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Detecting Kidney Stones Using Twinkling Artifacts: Survey of Kidney Stones with Varying Composition and Size

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Abstract

In recent years, work has been done to understand the mechanisms of Doppler ultrasound twinkling artifacts (TAs) and why they appear over kidney stones. In this work, twinkling artifacts were evaluated as a possible method of locating and characterizing kidney stones. Doppler ultrasound scanning was used to evaluate 47 stones of different types and sizes with a range of 1.31–55.76 mm² in cross-sectional area and an average of 9.65 mm². An isolated stone study was used to understand the behavior of the TAs. An *ex vivo* kidney study was conducted to determine if the renal tissue impeded the localization of the TAs to the stones. An *ex vivo* randomized stone placement study was used to evaluate the robustness of the method for detecting stones that were placed by an independent party. The TAs were found to be qualitatively consistent in appearance across stone types, sizes and scanning parameters in the isolated stone study. Quantitative assessment of TA amplitude for isolated stones was also found to be consistent for each class of stones across multiple days. The TAs were also shown to be isolated to the stone when placed in an *ex vivo* kidney. The randomized stone placement study showed that this method could find all 47 used stones in a clinical situation with only two false positives. A few limitations to this method were found with issues accurately sizing stones as well as difficulties in specificity for characterizing the stones. Further work will be done on these limitations by improving the Doppler acquisition and processing code as well as evaluating the use of TAs in human studies.

Keywords

Doppler ultrasound; kidney stones; twinkling artifact

Introduction

Kidney stones affect approximately 12% of the global population as of 2018 (Alelign & Petros 2018). Currently, the gold standard method of kidney stone location is via computed tomography (CT) as the stones are easily visible as bright white spots in the scan as they have a higher Hounsfield unit due to the stone's dense structure (Roberson et al. 2018, Ahmad

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et al. 2003, Cheng et al. 2012). Currently, there are no other comparable high contrast imaging methods for noninvasively locating kidney stones. The issues with using CT are numerous. It is expensive, time consuming, and subjects patients to ionizing radiation. Due to these issues, CT is limited in its integration into kidney stone treatment as it is used sparingly in the initial location of stones and in post treatment to confirm if stones are still present. If stones are found early enough and have the correct composition, they can be treated with simple lifestyle changes like increased water intake to dilute stone forming compounds in the renal system and diet restrictions to lower in take of sodium, calcium, oxalates, and animal proteins (Zisman 2017). Most often when symptoms of kidney stones arise, the stones are large enough that they are treated with surgical removal or lithotripsy.

Additional issues arise in the post-treatment phase. Once the treatment approach is complete, a CT scan is performed to check for remaining stones and depending on the results patients may be required to return to the hospital or clinic for continued treatment and scans until physicians are satisfied with the results. This cycle can often repeat itself for multiple days and can quickly become very expensive to treat (Fontenelle et al. 2019). Furthermore, because CT scanners require a large dedicated room, CT cannot be used to check for remaining stones during treatment. Even after a successful treatment, most patients will likely return some years later as known stone formers are likely to form more stones throughout their life (Stamatelou et al. 2003, Sakhaee 2008). Therefore, a method of locating kidney stones that is inexpensive, fast, and small enough to be used during treatment would be able to transform the way kidney stones are treated. Base costs (with no insurance applied) of ultrasound imaging are approximately \$500 and could provide significant base cost savings of approximately \$1500 compared to the use of CT imaging. (Mayo Clinic cost estimator, <https://costestimator.mayoclinic.org/>)

B-mode ultrasound has historically been insufficient in locating kidney stones due to the high amount of vasculature and collecting ducts in the kidney. It can be very difficult to distinguish stones from the surrounding tissue. Detection rates for ultrasound have been reported to be much lower than CT ranging from 59% to 86% with incidence of false positives reaching up to 51% (Yavuz et al. 2015, Masch et al. 2016, Dillman et al. 2011, Palmer et al. 2005).

