Fiscal Year:	FY 2017	**Task Last Updated:**	FY 03/10/2017
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
Human Research Program Elements:	(1) **ExMC**:Exploration Medical Capabilities		
Human Research Program Risks:	None		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2013 NSBRI-RFA-13-01 Postdoctoral Fellowships
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No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	1	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date changed to 12/31/2016 per NSBRI (Ed., 10/19/15)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Bailey, Michael (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. In the 3rd year renewal proposal, the aims are: AIM 1: Develop, refine, and test in space analogs improved ultrasound imaging protocols to enhance kidney stone detection. AIM 2: Determine the effect of breathing gas composition on twinkling in swine. AIM 3: Determine the role of bacteria in twinkling.

Task Description:

2. Key Findings

Twinkling was reduced when 9 swine were exposed to elevated carbon dioxide (CO2) levels (similar to what is found on the International Space Station (ISS)) with the degree of reduction in twinkling correlating with the concentration of CO2; twinkling increased when swine were exposed to 100% oxygen. When 4 swine were exposed to elevated CO2 levels versus normal air, there was an unrecoverable decrease in twinkling over the course of the study. Concentrations of gases in the blood and urine suggest both O2 and CO2 contribute to twinkling. Imaged 7 human subjects in the hyperbaric chamber and found a statistically significant increase in twinkling when subjects breathe 100% O2 at 1.6 ATA (the decompression stop) compared to initial twinkling levels. Growing several different species of bacteria on sterilized stones did not induce or increase twinkling; bacteria grown on agar plates also did not twinkle. Found evidence suggesting the contribution of internal micro-cracks to twinkling in addition to the surface crevice bubbles. Low frequency ultrasound was found to enhance twinkling if already present on stones, but did not cause non-twinkling stones to twinkle. Published 2 papers in peer-reviewed scientific journals; 4 additional papers are in preparation. Presented at 5 scientific conferences including an invited talk at the Acoustical Society of America Meeting in Honolulu, HI. Mentored a Pacific Science Center summer high school student and a summer undergraduate student. Organized a Wide World of Sound Booth at Engineering Discovery Days as Chair of the Outreach Committee, Cascadia Regional Chapter, Acoustical Society of America. Was interviewed for 2 National Space Biomedical Research Institute (NSBRI)/University of Washington promotional videos and a book on women in science. Accepted a tenure-track assistant professor position in the Graduate Program in Acoustics, Department of Aerospace Engineering at the Pennsylvania State University.

3. Impact

We have discovered that breathing CO2 significantly reduces twinkling in swine and have shown that breathing normal air (0.04% CO2) is insufficient to restore twinkling. The results also suggest that breathing elevated O2 may restore or enhance twinkling, which is supported in our human hyperbaric study. Bacteria grown on sterile stones or agar plates was found to be insufficient to induce or enhance twinkling; bacteria may need to be present in the stone formation process to contribute to twinkling. While increasing the energy delivered to the stone or lowering the transmitted frequency has been found to enhance twinkling, there remains some stones that do not twinkle. Further investigation into the stone formation process and/or the presence or absence of internal micro-cracks, which have been shown to play a role in twinkling in addition to the surface crevice bubbles, may help elucidate why some stones are resistant to twinkling so new techniques can be developed.

4. Proposed research

While this project is ended with NSBRI, we plan to finish recruiting and imaging the last subject for the human hyperbaric study and plan to submit 3 more journal publications. We are also looking to investigate in humans the effect of either an elevated CO2 or O2 environment on kidney stone twinkling.

