ABSTRACT

Bone demineralization, dehydration, and stasis put astronauts at an increased risk of forming kidney stones in space. The incidence of kidney stones and the potential for a mission-critical event are expected to rise as expeditions become longer and immediate transport to Earth becomes more problematic. At the University of Washington, we are developing an ultrasound-based stone management system to detect stones with S-mode™ ultrasound imaging, break stones with burst wave lithotripsy (BWL™), and reposition stones with ultrasonic propulsion (UP™) on Earth and in space. This review discusses the development and current state of these technologies, as well as integration on the flexible ultrasound system sponsored by NASA and the National Space Biomedical Research Institute.

1. INTRODUCTION

Astronauts are at an increased risk of kidney stone formation due to the dehydration, stasis, and bone demineralization that occur in space [1]–[3]. While stones are often innocuous in the kidney, they can cause debilitating pain when they move into the ureter and attempt to pass. Obstruction can lead to renal failure, severe urinary tract infection, or even death [4]–[6]. Over 30 symptomatic stone incidents have been reported in United States astronauts post-flight; one notable in-flight stone instance has been described in the Russian space program, where a crewmate was found “writhing in pain” [1], [7]. While no US astronaut has experienced a kidney stone event in-flight, the importance of kidney stones in space is expected to rise as missions become longer and immediate transport to Earth becomes more problematic.

There is currently no definitive pharmacological or dietetic solution to eliminate the risk of renal stone forma-

tion in long-term space expeditions or on Earth. Potassium citrate has been shown to be an effective prophylactic agent in reducing the risk of urinary stones on Earth and has been used by NASA as a countermeasure to stone formation on short duration flights [1], [2]. Another possible countermeasure under investigation by NASA involves a combination of resistive exercise plus bisphosphonates, which have been shown to reduce urinary calcium excretion during missions to the International Space Station (ISS) [8]. However, in an attempt to reduce the risk of visual impairment and increased intracranial pressure, NASA has been exploring the use of a medication known to elevate urinary pH, which increases the formation risk of certain types of kidney stones [9], [10]. The use of this agent could offset any stone risk reduction provided by potassium citrate and may synergistically increase the risk of stone formation in space [9], [10].

At the University of Washington, we are developing a suite of ultrasound-based stone management technologies to diagnose and treat kidney stones on Earth or in space. There are three primary system technologies: S-mode™, BWL™, and UP™. S-mode™ is a stone-specific ultrasound imaging mode optimized to visualize kidney stones. Burst Wave Lithotripsy (BWL™) is a non-shock based approach to break kidney stones into smaller fragments. Ultrasonic propulsion (UP™) is the application of acoustic radiation force to either facilitate passage by moving a stone or stone fragments towards the exit of the kidney or to relieve obstruction and pain by pushing a stone back into the kidney and allowing stone treatment to occur at a later time.

2. S-MODE™ ULTRASOUND IMAGING

Current ground-based technologies to detect stones, such as computed tomography (CT) and plain film x-ray are unsuitable for flight because of the size, power
requirements, and/or exposure to ionizing radiation. Standard B-mode ultrasound has been used to diagnose kidney stones, which ideally appear as hyperechoic objects with a posterior hypoechoic shadow; however, ultrasound sensitivity is low compared to CT and highly dependent upon stone size and the interpretation of the operator [11]. Sensitivity has been reported at 45% overall [12]–[14], with numbers as low as 13% for the detection of stones <3 mm and 71% for the detection of stones >7 mm [11]. The literature measurement of stone size with ultrasound is also variable and tends to be overestimated with clinical ultrasound [11], [13], [15], again particularly for small stones. Management decisions are in part based on the size of the stone, and overestimation of a small stone can lead to treatment when instead the stone potentially can be passed. The reverse can occur with larger stones, which are often asymmetric, and sometimes underestimated with ultrasound due to its 2D nature, where the largest stone dimension is missed. The color Doppler ultrasound “twinkling artifact”, which highlights stones with rapidly changing color as shown in fig. 1, is a supplement to B-mode to increase specificity [16]–[20]; however, because of the inconsistent appearance of the twinkling artifact, sensitivity is not significantly improved.

Early detection of small stones is critical in the space program as stone size is a significant predictor for the duration and severity of a stone incident [21]; small stones, generally defined as <5 mm diameter, pass spontaneously in 68% of cases, whereas less than 50% of stones 5-10 mm diameter pass naturally [22]. S-mode ultrasound imaging is under development to improve kidney stone detection and sizing by optimizing an ultrasound system to delineate hard structures. Commercial ultrasound systems are generally optimized to distinguish subtle differences in soft tissue, which can result in poor contrast and resolution when imaging hard objects such as kidney stones. Stone-specific ultrasound, or S-mode, improves the resolution of kidney stones, but as a tradeoff there is some reduction in soft tissue image quality, as shown in fig. 2.