Color and power Doppler ultrasound is typically used to assess the flow of blood in the body with color Doppler's ability to distinguish flow direction. In 1996, Rahmouni et al. discovered an artifact when using Doppler ultrasound that they termed a twinkling artifact (TA). The TA appears as a sparkling mosaic over the stone that rapidly changes between positive and negative velocities values. They came to the conclusion that the TA was generated from interactions of the ultrasound waves with the rough surfaces of a kidney stone. In a later study, Kamaya, et al. (2003) expanded on this work to further understand the cause of the TA. They concluded that the TAs were primarily dependent on the machine and settings used and also on the roughness of the object. They tested renal stones as a clinical source. While this twinkling artifact has been previously identified and used for detection of kidney stones, the source of this artifact is still under investigation (Khokhlova et al. 2013, Sorensen et al. 2013, Cunitz et al. 2014). Current research into why this signal appears on only kidney stones has developed into a theory that when ultrasound waves interact with the

rough surface of a stone, the waves produce microscopic air bubbles (Lu et al. 2013, Sapozhnikov et al. 2013, Simon et al. 2018). The goal of this present work was to explore how stone size and composition affect TAs and the ability to locate stones with TAs in an *ex vivo* kidney.

Methods and Materials

Isolated Stone Study

The 47 stones used, as detailed in Table 1, were surgically removed from patients by a urologic surgeon and characterized by the Metals Laboratory at Mayo Clinic, Rochester, MN. Ethical approval for use of the stones for this study was not required. Some stones were intact but most stones had been fragmented, possibly treatment like sonication or physical manipulation causing a breakage. The types of stones were a combination of calcium oxalate monohydrate, calcium oxalate dihydrate, apatite, magnesium ammonium phosphate, brushite, uric acid, and sodium/potassium urates. The length and width of the stones were measured using digital calipers (799A, Starrett, Athol, MA) with a cross-sectional area range of 1.31-55.76 mm². As stones are often rounded shapes, the cross-sectional area (as would be detected in a B-mode image) was calculated using the equation for cross-sectional area of an ellipse.

Experiments were performed in a cylindrical water tank (16 cm diameter, 17 cm height) with degassed water. Degassed water was used to reduce any introduction of microbubbles on the surface of the stones other than possibly due to ultrasound excitation. The gauze bridge was made by folding gauze (Dermecea USP Type VII Gauze Sponges, 4"x4", 12-Ply, Cardinal Health, Dublin, OH, USA) bandages width wise until the width of the bridge was just large enough to hold the largest stones. This was done to limit the appearance of the gauze in the image and thus limit the signal to primarily the stone and not the gauze. The ultrasound probe was also orientated perpendicular to the gauze bridge to limit appearance of the gauze and was set up to have the stone located at least 50 mm and no more than 100 mm from the probe. This setup is shown in Figure 1. The cross-section of the gauze is shown in the diagram with the stone placed upon the gauze. Scanning was performed using a C5-2 curved linear array (Philips Healthcare, Andover, MA) on a Verasonics research system (V1, Verasonics, Inc., Kirkland, WA). All scanning was performed on a motorized translation stage with three degrees-of-freedom to maintain positioning precision and stability. The stepper motors that drove the translation stage all had resolutions of 2.5 µm/step. Each stone was individually suspended on the bridge and allowed to rest until no bubbles were seen moving in the real time B-mode imaging. At that point, the Doppler acquisition code obtained from the University of Washington (Cunitz et al. 2014) was executed in MATLAB (MATLAB R2016a, Mathworks, Natick, MA) and the Doppler transmit voltage was varied until the epicenter of the TA signal was just covering the stone. The B-mode imaging was performed with pulse-inversion imaging with a 2.25 MHz transmit frequency and 4.50 MHz harmonic imaging frequency. The Doppler acquisitions were also performed with a pulse inversion sequence transmitted at 2.25 MHz with 3 cycles for each positive-signed and negative-signed pulse at a rate of 5.0 kHz. The finite-duration impulse response (FIR) wall filter in the MATLAB Verasonics system acquisition code was set to 'FIRhigh' for all

