ISTU 2016

Program Booklet

The 16th International Symposium on Therapeutic Ultrasound

March 14–16, 2016
Dan Panorama Hotel, Tel Aviv, Israel

www.istu.org

61 FEASIBILITY OF TRANSCUTANEOUS VOLUMETRIC BOILING HISTOTRIPSY ABLATION OF LIVER AND KIDNEY IN A PIG MODEL

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OBJECTIVES

Boiling histotripsy (BH) uses millisecond-long pulses of HIFU shock waves emitted at low duty cycle to induce localized boiling in tissue within each pulse. Further interaction of ultrasound with the vapor cavity for the rest of the pulse results in mechanical fractionation of tissue into subcellular debris. Our group is developing BH as a non-invasive treatment of renal and hepatic masses. The feasibility of producing single BH lesions *in vivo* in an exposed porcine liver has been demonstrated previously. The goal of the present work was to evaluate the feasibility and safety of transcutaneous, volumetric BH ablation of porcine liver and kidney in acute pig studies.

METHODS

Pigs (37-40 kg, n=4) were anesthetized and placed on the surgical table in either lateral (for kidney treatment) or supine (for liver treatment) position. A 1.5 MHz HIFU transducer (12-element sector array of 7.5 cm aperture, F#=1.07) with a central opening (2 cm) to allow for ultrasound treatment guidance was attached to a 3D positioning system and submerged in a degassed water bath coupled to the abdomen (Figure 1). The HIFU focus position, pre-recorded with the ultrasound imaging system, was aligned with the targeted region at the depth of 2.5-4.5 cm from the skin surface. The pulse-average power output threshold for initiating BH at each location was measured by sonicating the focal point with BH pulses at gradually increasing amplitude until a hyperechoic region was observed at the focus, indicating boiling. Prior to the *in vivo* experiments, similar measurements of threshold output power were performed in freshly harvested *ex vivo* porcine liver and kidney for comparison to the transcutaneous *in vivo* setting. The subsequent *in vivo* sonications were performed slightly above the threshold (10-15% increase in driving voltage). The following treatment parameters were used: pulse duration 5 or 10 ms, pulse repetition frequency (PRF) 1 or 2 Hz (with the duty factor fixed at 1%). A total of 10-30 pulses were delivered per focal point (this number will be further referred to as BH dose), with the focal points spaced 1-1.5 mm apart in a rectangular grid with 0.5-1.5 cm linear dimensions. The BH treatment was not gated by or synchronized with the respiratory motion. Following BH exposure, higher resolution ultrasound assessment of the treated regions was conducted. Necropsy was then performed and the treated portions of the liver and the kidneys were collected for gross and histologic assessment.

RESULTS

Kidney treatments. Lower poles of 7 kidneys were targeted and n=11 volumetric lesions containing cortex, medulla, and renal sinus were created. The transducer driving voltage required to initiate the subcostal transcutaneous treatment in the kidneys was 30 – 50% higher than that observed in the exposed *ex vivo* tissue; the partially transcostal exposures (30-40% of the beam obstructed by the ribs) required 120-150% larger driving voltage. The respiration-induced motion of the target did not appreciably interfere with the treatment Post-BH, higher resolution ultrasound images revealed well-defined hypoechoic cavities. At necropsy no gross evidence of collateral damage was appreciated within the beam path and no subjects had gross hematuria. On gross inspection of the kidney, small clots were seen within the collecting system in all treated kidneys with regions of petechial hemorrhage surrounding a centrally located fractionated volume of parenchyma. Histologically, all BH exposures produced completely fractionated cortex sharply demarcated from histologically normal untreated tissue (Figure 2). In the medulla, blood was noted within the collecting ducts with areas of focally fractionated tissue at higher dose exposures (20-30 pulses per focal spot). Within the wall of the collecting system, focal petechial hemorrhage was visualized only at the higher dose exposures without disruption of the wall.

A treatment acceleration strategy was attempted, in which a smaller number (10 vs 30) of shorter (5 ms vs 10 ms) pulses were delivered per focal spot at higher PRF (2 Hz vs 1 Hz) at a larger driving voltage (15% increase). This strategy reduced the overall treatment time 6-fold (resulting in the lysis rate of 3.8 cc/hour), yet achieved the same degree of tissue fractionation as found with the slower treatment.

Liver treatments. Subcostal BH lesions were successfully produced in two out of three livers where treatment was attempted. The threshold for treatment initiation in terms of driving voltage was larger than in the *ex vivo* porcine liver by 70-200% and was also larger than in the transcutaneous kidney exposures despite very similar treatment depth and body wall thickness.

Most probably, the higher thresholds arose from the aberrative effects of fat within the HIFU beam, as the central section of the body wall contained a much thicker fat layer compared to that overlying the kidney (1.5 cm vs 0.5 cm). The respiration-induced motion of the target was much more pronounced compared to the case of kidney treatments, and led to a noticeable spread of the lesion relative to the planned shape. The hepatocytes in the central region of the lesion were completely fractionated, while at the lesion periphery the treatment effect was less demarcated. Connective tissue structure of the liver lobules, as well as the liver capsule remained intact, consistent with our *ex vivo* findings (Figure 2). In the cases where higher power outputs were used (150-200% increase compared to the exposed *ex vivo* liver), bruising and thermal damage confined to the fatty layer of the body wall were observed.