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:

Kidney stones currently affect approximately 1 in 11 Americans and the prevalence is increasing worldwide. In the US alone, more than 3 million diagnoses and treatments are made annually at an estimated annual cost of over $10 billion. Further, more than 50% of stone-formers have a repeat stone event within 5 years. The risk of renal stone formation (Exploration Medical Capabilities--ExMC 4.13) is considered a "shall" for all missions beyond the International Space Station. Specific in-flight conditions including bone demineralization, dehydration, stasis, and increased alkalinity of the urine contribute to an increased risk of renal stone formation in space. US astronauts have reported more than 30 symptomatic stone events that have occurred pre- or post-flight; one noteable 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 70% of cases where stones are small (<6 mm diameter). However, as stones increase to >6 mm, only 20% of stones are predicted to pass safely and spontaneously. 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. On Earth, computed tomography (CT) is considered the gold standard for kidney stone detection; plane film, kidney-ureter-bladder x-ray is also used to detect kidney stones. Both of these technologies expose patients to ionizing radiation. Our goal is to make ultrasound a more robust tool to detect small kidney stones, thereby reducing patient exposure to ionizing radiation and reducing the costs associated with kidney stones.

Improving ultrasound for kidney stone detection would allow emergency rooms to diagnose kidney stones immediately rather than sending the patient to radiology for an x-ray or CT. Ultrasound could also be used for more routine monitoring of kidney stones so that steps could be taken to avoid emergency surgery. While we have not found a way for ultrasound to predict stone composition, significant improvements have been made in kidney stone imaging and sizing. We have shown that surface crevice bubbles and internal micro-cracks contribute to the ultrasound twinkling artifact and we continue to increase our understanding of kidney stone formation. Furthermore, we have found that breathing elevated levels of oxygen may enhance twinkling, which could help make kidney stones even easier to diagnose, particularly for non-expert sonographers. 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, refine, and test in space analogs improved ultrasound imaging protocols to enhance kidney stone detection. Our experimental results in ex vivo human kidney stones showed that increasing the acoustic energy delivered to the stone and reducing the ultrasound frequency enhances the color Doppler ultrasound twinkling artifact. On a flexible ultrasound system, twinkling can be further enhanced by increasing the number of cycles and amplitude of the Doppler pulse. Low frequency ultrasound has been shown to enhance twinkling in stones, yet there remains some stones that do not twinkle. We found that internal micro-cracks within the stone contribute to twinkling, in addition to the surface crevice bubbles, but thus far no structural patterns have been identified that might lead to the prediction of stone type with ultrasound. AIM 2: Determine the effect of breathing gas composition on twinkling in swine. A total of 13 swine have been exposed to elevated levels of carbon dioxide (CO_2) in air at 0.8%, 0.54%, and 0.27% (approximately 6, 4, and 2 mm Hg, respectively). The 9 swine initially breathing 100% oxygen (O_2) show a statistically significant reduction in twinkling when the swine were exposed to air with elevated CO_2 with the degree of decrease in twinkling proportional to the concentration of CO_2 (i.e., higher CO_2 levels causes more reduction in twinkling: 0.8% > 0.54% > 0.27%). A second set of 4 swine were oscillated between normal air (0.04% CO_2) and elevated CO_2 at 0.54%. These swine showed a significant decrease in twinkling over the course of the study with only minor increases in twinkling when the exposure was shifted from the elevated CO_2 to normal air. The slight increases in twinkling from exposure to normal air were not sufficient to recover from the loss in twinkling from exposure to the elevated CO_2. Results from measuring the concentrations of gases in the blood and urine suggest both O_2 and CO_2 contribute to twinkling as fluctuations from oscillating the respiratory gas and overall trends are observed for both O_2 and CO_2. The results in swine are supported by the human hyperbaric study where a statistically significant increase in twinkling was observed when subjects breathe 100% O_2 at 1.6 ATA (the decompression stop) compared to initial twinkling levels on ambient air. AIM 3: Determine the role of bacteria in twinkling. Preliminary studies where twinkling was evaluated in fresh kidney stones before sections of the stone and surrounding solution were analyzed for bacteria suggest that bacteria may play a role in twinkling. In the lab, growing two different types of bacteria on sterilized human kidney stones did not induce or increase twinkling. Further testing showed bacteria grown on agar plates did not twinkle. It remains possible that bacteria present in the stone formation process contribute to twinkling, but bacteria, alone or in a biofilm, do not show twinkling with the current ultrasound equipment.
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