measurements. This is a 13 tap filter that obtains -65 dB below 0.035-PRF and -3 dB at 0.18-PRF where PRF is the pulse repetition frequency. It should be noted that the B-mode beams are focused on transmit while those for the Doppler were not focused on transmit. Power Doppler display was used for real-time imaging. At that point the last twelve frames of the real time Doppler; in-phase/quadrature (IQ) data were saved and averaged together for data analysis. The analysis was performed according to the methods described by Lu et al. (Lu et al. 2013). Briefly, the magnitude of the acquired (IQ) is taken and the average power is calculated. The TA was outlined in MATLAB as shown in Figures 2(a,b) for sizing the stone and calculation of signal intensity only over the stone. The stone was then placed in a vial filled with degassed water for storage. This process was repeated for all 47 stones. Each stone was tested on three consecutive days to evaluate variation among days. The stones were always kept in water filled vials after the initial isolated stone scans and were opened while submerged to avoid any introduction of air for the additional studies described below. The exact placement and orientation of the stones on the bridge was not held strictly constant to better analyze the ability of the stone to produce TA signal regardless of the side scanned.

Hydrophone Study

To evaluate possible mechanisms of the TA, a hydrophone study was conducted to measure the pressure and intensity of the ultrasound waves over the range of available transmit levels. This was performed in a water tank (104 x 63 x 38 cm) as shown in Figure 3 with a hydrophone in place of a plastic membrane and did not include a kidney sample. The membrane hydrophone (GEC-Marconi Type Y-33-7611, GEC-Marconi Research Centre, Essex, United Kingdom) had an active element diameter of 1.0 mm and was placed at a distance of 6 cm from the probe. An oscilloscope was connected to the hydrophone to measure the voltage output from the hydrophone. The pulses were measured at transmit levels from 5-50V in 1 V increments. From the isolated pulse the effective mechanical index (MIE) was calculated as $MIE = P_r / \sqrt{f}$, where P_r is the peak negative pressure in MPa and f is the center frequency in megahertz (MHz) (Herman & Harris 2002, Nightingale et al. 2015). Measurements were not derated in these cases.

Ex Vivo Kidney Study

After scanning the stones isolated in a water bath, we evaluated if detection of stones would be mitigated by kidney tissue. To scan the stones, an *ex vivo* porcine kidney was cut almost completely in half to allow for opening of the kidney like a clam shell for easy placement of stones in the medulla and then the stone was covered with the other half of the kidney. The kidney was suspended on a semi-rigid plastic membrane in a large water tank to limit noise generated from the suspension platform. This setup is shown in Figure 3. The stones were scanned to determine if the Doppler signal could penetrate through the tissue and still have enough energy to induce TAs. The ability of the TA to precisely locate the stone was tested by using a range of Doppler transmit voltage levels. This range was from 22-39 V with three settings in between of 26.6 V, 31.0 V, and 35.6 V. The transmit levels were determined as the values that contained 75% of the transmit voltages that generated TAs over the stones in the isolated stone study. This was chosen to ensure that the power would be high enough to

generate TAs on all stones besides the sodium/potassium urates while low enough to not saturate the region of interest with the TA. The transmit levels in between were chosen based on the user interface slider that changed the Doppler transmit voltage by a set amount. The stones were also scanned at the maximum Doppler transmit level of 50 V to determine if this setting could be used as a starting point for general detection before lowering the transmit level for more precise location. Images from the real-time scanning display were recorded.

Ex Vivo Kidney Randomized Stone Placement Study

The basic setup for this experiment was the same as the previous *ex vivo* studies. This time, a colleague chose a random assortment of four to six stones varying in size and type and placed them in different positions in the medulla of the kidney. He then closed the kidney and made note of which stones were used and the order in which they were placed. One of the authors (B.G.W.) would then scan through the length of the kidney at 50 V until a TA signal was found. To ensure the signal was from a stone and not from the movement of the transducer the probe motion was halted over the potential signal source for at least 30 seconds to let the kidney and signal settle. If the signal remained, the Doppler transmit level was slowly lowered to 21 V and if the TA still remained then this would be marked as a possible stone location. Further scanning of the kidney would be performed trying to find the other stones. After the entire kidney was scanned and it had been confirmed that all the stones were located, the same colleague removed the stones and placed the next round of stones in the kidney. This was repeated for 47 stones. Images from the real-time scanning display were recorded.