CONCLUSIONS

These data indicate that transcutaneous and partially transcostal volumetric BH treatment of the kidney and liver is feasible in the porcine model. In the kidney, delivering shorter pulses at higher PRF and higher amplitude with constant duty cycle allowed for more rapid, yet equally efficacious tissue fractionation. In the liver, the lesions were successfully generated through a thicker fat layer, without control for respiratory motion. The treatment precision and efficacy can be further enhanced by implementing strategies for phase correction and gating based on respiratory motion. This work was supported by NIH R01 EB7643, K01 EB 015745, NSBRI through NASA NCC 9-58, and Urology Care Foundation.

Figure 1: 12-element 1.5 MHz HIFU sector array transducer integrated with an ultrasound imaging probe (ATL P7-4).

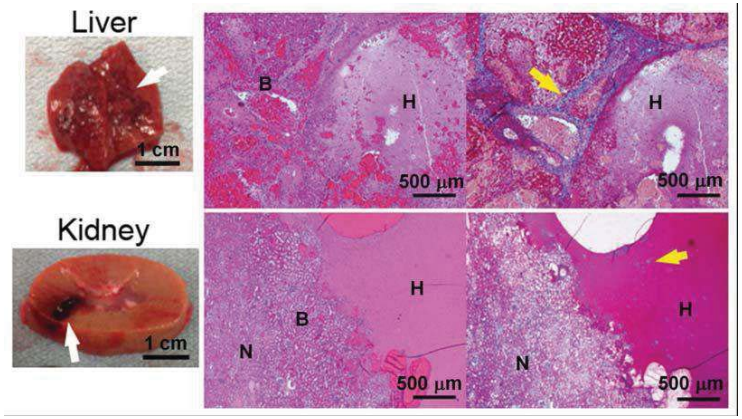

Figure 2: Representative photos (left) and tissue sections stained with hematoxylin and eosin (middle) and Masson's trichrome (right) of porcine liver (top) and kidney (bottom) tissue treated transcutaneously *in vivo*. Photos show bisected BH lesions (white arrows) with the contents washed out. Histological evaluation reveals regions of completely homogenized tissue (H). Within the lesion, intact collagenous structures (yellow arrow) were present in both organs treated. In the kidney, distinct borders with normal tissue (N) were observed. Small haemorrhagic regions (B) were present in both tissues within and around the border of the lesions.

62 NONINVASIVE, RAPID ABLATION OF LARGE TISSUE VOLUME USING HISTOTRIPSY

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OBJECTIVES

Current tumour ablation techniques are typically thermal-based, including radiofrequency (RF), microwave, and high intensity focused ultrasound (HIFU). RF and microwave ablation methods are limited to treating tumours no greater than 3 cm in diameter and at a rate of approximately 2 cm^3/minute. While HIFU is capable of treating larger volumes, the treatment duration is excessive. Perfusion-mediated convection (commonly referred to as the "heat sink effect") presents a major challenge for thermal ablation in highly vascularized tissues. The heat sink effect has been shown to prolong treatment times and result in heterogeneous tissue necrosis. Histotripsy is a noninvasive, non-thermal, ultrasound ablation method that uses high-amplitude, very low-duty cycle focused ultrasound pulses to generate controlled cavitation and thereby mechanically homogenize target tissues into liquid-appearing acellular debris. Our previous *in vivo* studies have shown that histotripsy is not affected by the heat sink effect and can produce homogenous tissue disruption in the highly vascular liver and kidneys noninvasively through the ribcage and other overlying tissues. Because histotripsy uses microsecond-duration pulses separated by up to seconds of off-time for a given focus, it is possible to electronically steer the focus of a phased array transducer to excite cavitation events throughout a large volume consisting of many overlapping foci during the off-time period. We hypothesize that histotripsy combined with electronic focal steering can achieve rapid ablation of a large target volume. As such, histotripsy can be used to treat tumours that cannot be treated by RF and microwave ablation at a rate exceeding that of these methods. This study presents the first investigation of this hypothesis.

METHODS

Histotripsy was applied using a 250 kHz, 256-element phased array transducer with a 30 cm diameter aperture and 15 cm focal distance, generating 1.5-cycle, 6-microsecond acoustic pulses. First, to establish treatment parameters including pulse repetition frequency (PRF) and the number of pulses to deliver, a single-focus lesion was generated in tissue-mimicking phantoms. Tissue-mimicking agarose hydrogel phantoms containing a layer of red blood cells (RBC) allow direct visualization of cavitation and cavitation-induced damage. Cavitation activity and lesion progression during histotripsy treatment were monitored by high-speed optical imaging (Phantom V210, Vision Research) as a function of PRF and the number of pulses applied. Based on the RBC phantom results, *ex vivo* bovine hepatic tissue was treated by electronically scanning the therapy focus at 200 Hz over 1000 sites (or .2 Hz per focal site). 120 pulses were delivered per site to cover approximately 43 cm^3 and 58 cm^3 volumes of target tissue (equivalent to spheres 4.3 cm and 4.8 cm in diameter, respectively) over the course of a total treatment time of 10 minutes. The *in situ* peak rarefactional pressure amplitude was estimated to be 71 MPa at the geometric focus and 49 MPa at the most distal electronic steering foci. Lesion size and morphology were assessed by gross sectioning and magnetic resonance imaging (MRI). Tissue damage was examined by histology using haematoxylin and eosin (H&E) staining of 5-micron sections.