Published in final edited form as:

Proc Meet Acoust. 2013 June ; 19(1): . doi:10.1121/1.4800361.

3aBAb5. Ultrasound intensity to propel stones from the kidney is below the threshold for renal injury

Yak-Nam Wang*, Julianna C. Simon, Bryan Cunitz, Frank Starr, Marla Paun, Denny Liggitt, Andrew Evan, James McAteer, James Williams, Ziyue Liu, Peter Kaczowski, Ryan Hsi, Mathew Sorensen, Jonathan Harper, and Michael R. Bailey

Abstract

Therapeutic ultrasound has an increasing number of applications in urology, including shockwave lithotripsy, stone propulsion, tissue ablation, and hemostasis. However, the threshold of renal injury using ultrasound is unknown. The goal of this study was to determine kidney injury thresholds for a range of intensities between diagnostic and ablative therapeutic ultrasound. A 2 MHz annular array generating spatial peak pulse average intensities (ISPPA) up to 28,000 W/cm² in water was placed on the surface of in vivo porcine kidneys and focused on the adjacent parenchyma. Treatments consisted of pulses of 100 μ s duration triggered every 3 ms for 10 minutes at various intensities. The perfusion-fixed tissue was scored by 3 blinded independent experts. Above a threshold of 16,620 W/cm², the majority of injury observed included emulsification, necrosis and hemorrhage. Below this threshold, almost all injury presented as focal cell and tubular swelling and/or degeneration. These findings provide evidence for a wide range of potentially therapeutic ultrasound intensities that has a low probability of causing injury. While this study did not examine all combinations of treatment parameters of therapeutic ultrasound, tissue injury appears dose-dependent.

INTRODUCTION

The clinical uses of ultrasound (US) span diagnostic to therapeutic applications, including diagnostic/therapeutic hybrids. This broad range of applications is due to the variety of bioeffects that can be elicited in tissue. Therefore, patient safety needs to be carefully evaluated for these individual applications. One such new application involves using US to expel renal calculi (Shah 2010, 2012). We have reported the use of a custom research device to expel calculi from the kidney (Shah 2012), and are currently modifying a diagnostic/therapeutic US hybrid for clinical trials. In the therapeutic mode, the maximum total energy that can be produced by the new device is approximately half that of current lithotripters. Due to the damage that has been observed with shockwave lithotripsy (SWL), the goal of this study was to evaluate the thresholds of kidney tissue injury when treated with US spanning from traditional diagnostic to therapeutic levels such as SWL or high intensity focused ultrasound (HIFU) at 2 MHz in the kidney. It was hypothesized that the levels required to push renal calculi using the new custom diagnostic/therapeutic hybrid are well

*Corresponding author's address: Applied Physics Laboratory, University of Washington, Seattle, WA 98102, ynwang@u.washington.edu.

below the thresholds that would result in kidney injury and that injury would be dose dependent.

METHODS

The renal parenchyma of domestic swine were treated in vivo following a protocol approved by the Institutional Animal Care and Use Committee at the University of Washington. A total of 28 female pigs weighing 101–141 lbs were used in this study. After the US transducer was positioned on a surgically exposed kidney, the renal parenchyma was targeted and treated. The settings used for each exposure were randomly selected at each treatment spot. With a fixed duty cycle of 3.3%, treatment intensities ranged from 0–28,000 W/cm². Up to seven distinct locations were treated in each kidney. During treatment, the B-mode image was examined for evidence of any hyperechoic areas, which were noted. After each exposure the kidney was inspected, and the treatment location marked with histology ink. Any visible damage was noted.

The kidneys were perfusion-fixed in situ before removing for routine histological evaluation (Shao 2003). Individual treatment locations as indicated by the histology ink, and control tissues were embedded separately. Perfusion-fixed tissue were embedded in paraffin, and sections were stained with Haematoxylin and Eosin (H&E) and periodic acid Schiff (PAS). Stained slides from treated and control samples were randomized and reviewed by three independent experienced reviewers blinded to the experimental conditions. Samples were considered to have no injury (negative) if there was no evidence of injury, background damage, or at most, minor damage (e.g proteinuria). Samples were considered to be positive for injury if they showed significant injury (e.g, hemorrhage, emulsification, degeneration, coagulative necrosis). The proportion of positive samples for each particular treatment setting was determined.

RESULTS

The proportion of samples that show injury versus the special peak pulse averaged intensity (I_{SPPA}) at a duty cycle of 3.3% is presented in Fig. 1. The threshold for a significant proportion of samples to demonstrate tissue injury is greater than 16,620 W/cm². The majority of injury observed above this threshold intensity included emulsification, necrosis and hemorrhage. Lesion size was on the order of millimeters. Below this threshold, the probability that injury was observed remained constant at less than 0.2. Almost all injury observed below the threshold presented as focal cell and tubular swelling and/or degeneration.

DISCUSSION AND CONCLUSIONS

These findings provide evidence for a wide range of potentially therapeutic ultrasound intensities that have a low probability of causing injury. A higher probability of injury and more significant injury was histologically observed at intensities greater than 16,620 W/cm², which is approximately the intensity of shockwave lithotripsy pulses. While this study did not examine all combinations of treatment parameters of therapeutic ultrasound, tissue

injury appears dose-dependent. At 3.3% duty cycle, the intensity range required to propel kidney stones ($<2,500 \text{ W/cm}^2$) lies well below the $16,620 \text{ W/cm}^2$ threshold.

ACKNOWLEDGMENTS

This work was supported by the National Institute of Health (DK43881, DK092197) and the National Space Biomedical Research Institute through the National Aeronautics and Space Administration NCC 9–58. The authors would also like to thank the staff and researchers at the Center for Industrial and Medical Ultrasound (CIMU).

REFERENCES

- Shah A, Harper JD, Cunitz BW, Wang YN, Paun M, Simon JC, Lu W, Kaczowski PJ, Bailey MR. Focused ultrasound to expel calculi from the kidney. *J Urol*. 2012; 187(2):739–743. [PubMed: 22177202]
- Shah A, Owen NR, Lu W, Cunitz BW, Kaczowski PJ, Harper JD, Bailey MR, Crum L. A Novel ultrasound method to reposition kidney stones. *Urol Res*. 2010; 38(6):491–495. [PubMed: 20967437]
- Shao Y, Connors BA, Evan AP, Willis LR, Lifshitz DA, Lingeman JE. Morphological changes induced in the pig kidney by extracorporeal shock wave lithotripsy: nephron injury. *Anat Rec*. 2003; 275A:979–989.

FIGURE 1.

Proportion of the samples that show injury versus the derated spatial peak pulse averaged intensity I_{SPPA} . All exposures were at 3.3%. Markers indicate the mean $\pm$ s.d.