Statistical Analysis

To evaluate if there were differences in the magnitude from the different types of stones we performed an analysis of variance (ANOVA) using GraphPad Prism (GraphPad Software, San Diego, CA) with a significance threshold set at $p < 0.05$. Additionally, to compare the stone sizing performed with the TA we performed a least squares regression using MATLAB between the cross-sectional areas measured using the calipers and the TA. GraphPad Prism and MATLAB were used to plot Figures 4(a) and 4(b), respectively.

Results

Isolated Stone Study

From these experiments, we observed that all stones were successful in producing TAs. The stone type had a minor effect on the TA signal except for the sodium/potassium urate stones, which required more power to produce adequate signal. Figure 4(a) shows that for all the stone types except the sodium/potassium urates, there was no significant difference in the amplitude of the TA at 22.0 V ($p = 0.70$; ANOVA). For urates there was a significant difference between the means ($p > 0.023$). The ability of the TA to be used to size the stones was also evaluated and the results are shown in Fig. 4(b). The results were taken over three consecutive days to test for any possible variation in TA generation. The slope reported in Fig. 4(b) is the ratio of the TA area to the area of the stones and was fit using a least squares linear regression. The equation for this fit line was $y = 1.19x + 4.37$ (mm²) and had $r^2 = 0.53$. Figure 4 shows the TAs generated over the stones in the Doppler image with the

corresponding B-mode image as reference. Figure 5 is organized in columns for a specific stone referenced in the first row with Doppler and B-mode images in the second and third row, respectively. Figure 5(a) shows the Doppler image of a calcium oxalate monohydrate stone with a cross-sectional area of 35.29 mm². Figure 5(b) shows the Doppler image of a 60% apatite, 40% magnesium ammonium phosphate stone with a cross-sectional area of 9.19 mm². Figure 5(c) shows the Doppler image of a 60% brushite, 40% apatite stone with a cross-sectional area of 6.36 mm². Figure 5(d) shows the Doppler image of an 80% uric acid, 20% calcium oxalate monohydrate stone with a cross-sectional area of 16.54 mm². It can easily be seen that the bright TA signal is only seen over the stones for all major stone types. The small artifact seen under the stone is due to the gauze bridge used to suspend the stone. This is easily distinguished due to the visible gap in separating the two signals.

Hydrophone Study

Both the positive and negative peak pressures increased as the Doppler transmit voltage increased. The blue line in Fig. 6(a) shows that the positive peak pressure increases the most between 23-33 V. The red line in Fig. 6(a) shows that the negative peak pressure increased linearly as transmit voltage increased. The greatest negative peaks from each waveform were used to calculate the MIE. This trend is shown in Fig. 6(b) with a maximum MIE of 1.32.

Ex Vivo Kidney Study

From these studies, it was observed that the kidney tissue had no significant effect on the generation and appearance of TAs as all stones were clearly visible and showed similar TAs between the kidney being open and closed. As seen in Fig. 7, the arcing artifact was still apparent for stones when the Doppler transmit signal reached a sufficiently high level. The stones used in Fig. 7 were the same as those used in Fig. 5. Most importantly, throughout the study there were no TAs generated by the kidney tissue. This is seen in Fig. 7 as there was only signal centered over the stone regardless of Doppler power. The signal over the stone generally increased in size as the transmit level was increased but started to plateau around 39 V. Beyond this point, most stones produced a signal that did not increase in size on the z-axis but the intensity of the signal did. When using the maximum transmit level of 50 V, the maximum TA size remained around 10 mm in depth for all stone sizes and types besides the sodium/potassium urates. It was seen that for some stones, the intensity of the signal increased to the point that the color range saturated and was not large enough to give an accurate value to the TA and therefore showed a blank spot in the arc centered over the stone.

