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PI Name:	Simon, Julianna Ph.D.		
Project Title:	Improving Kidney Stone Detection in Space Analogs		
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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Space Biology Special Category:	None		
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Comments:			
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No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
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Contact Monitor:		**Contact Phone:**	
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Key Personnel Changes/Previous PI:			
COI Name (Institution):	Bailey, Michael Ph.D. (MENTOR/ University of Washington)		
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POSTDOCTORAL FELLOWSHIP
1. Project Aims

The twinkling artifact (TA) is a rapid color-shift that selectively highlights hard objects such as kidney stones in color-Doppler ultrasound images; however, its inconsistent appearance has limited its clinical use. Our objective is to develop an ultrasound imaging protocol to enhance kidney stone detection in space, addressing ExMC Gap 4.13.

AIM 1: Develop ultrasound imaging protocols to enhance kidney stone detection in space.

AIM 2: Manipulate existing elastic wave and bubble dynamic models to aid in refining kidney stone detection protocols.

Task Description:

AIM 3: Determine how hypobaric and hyperbaric conditions alter the TA.

AIM 4: Determine how urine pH and stone type affect the TA.

AIM 5: Determine how exposure to gas concentrations unique to space travel vehicles alters the TA.

2. Key Findings

Exposing swine to 6 mm Hg carbon dioxide in air, the upper end of what is found on the International Space Station (ISS), significantly reduces or eliminates the TA. In ex vivo kidney stones of all major stone types, we found that increasing the acoustic energy delivered to the stone enhances the TA. A damped, shock wave lithotripter pulse can be used to expand bubbles on the stone surface and introduce transient twinkling. We proposed a modification to the current crevice bubble hypothesis of twinkling to include internal microcracks. A variety of bacterial species have been found on 6/6 fresh human kidney stones. Results on twinkling in these stones suggest a relationship between bacteria type and bubbles (or the TA). Published 2 papers in peer-reviewed scientific journals; 2 additional publications are currently in draft form. Presented at 5 scientific conferences, including an invited talk at an International Medical Physics conference. Represented the National Space Biomedical Research Institute (NSBRI) with an ultrasound and kidney stone demo at the 2015 SpaceCOM Expo. Mentored a summer high school student who finished with a demo at the Pacific Science Center. Mentored a high school student senior project. Organized a booth at the University of Washington Engineering Discovery Days. Was approved to begin the hyperbaric human subjects research study to verify bubbles exist on in situ human kidney stones. Grew calcium oxalate crystals in the lab with and without protein and found that they differed significantly from human kidney stones.

3. Impact

We have discovered that breathing CO2 significantly diminishes or eliminates twinkling, which has important implications for detecting kidney stones in flight and suggests the need for an effective countermeasure. We also found that bacteria may form the bubbles that cause stones to twinkle. As bacteria behave differently in space, it is important to determine the relationship between bacteria and bubbles. While increasing the energy delivered to the stone has been found to enhance twinkling, there remains some stones that do not show the TA. We are focusing on new ways to enhance twinkling such as low frequency or dual frequency ultrasound. We also are investigating whether we can predict stone composition based on the reflected Doppler ultrasound signal. Finally, we propose a caveat to the crevice bubble hypothesis of twinkling to include the contribution of internal microcracks, increasing our understanding of the fundamental physics of the TA.

4. Proposed research

We will continue our efforts to recruit subjects for the human hyperbaric experiment. In swine, we will test the influence of CO2 levels on kidney stone twinkling and whether oxygen is a potential countermeasure to restore twinkling. We plan to collect more fresh kidney stones for bacterial analysis, in addition to growing calcium oxalate crystals in the presence of bacteria in the lab to see if we can mimic human kidney stone formation. We will determine whether low frequency or dual frequency ultrasound can make all kidney stones twinkle. We will also determine whether the twinkling signal can be used to predict stone composition.