Figure 1. An example of the kidney stone twinkling artifact in a pig kidney, which shows the stone as a mosaic of colors in a grayscale ultrasound image.

Figure 2. Ultrasound images of (upper) a human kidney and (lower) stones on a tissue phantom taken with (left) conventional B-mode ultrasound and (right) with S-mode ultrasound developed at the University of Washington. Left: Conventional B-mode ultrasound clearly shows kidney structures including the collecting system, calyces, and papilla of the kidney; however, the lower image shows that the kidney stone brightness is not different than the tissue phantom and small stones of 1-2 mm diameter spaced 3-4 mm apart cannot be resolved. Right: S-mode ultrasound clearly shows the collecting system and calyces of the kidney, though without the same degree of soft tissue resolution as shown in the conventional B-mode ultrasound image; however, the lower image shows that stones appear significantly brighter than the soft tissue phantom and the small stones can be resolved.
Figure 3. (a) Ultrasound image of an ex vivo human kidney stone showing the difference in stone size measurements between the hyperechoic stone and the posterior acoustic shadow. This image was featured on the cover of the Journal of Urology (January 2016) and is reprinted with permission from Elsevier Publishing [24]. (b) Ultrasound images of a 4.4 mm stone in the lower pole of a human kidney. Measurement of the stone width (blue) overestimates the stone size by 3.2 mm, whereas measurement of the posterior acoustic shadow (yellow) overestimates the stone size by 1.0 mm.

Using a flexible Verasonics® ultrasound system, which allows the user to specify the transmit, receive, and post-processing of the ultrasound signal, traditional B-mode imaging has been refined to detect kidney stones [23], [24]. These custom stone-specific algorithms include an ultrasound transmit pattern called high density ray line imaging, with a defined focus just proximal to the kidney stone to improve stone resolution. The compression of the received ultrasound signal is designed to increase the contrast of the high intensity signals (i.e., stones). Lastly, the use of filtering and smoothing algorithms, such as spatial compounding, or the averaging of multiple frames imaged from different angles, is minimized. These algorithms can blur the stone and posterior acoustic shadow, and their respective boundaries. The ultrasound focal depth and gain can also be automatically adjusted by the system to reduce user dependence and the stone boundary can be outlined by an algorithm to predict the size of the stone [23]. Automation of signal settings and sizing potentially will reduce operator variability; i.e., these techniques might prevent a novice user from increasing the gain too much, which would inflate the size of the stone in the image. Using our current version of S-mode™, we reduced the average stone size overestimation in 45 ex vivo human kidney stones to 1.4 ± 0.8 mm [24]. This error in stone sizing was further reduced by measuring the posterior hyperechoic shadow as shown in fig. 3, which for the same stones and settings was found to be 0.2 ± 0.7 mm [24]. In human subjects, the average stone size error between S-mode™ and CT was 0.7 ± 1.5 mm for measuring the stone and -0.2 ± 1.4 mm for measuring the shadow [25]. Clinically, 74% of stones and 70% of shadows measured within the same size category (<5 mm, 5-10 mm), with 74% of stone measurements and 88% of shadow measurements within 2 mm of the CT measurement for stones [25].

S-mode™ also includes improvements to enhance the detection of the stone based on the color Doppler twinkling artifact, as it makes stones easier to identify, particularly for non-expert sonographers. Studies suggest that the underlying etiology for the twinkling artifact is micron-sized trapped gas pockets on the kidney stone surface that scatter the ultrasound wave [26], [27]. The crevice-bubble hypothesis was tested by applying hydraulic overpressure to ex vivo human kidney stones, which shrinks the crevice bubbles and reduces twinkling [26], [27]. To improve the appearance of twinkling, Cunitz et al. found that increasing the number of cycles in the Doppler ensemble, increasing the amplitude of the transmitted ultrasound wave, and lowering the pulse center frequency increased the amplitude of the twinkling signal, while the number of pulses in the Doppler ensemble, the pulse repetition frequency, and transducer angle had no effect on twinkling [28]. These results support the theory that twinkling is caused by micron-sized bubbles trapped on the kidney stone surface.