Ex Vivo Kidney Randomized Stone Placement Study

In this experiment, all 47 stones were found by using TAs as the primary indication of the location. The stones used in in Fig. 8 were the same as those used in Fig. 5 except for the calcium oxalate monohydrate stone as used in Fig. 5(a). By starting at the maximum transmit level of 50 V, the stones were easily located which is seen in Figs. 8(c,f,i). The stones were more precisely located by decreasing the Doppler transmit level to the point before the yellow signal over the stone expanded out into the arc. This can be seen in Figs. 8(b,e,h). It was observed that the TAs also effectively located two stones that were located in the same plane. This was shown in Fig. 9 when scanning two 60% brushite, 40% apatite

stones with cross-sectional areas of 6.00 mm² and 6.36 mm². They were initially located using a transmit level of 50 V as shown in Fig. 9(c). After decreasing the transmit level to 35.4 V for precision location it was noticed that there were two epicenters as shown in Fig. 9(b). Only two false positive signals were found and are seen in Fig. 10. It is difficult to distinguish these from TAs from actual stones but it is important to note the location of these signals were in the renal pelvis and the ureter as opposed to the medulla.

Discussion

Over the course of this work, the viability of using TAs for the detection and location of kidney stones was studied under different conditions. The isolated stone study was fundamental in understanding the behavior of TAs over a range of stone types and sizes. From the results shown in Fig. 5, it was shown that the TA is centralized on just the stones and TA signal did not originate from the tissue or other sources. In the implementation used, we observed an arcing artifact with the stone as the epicenter. The arcing artifact is a beamforming result from using unfocused Doppler transmit beams. Without focusing on transmit, the beam and resulting side lobes of the received signal from a bright target can be very wide giving rise to the arcing artifact (Montaldo et al. 2009). The images shown in Fig. 5 are generated from processing the IQ data taken from the scans. This image was different from the TA seen in the real-time scans. This finding led to using output images from the real-time Doppler scans for analysis.

To better understand the mechanism behind the formation of the TAs, a hydrophone study was conducted to evaluate how the pressure and MIE change in response to a change in Doppler transmit voltage. As shown in Fig. 6(b), the MIE increased linearly with the drive voltage and reached a maximum effective value of 1.32 without performing any derating from the water tank measurements. This is important as the FDA approved limit for MI is 1.9. Even at maximum transmit voltage, the MIE for this method is well within this limit, and would be further decreased if derated to account for tissue attenuation. The effect of increasing Doppler transmit voltage on the positive and negative peak pressures of the pulse waveform was shown in Fig. 6(a). The blue line showed a continuous yet nonlinear increase in positive peak pressure with drive voltage. The red line showed a constant increase in negative peak pressure with drive voltage. This is important as the negative pressure can cause cavitation. This continuous increase supports the theory of microbubbles being the cause of the TAs as the higher the negative pressure the larger and more intense of a TA would be generated.

The case of the isolated stone is not analogous to the clinical situation, so we evaluated if placing the stones in *ex vivo* porcine kidneys would affect the TA behavior. The main concern was to see if the incident waves would have enough energy to propagate through the tissue and still produce an adequate signal for producing a TA. To evaluate this, the stones were scanned through a large range of Doppler transmit levels. As shown in Fig. 7, the stones still produced adequate TAs across a large range of Doppler transmit levels. Figures 7(a,d,g,j) show the stones producing a TA at the lowest transmit level used. As the transmit level was gradually increased, the TA would grow in size over the stone as well as in amplitude intensity progressing from red through orange to bright yellow. Figures 7(b,e,h,k)