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:

The risk of renal stone formation (ExMC 4.13) is considered a shall for all missions beyond the International Space Station. On Earth, currently 1 in 11 Americans have been diagnosed with kidney stones and the prevalence is increasing worldwide. In the US alone, more than three million diagnoses and treatments are made annually at a cost calculated to be over ten billion dollars. Specific in-flight conditions that contribute to an increased risk of renal stone formation include bone demineralization, dehydration, and stasis. US astronauts have reported more than 30 symptomatic stone events that have occurred pre- or post-flight; one notable in-flight stone incident has been described by the Russian space program, where a crewmate was found writhing in pain. While no US astronaut has experienced an in-flight kidney stone event, the incidence of kidney stones in space is expected to rise as missions become longer, astronauts are exposed to gravitational changes, and immediate transport to Earth becomes more problematic. Stone size is a significant predictor for the severity of a stone incident, as small stones may pass on their own causing relatively little pain.
The Integrated Medical Model team defines two renal stone scenarios; the best case scenario (i.e., where stones pass safely and spontaneously) is predicted to occur in 68% of cases where stones are small (<5 mm diameter). However, as stones increase to 5-10 mm in diameter, stones are predicted to pass safely and spontaneously in less than 50% of cases. These data show the need for a diagnostic tool that allows for routine monitoring of people at risk for developing kidney stones both on Earth and in space. Currently, kidney stones are detected with x-ray or computed tomography (CT), both of which expose the patients to ionizing radiation. Our technology will make ultrasound a more robust tool to detect small kidney stones, thereby reducing patient exposure to ionizing radiation and reducing the cost associated with kidney stones. This technology would allow emergency rooms to diagnose kidney stones immediately, rather than sending the patient to radiology for a CT. In addition, more than 50% of stone-formers have a repeat stone incident within 5 years. Our technology would allow for more routine monitoring so steps could be taken to avoid emergency surgery. Should we find that ultrasound can be used to predict stone type, doctors can help direct treatment to those that are known to be successful for that stone type. Further, if bacteria are found to play a significant role in stone formation or detection, it may help in the development of medication to prevent stone formation in the first place! In space, ultrasound is one of the few imaging technologies that can be safely flown, and our improved kidney stone detection protocols will make ultrasound a more robust tool for early stone detection, which is critical for minimizing mission disruption and reducing the risk of an unpredictable and life-threatening renal stone incident.

Task Progress:	AIM 1: Develop ultrasound imaging protocols to enhance kidney stone detection in space. Our experimental results in ex vivo human kidney stones showed that increasing the acoustic energy delivered to the kidney stone enhances the Doppler ultrasound twinkling artifact (TA). On a flexible ultrasound system, the TA can be enhanced by increasing the number of cycles and amplitude of the Doppler pulse. We also found that low amplitude lithotripter pulses can be used to induce strong, but transient, bubble growth and twinkling, even for non-twinkling stones. AIM 2: Manipulate existing elastic wave and bubble dynamic models to aid in refining kidney stone detection protocols. The linear elastic wave model was successfully coupled to the bubble dynamics model and then used to guide the development of stone imaging protocols. AIM 3: Determine how hypobaric and hyperbaric conditions alter the TA. Recruitment is currently ongoing for the human hyperbaric research study to verify bubbles are present on in situ stones. In the lab, twinkling on macroscopically rough-surfaced stones has always decreased as expected upon exposure to hyperbaric pressure and increased when exposed to hypobaric pressure. Macroscopically smooth-surfaced stones do not always respond as expected to hypo- or hyperbaric pressure, which has led to the addition of internal microcracks to the crevice bubble hypothesis of twinkling. AIM 4: Determine how urine pH and stone type affect the TA. Imaging ex vivo stones across physiologically-relevant pHs indicated that the TA is only minimally influenced by pH. Yet stone composition was found to significantly influence twinkling through surface roughness. We discovered large differences in composition and architecture in stones classified as the same type, which was reflected in the amplitude and stability of the twinkling signal. This prompted the creation of a calcium oxalate stone farm, where essentially an artificial kidney was fed solutions supersaturated with calcium and oxalate. The grown crystals were much more fragile and less dense than real stones, suggesting that urine salt supersaturation alone is insufficient to form kidney stones. AIM 5: Determine how exposure to gas concentrations unique to space travel vehicles alters the TA. When 4 swine were exposed to increased carbon dioxide at levels 20x that found on Earth (8000 ppm, 6 mm Hg), the TA was significantly diminished or eliminated in 10-15 minutes. Twinkling remained at the low to non-existent level until the pig was returned to oxygen, where twinkling reappeared within 15 minutes. The same pattern in the TA repeated when the pigs were again exposed to carbon dioxide and then oxygen. While the blood showed large changes in carbon dioxide and oxygen concentrations, only small changes were found in the urinalysis. Based on how quickly twinkling responded to the change in breathing gas, we expect that gas exchange is the mechanism by which twinkling is reduced.
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