Specific conditions that occur in space, such as changes in ambient pressure and gas composition, have been found to affect twinkling [27], [29]. On the International Space Station (ISS), astronauts are...
exposed to elevated levels of carbon dioxide 10-20 times the carbon dioxide concentration on Earth [30]–[32]. In pigs implanted with kidney stones, twinkling was found to be significantly reduced or eliminated upon exposure to elevated levels of carbon dioxide at the upper end of what is found on the ISS [29]. If elevated inspired carbon dioxide adversely effects twinkling, it could make kidney stone detection with twinkling difficult in space, unless the ultrasound detection algorithm is refined, the ambient carbon dioxide levels are reduced, or effective countermeasures are employed to restore twinkling, such as exposure to oxygen or hypobaric pressure (shown in the lab to increase twinkling by enlarging the bubbles) [27]. Work is continuing on methods to enhance twinkling for improved kidney stone localization on Earth and in space, and to understand the effect of carbon dioxide and inspired gas composition on twinkling.

3. BURST WAVE LITHOTRIPSY (BWL™)

As stones larger than 6 mm are unlikely to pass spontaneously, large, symptomatic stones are likely to require treatment, even in space. This is particularly important for missions beyond low Earth orbit where transport to Earth changes from hours to days, weeks, or months. On Earth, these stones would be treated through shock wave lithotripsy, ureteroscopy laser lithotripsy, or percutaneous nephrolithotomy, depending on the exact circumstances of the case [33]. However, these treatments are not feasible for spaceflight because of the size or amount of equipment needed, the invasive nature of the procedure and/or the need for a trained physician and surgical suite.

BWL™ is an emerging technology that uses short bursts of low frequency, broadly focused ultrasound to comminute kidney stones noninvasively. Maxwell et al. described the development of the BWL™ technology to fragment kidney stones in vitro [34]. Artificial and natural stones of various compositions and 5-15 mm in diameter were treated with BWL™ in a water bath with ultrasound frequencies of 170, 285, and 800 kHz. All natural and artificial stones were fragmented in 36 seconds (for the softest, uric acid, stones) to 14.7 min (for the hardest, cystine, stones). Fragment size was observably uniform and was found to depend on the frequency of the ultrasound source, with a maximum fragment size of 4 mm when treated at 170 kHz and a maximum fragment size of 1 mm when treated at 800 kHz.

A preclinical therapy prototype has since been developed for BWL™ [35] and is shown in fig. 4. A 330 kHz focused transducer of 8-cm diameter with a focal length of 12 cm was designed to disintegrate stones smaller than 10 mm into fragments of less than 1 mm diameter. The transducer is powered by a small, custom high-voltage pulser and image guidance is achieved with a coaxially aligned, commercially available imaging transducer. In vitro studies in a water bath indicated that the transducer performed close to expectations with all fragments less than 2 mm and 87% of fragments less than 1 mm for artificial stones [35]. Furthermore, preliminary in vivo studies in pigs have shown that imaging feedback can be used to monitor for injury during therapy and stones were comminuted in a high carbon dioxide environment. Future work in BWL therapy includes further in vivo testing of stone comminution and development of the injury feedback technique before application to the US Food and Drug Administration (FDA) for feasibility trials in human subjects.

4. ULTRASONIC PROPULSION (UP™)

For stones smaller than 6 mm, conservative treatment is common and includes medication and watchful waiting for stones to pass spontaneously. Certain occupations such as airline pilots have at times required intervention to prevent a small, asymptomatic stone from becoming symptomatic at an inopportune critical time. For astronauts, a small stone could suddenly become obstructive
and cause intense pain during a mission- or life-critical activity. The infrastructure, technology, and personnel are in place should there be a reason to treat such a stone on Earth, but as described in the section on BWL™, these solutions are not ideal for spaceflight.

UP™ is a novel technology based on acoustic radiation force that uses short, focused bursts of ultrasound to reposition stones within the renal collecting system [36]. This would allow astronauts to prophylactically expel a small, asymptomatic stone, temporarily relieve symptoms of an obstructing stone, or aid in the passage of stone fragments after BWL™, as left behind they could serve as nuclei for new stone formation or an infection.

The prototype device was described in 2010 by Shah et al. [37]. The device consisted of a 2 MHz, 8-element annular transducer driven by an 8 channel function generator with 8 individual amplifiers; a coaxially aligned imaging transducer was used to guide the treatment. Separate systems were required to image and move the stones. With 2-5 second pulses, 50% duty cycle, and instantaneous acoustic powers of 5-40 W, the device was able to reposition glass beads and calculi up to 8 mm diameter in a fluid-filled artificial collecting system molded within a tissue-mimicking phantom. This same system was later used to reposition stones and beads in vivo in a porcine model, where both objects were moved from renal calyces to the renal pelvis or exit of the kidney in all six pigs [38].