show the stone scanned at a Doppler transmit level that produced a TA just large enough to cover the stone. It was at this transmit level that the arcing artifact was observed to increase in size along with the TA over the stone. As the arcing artifact continues to appear it was actually found to be useful in originally locating the stone as it was never found to be generated by the kidney tissue itself. The transmit level was again increased up to the maximum of 50 V to understand how the TA behaved at this level. As seen in Figs. 7(c,f,i,l), the size of the arcing artifact depth in the z-direction did not increase much beyond 10 mm. This is important as the artifact is centralized around the stone and will not drown out the rest of the scanned area. Due to this, it was determined that initial detection and location of stones can be done at 50 V as it will only show up when a stone is under the probe. Once the stone has been found, the transmit level can be lowered gradually until it just covers the stone to more precisely locate the stone. It was also seen that for some stones the signal intensity was high enough that the color range could not accurately show the signal and became saturated so the TA would disappear (blank pixels) directly over the stone and the area of this void would increase as the drive voltage was increased.

Due to the absence of any issues in scanning stones in *ex vivo* kidney, it was decided to rigorously test the TA with the randomized location study. By following the protocol set in the study where the stone was placed in the *ex vivo* kidney, similar results to Fig. 7 were produced and are shown in Fig. 8. The same apatite, magnesium ammonium phosphate, and uric acid stones were used in both the initial *ex vivo* study and the randomized study. By comparing the resulting figures in both studies, it can be seen that the resulting shape of the TAs were similar and were also produced at similar Doppler transmit levels. This further confirms that the TAs were generated from a stone and were not false signals. In one of the randomized rounds there were two stones placed next to each other on purpose to determine if the TA would be able to show a distinction between the two or if they would appear as one stone. The results of this situation shown in Fig. 9(c) at the maximum transmit level do not give much indication of more than one stone besides the small protrusion under the center of the TA. As the transmit level was lowered to precisely locate the stone, it was observed that there were two distinct bright epicenters in Fig. 9(b). The individual stones are further distinguished as the transmit level was lowered to the minimum TA generation level. In Fig. 9(a), two separate TAs are shown. This indicates that there were two stones as the TAs only appear over the center of a stone when the initial transmit level threshold is reached. This ability of the TA to distinctly show multiple stones that may be in the same plane as the probe is essential to its effectiveness and shows that the arcing artifact will not mask other stones.

In the randomized stone placement study we observed that out of all 47 stones, there were only two false signals that were found as shown in Fig. 10. The TAs shown are very similar to those generated from actual stones but there are a few distinctions that can be used to determine these as false as the images were analyzed in retrospect. The arcing artifact that accompanies TAs generated over stones is symmetrical in appearance. The signals shown in Figs. 10(b,c) are noticeably asymmetric with the left side of the arc being much weaker in intensity than the right. Another indication of a false signal is the absence of acoustic shadowing under the stone. In all the other figures there is noticeable shadowing directly beneath the epicenter of the TA. Even with the smaller stones like what is seen in Figs.

9(b,e), there is a small amount of shadowing under the TA. In Figs. 10(b,e) there is no apparent shadowing under the TA. It is unknown as to what exactly caused these false signals, but the location of the epicenter in the kidney itself gives a possible answer. Due to the signal appearing in the renal pelvis and the ureter, it is possible that not all of the air bubbles were let out of the kidney and were trapped in the ureter. If this was the case, then by a current theory of TA generation being due to microbubbles on the stones then this is a feasible explanation.

Despite the success that was seen in the randomized study at locating kidney stones, there are still a few limitations with this method. In this study, we did not evaluate the TA production in an *in vivo* setting which may pose difficulties in discerning the location of the stones due to the high vascularization of the kidney and physiological motion. This becomes an issue in the kidney as the organ is highly perfused and may produce Doppler signals that may be similar to the TA. Fortunately, the flow of the fluids will not change as the TA does but this may make the location of smaller stones difficult. Additionally, we used a research ultrasound system for this study. This method will need to be evaluated in human patient studies to evaluate its efficacy for stone detection. At that stage, translation to a clinical scanner could provide better signal-to-noise ratio and improved functionality for integration into clinical practice.

