessary surgeries, and underestimated stone size leads to obstructions and Emergency Room visits. Stone size similarly determines risk and course of action in space.

4. Proposed Research

We have undertaken a prospective study to see how commonly the shadow is seen and to compare accuracy of stone size from the stone or the shadow. We are beginning a clinical trial of S-mode for automatic stone detection and stone sizing. We have built a new ultrasound propulsion probe and optimized outputs with the old probe. We are now completing preclinical testing and an FDA modification for human testing. We continue to refine the BWL probe and now have built a BWL probe for transcutaneous testing. We are testing safety and effectiveness in clinical simulation in animal studies. We are testing new image guidance technologies.

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:

Kidney stones have long been near the top of NASA's list of concerns; mitigating Gap 4.02 medical condition Nephrolithiasis is a shall for all missions beyond the International Space Station (ISS). Likewise, stones have plagued humans since ancient Egypt. Currently, one in eleven Americans has suffered from stones -- more than have diabetes or cardiovascular disease. Dehydration, stasis, and bone demineralization are strong contributors to kidney stones, and occur in microgravity, increasing the risk of stones in space. Stones are often debilitating, and pilots cannot fly with stones. Stones occurred on a Russian space mission, and the mission was nearly aborted before the stone passed. Over 30 stones have occurred shortly following even short duration space flights. NASA has collected compelling evidence for concern on its website. Additionally, since the website publication, the total number of astronaut stone episodes has more than doubled, and a drug introduced to combat visual impairment/intracranial pressure has exacerbated the risk. Science, experience, and the negative medical consequences support concern for the risk of stones in space. NASA and NSBRI have focused considerable attention on stones and made progress. However, there are many types of stone disease, and it is unlikely that stone disease will ever be completely prevented on Earth or in space. We propose a way to

Research Impact/Earth Benefits:

prevent or minimize the consequences of any stones that form while in space. The treatment for most kidney stones is to encourage natural passage. To quote NASA's expectations in space Based on current Lifetime Surveillance of Astronaut Health (LSAH) data, 80 to 85% of in-flight cases of nephrolithiasis are expected to be best case scenarios (defined as a renal stone that responds to conservative treatment, e.g., analgesics and hydration), and 15 to 20% would be worst case scenarios (defined as a renal stone that does not respond to conservative treatment, e.g., requires lithotripsy or surgical treatment). Even surgery leaves residual fragments that must pass. Our technology provides the capability to reposition stones within the kidney and ureter, which will enhance conservative treatment or surgery by accelerating and facilitating passage of stones or fragments. However, this does not have to be the only use. The technology can also be used to reposition a stone to a non-obstructing location within the kidney to postpone surgery or to accelerate passage through the ureter, as proposed here. Finally, the technology proposed in this grant also provides the capability to comminute the stone as in shock wave lithotripsy (SWL) with what we call burst wave lithotripsy (BWL).

Task Progress:

Task 1.1. Select imaging probe for stone repositioning. Major activities include refining our instrumentation and validation studies in humans. We have made ultrasonic propulsion work in vitro on two flexible ultrasound systems and with half a dozen probes. We are awaiting delivery of the abdominal probe used with the GE Flexible Ultrasound System for testing. We have built three prototype probes that are being tested. We have reported our work at conferences and in publications and participated in many outreach events and demonstrations.
Task 1.2. Custom design probe to image, reposition, and fragment stones. Three transducers have been built and demonstrated to break stones under both in vitro and in vivo conditions. Patents have been submitted on the amplifier and probe design. The results were published in the Journal of Urology.

Task 2.1. Validate capability to displace an obstructing stone.

Task 2.2. Validate capability to displace a ureter stone. Stones were moved in humans causing a relief from releasing obstruction at the ureter. This result was reported in our report on the clinical trial. Experiments continue in pigs to improve the stone pushing capability.

Task 2.3. Validate capability to comminute a stone.

Task 2.4. Validate capability to expel an attached stone. Small stones have been implanted ureteroscopically in a kidney and fragmented transcutaneously at 5 MPa. The threshold of cavitation (as detected on B-mode) and injury was measured in 7 animals and determined to be 7 MPa at 330 kHz. Cavitation detection correlated with injury and provides safety feedback. Results have been reported at the International Symposium on Therapeutic Ultrasound.

Task 3.1. Refine and validate stone size measurement. We showed measurement of the shadow width was significantly more accurate then measurement directly of the stone width in the Image in 3 studies -- preclinical, retrospective, and prospective. Preliminary results were presented at the World Congress of Endourology in 2014 and will be presented at the American Urological Association (AUA) annual meeting in 2015. The preclinical paper is in press in the Journal of Urology.

Task 3.2. Refine capability to localize a stone. To date 12 subjects have been enrolled in a study of the ability to detect stones with S-mode and we are actively enrolling about 2 per week. The system and technique as well as preclinical studies were published in the Proceedings of the IEEE International Ultrasonics Symposium in 2014.

Task 3.3. Refine and validate capability to detect a ureter stone. Our system was further improved to improve resolution of kidney stone size on the image by several changes to the image process. Part of the paper in press also shows data supporting how to set the knobs on the ultrasound for the best sizing accuracy.

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