The second generation ultrasonic propulsion device, reported in Harper et al., used a single, commercially available transducer for imaging and therapy [39]. Compared to the initial prototype, the second generation system was significantly smaller, used lower energies, and electronic focusing allowed the pushing pulse to be focused anywhere in the B-mode image. Using short pulses of ultrasound distributed over a 1-s burst at a 3% duty cycle, 65% of 2-8 mm artificial or calcium oxalate stones were successfully repositioned from the calyces to the renal pelvis or ureter in pigs; seven additional stones were moved within the calyx but not successfully repositioned to the renal pelvis. There were no signs of histologic injury associated with the treatment.

Based on observations from the initial animal studies, the pushing pulse was changed to a concentrated, 50-ms burst of ultrasound energy at 73% duty cycle. In pigs, 6 calcium oxalate stones of 2-5 mm diameter were successfully repositioned from the lower pole of the kidney to the renal pelvis in 14 ± 8 min. using an average of 13 ± 6 bursts of ultrasound [40]. Seven-day survival studies were performed assuming 20 minutes of treatment delivered at a rate of 0.5 Hz with no evidence of injury as evaluated through blood tests, urine tests, and histologic analysis.

The US FDA approved a feasibility study to assess whether stones could be repositioned in 15 adult human subjects [41]. There were no restrictions on stone size or position. The study population included subjects with 1-5 individual de-novo stones ranging from 2-14 mm and postlithotripsy subjects with clusters of sub-micron to 2 mm fragments. Thirteen study participants underwent UP™ in the clinic without sedation, while two underwent UP™ under general anesthesia, as UP™ was applied during their ureteroscopy procedure. The primary outcome of the study was stone repositioning, with secondary outcomes of pain, safety, and controllable stone movement. Adverse events were assessed weekly for 3 weeks through verbal follow-up and over 90 days by monitoring records for unplanned physician or emergency department visits.

Kidney stones were successfully repositioned in 14 of 15 subjects and in 65% of the targets. Four of six post shock wave lithotripsy subjects passed in total over 30 stone fragments within 48 hours after the UP™ treatment. The
largest stone moved was 10 mm and one patient experienced pain relief when a large, obstructing stone was moved back into the kidney from the junction between the kidney and ureter. There were no adverse events associated with treatment and discomfort during the treatment was rare, mild, and self-limited.

Future directions for the UP™ technology include additional clinical trials looking at the effectiveness of relieving pain and obstruction in the emergency medicine department and on expelling large volumes of small fragments. Current refinements to the system include integration with S-mode™ imaging and modification of specific features to work synergistically with BWL™ to make a comprehensive stone management system.

5. IMPLEMENTATION ON THE FLEXIBLE ULTRASOUND SYSTEM

NASA and the National Space Biomedical Research Institute (NSBRI) have been working to develop a flexible ultrasound system (FUS) as the next ultrasound instrument for the ISS and expedition missions. The FUS will fulfill current medical needs of ultrasound in space, as well as accommodate advanced diagnostic and therapeutic ultrasound capabilities developed for space-specific conditions, now and in the future. Currently, in addition to S-mode™ and UP™, this includes technologies for bone fracture and bone loss mitigation led by Dr. Yi-Xian Qin and technologies to image and diagnose visual impairment and intracranial pressure led by Dr. Aaron Dettinger. A custom-built pinout board developed by the Exploration Medical Capabilities (ExMC) team at NASA Glenn Research Center and consultants at ZIN Technologies has allowed for using the NASA FUS imaging probe, from the as yet unreleased FUS, for testing the imaging and propulsion capabilities on the UW Verasonics®-based FUS. Using the center 128 elements of the C1-5 transducer (196 elements), a kidney stone within the collecting space of a renal mannequin model was successfully imaged with S-mode™ as shown in fig. 5; the stone was also successfully repositioned. Although not yet tested, it is anticipated that the NASA FUS system will accommodate BWL™ as well.

6. CONCLUSIONS

The risk of kidney stone formation is considered partially controlled for missions to the ISS and the moon with rapid deployment back to Earth, but is considered uncontrolled for deep space and planetary missions. Pharmacological countermeasures may not be employed in all crewmembers due to the potential for other spaceflight medical conditions, which may limit their use. Significant progress has been made to allow for complete ultrasonic management of kidney stones including improvements in imaging for stone diagnosis, the ability to fragment large stones with bursts of ultrasound, and the development of ultrasonic propulsion for scheduled repositioning of small stones, temporary relief of symptoms from obstructing stones, or removal of fragments after BWL™. Ultrasound technologies such as these to diagnose or treat a variety of space specific conditions are currently being implemented on NASA’s FUS. As detection and treatment of kidney stones with ultrasound continues to be optimized, it is the hope that the NASA-identified risk of renal stone formation in space will be changed from uncontrollable to controlled for all planned missions.

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8. REFERENCES


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