Another issue is seen in the limited ability to characterize the stones from the TA amplitude. Initially, a goal of this work was not only to locate but evaluate the ability to characterize stones of different type and size based on the TA characteristics. After our initial studies on isolated stones, it was found that there was some distinction between the stone types but there was not a significant difference to accurately determine the type of stone scanned. Accurately sizing the stone was also difficult due to the limitations in B-mode ultrasound. In order to avoid over- or under-sizing the stone, the TA had to be compared to the B-mode behind it, but when the stones were smaller than around 15 mm² in cross-sectional area, locating the edges of the stone became difficult. In our randomized stone study, we did not use any control cases where no stones were inserted, but the occurrence of only two false positives was highly encouraging with respect to the accuracy of stone detection. Additionally, we intend to use the combination of TA and acoustic shadowing for identification of stones in future studies.

From the results of this work, there are a few applications of this method that would improve the treatment of kidney stones. These are directed at addressing the limitations of CT with the inability to simultaneously scan a patient during treatment as well as the cost and the limitations preventing its use as a screening tool. As ultrasound is highly mobile it can be used in the treatment suite to help evaluate location of stone for therapeutic intervention as well as to confirm the effectiveness of the treatment. Furthermore, due to the absence of harmful radiation and the cost effectiveness of ultrasound, it can be used in a preventative care setting. This would likely be used to screen patients that have a higher risk to form stones once a year or every few years to locate stones in the early stages of formation where simple lifestyle changes can treat the stones. The next steps for this method are to test this methodology in human subjects, as well as further explore the possibility of characterizing

and sizing the stones. The experiments in this work also need to be done without the use of the motorized stage to simulate the freehand scanning of a sonographer or physician.

Conclusion

In this work, the use of TAs was evaluated as a method for locating and possibly characterizing and sizing kidney stones. The results showed that the generation of TAs was consistent over a range of stone types and sizes as well as isolated to the stone even when in an *ex vivo* environment. The randomized placement study thoroughly showed the efficacy of this method to find stones in a simulated clinical environment with a minimal amount of false positives. There were a few limitations to this method with accurate sizing and characterization of stones as well as the possibility of the vascularization of an *in vivo* kidney affecting the TA. These limitations will be addressed in further work to improve the Doppler acquisition and processing code as well as evaluating the use of TAs in human studies.

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Figure 1:

Isolated stone gauze bridge scanning setup. A medium sized water bath was filled with degassed water and two aluminum cylinders were placed on the bottom to act as anchors for the gauze bridge. The bridge was affixed to the anchors using surgical tape. The stone was placed on the bridge and scanned with the C5-2 array position perpendicular to the length of the bridge and held in orientation by a ring stand. The cross-section of the gauze is shown in this diagram. This figure is not drawn to scale.

Figure 2:

(a-c) Real time images of 2.54 mm² brushite stone placed in *ex vivo* kidney at drive voltages of 18.6, 25.8, and 50.0 V, respectively. (a) This voltage setting was the lowest required to produce a TA seen within the light blue outline used to indicate the location of the stone. (b) This voltage was the level at which the bright yellow section of the TA was large enough to just cover the stone. The blue outline shows how the TA would be outlined in MATLAB code for analysis. (c) This voltage was the maximum drive voltage allowed and was used for initial location of the stone.

Figure 3:

Water tank setup for *ex vivo* kidney scans. A large water tank was used to limit apparent noise in the ultrasound images. A semi-rigid plastic support was submerged in the tank and held in place by one arm of the motorized stage. A kidney with a stone placed inside was set on the plastic support and scanned by the C5-2 array oriented with the long axis of the array perpendicular to the long axis of the kidney. The translational stage was used to smoothly move the array along the length of the kidney while scanning. This figure is not drawn to scale.

Figure 4:

(a) Amplitude of TA signal averaged over three days being submerged in degassed water and scanned at a constant transmit voltage level of 22.0 V. COM, APA, NaK, UA, and BRU are the stone abbreviations for calcium oxalate monohydrate, apatite, sodium/potassium urates, uricacid, and brushite, respectively, (b) Measured Doppler area compared to the actual stone size. The red line has an equation of $y = 1.19x + 4.37$ (mm²). A line of equality with a slope of 1 is shown by the blue dashed line and indicates the size of the TA being the same as the stone. The red cross, green asterisk, and blue circle data points correspond to days 1, 2, and 3, respectively when scanning the stones over three consecutive days to evaluate any daily variation.

Figure 5:

(a) Doppler image for calcium oxalate monohydrate stone (35.29 mm^2) with stone shown above. (b) Doppler image for apatite (60%) magnesium ammonium phosphate (40%) stone (9.19 mm^2) with stone shown above. (c) Doppler image for brushite (60%) apatite (40%) stone (6.36 mm^2) with stone shown above. (d) Doppler image for uric acid (80%) calcium oxalate monohydrate (20%) stone (16.54 mm^2) with stone shown above. (e,f,g,h) B-mode only images for (a,b,c,d), respectively. The top row provides photographs of the individual stones shown in the Doppler and B-mode images.

Figure 6:

(a) Plot of positive and negative peak pressures of each waveform from 5-50 V. (b) Plot of effective mechanical index (MIE) versus Doppler drive voltage. The graphs were plotted in MATLAB.

Figure 7:

(a-c) Real-time images of calcium oxalate monohydrate stone at Doppler transmit levels of 22, 39, and 50 V, respectively (35.29 mm^2). (d-f) Real-time images of apatite (60%) magnesium ammonium phosphate (40%) stone at Doppler transmit levels of 31, 39, and 50 V, respectively (9.19 mm^2). (g-i) Real-time images of brushite (60%) apatite (40%) stone at Doppler transmit levels of 21, 31, and 50 V, respectively (6.36 mm^2). (j-l) Real-time images of uric acid (80%) calcium oxalate monohydrate (20%) stone at Doppler transmit levels of 31, 35.6, and 50 V, respectively (16.54 mm^2). The scale bar in the top right image applies for all images in the figure.

Figure 8:

(a-c) Real-time images of apatite (60%) magnesium ammonium phosphate (40%) stone at Doppler transmit levels of 30, 37.8, and 50 V, respectively (9.19 mm^2). (d-f) Real-time images of brushite (60%) apatite (40%) stone at Doppler transmit levels of 8.8, 18.6, and 50 V, respectively (6.36 mm^2). (g-i) Real-time images of uric acid (80%) calcium oxalate monohydrate (20%) stone at Doppler transmit levels of 33, 47.6, and 50 V, respectively (16.54 mm^2). The scale bar in the top right image applies for all images in the figure.

Figure 9:

Real-time images of two brushite (60%) apatite (40%) stones placed next to each other and scanned at 21, 35.4, and 50 V, respectively. The stones were 6.00 mm² and 6.36 mm² in size. The arrows in (b) point out individual TAs due to two separate stones. The scale bar in the right image applies for all images in the figure.

Figure 10:

Two false positive TA signals that were found in the renal pelvis/ureter area of the kidney. (a-c) False signal scanned at Doppler transmit levels of 16.2, 33, and 50 V, respectively. (d-f) False signal scanned at Doppler transmit levels of 23.4, 47.6, and 50 V, respectively. The scale bar in the bottom right image applies for all images in the figure.

Table 1:

List of kidney stones used with the stone type referring to the majority element that comprised the stone and the composition detailing the percentage at which the stone type makes up the stone. Com+Cod stones are made of calcium oxalate monohydrate (Com) and calcium oxalate dehydrate (Cod). The exact percent composition was unknown. The majority stone types were calcium oxalate monohydrate (Com), apatite (Apa), sodium/potassium urates (NaK), uric acid (UA), and brushite (Bru).

Stone Type	COM					APA		NaK	UA	BRU
Composition	Pure	80%	60%	50%	Com+Cod	70%	60%	Pure	80%	60%
Number	15	1	1	1	7	1	2	3	7	9