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Spatial specificity and sensitivity of passive cavitation imaging for monitoring high-intensity focused ultrasound thermal ablation in ex vivo bovine liver

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Abstract

Passive cavitation images (PCIs) generated from scattered acoustic waves are a potential technique for monitoring lesion formation during high-intensity focused ultrasound (HIFU) thermal ablation. HIFU lesion prediction by PCIs was assessed in ex vivo bovine liver samples (N=14) during 30-s sonications with 1.1-MHz continuous-wave ultrasound (1989 W/cm² estimated spatial-peak intensity). Treated samples were sectioned, optically scanned, and the HIFU lesions segmented based on tissue discoloration. During each insonation, a 192-element, 7-MHz linear array (L7/Iris 2, Ardent Sound) passively recorded emissions from a plane containing the HIFU propagation axis oriented parallel to the image azimuth direction. PCIs were formed from beamformed A-lines filtered into fundamental, harmonic, ultraharmonic, and inharmonic frequency bands. Lesion prediction was tested using binary classification of local tissue ablation based on thresholded PCIs, with spatial specificity and sensitivity of lesion prediction quantified by the area under receiver operating characteristic curves (AUROC). Tadpole-shaped lesions were best predicted by harmonic emissions (AUROC=0.76), prefocal lesions were best predicted by harmonic or ultraharmonic emissions (AUROC=0.86), and cigar-type focal lesions were best predicted by fundamental and harmonic emissions (AUROC=0.65). These results demonstrate spatial specificity and sensitivity when predicting HIFU lesions with PCIs.

Background

Cavitation detection has long been recognized as an important tool in the study of the interaction of ultrasound with microbubbles (Atchley *et al.*, 1988; Roy *et al.*, 1990). Passive cavitation detection is particularly attractive because it minimizes interactions between the measurement system and the microbubble activity of interest. Therefore, many biomedical acoustics experiments incorporate a passive cavitation detector (PCD) (Coussios and Roy, 2008). The vast majority of experiments have used single-element passive cavitation detectors. This approach has played a role in elucidating mechanisms related to sonothrombolysis (Everbach and Francis, 2000; Prokop *et al.*, 2007; Datta *et al.*, 2008; Maxwell *et al.*, 2009; Hitchcock *et al.*, 2011), sonophoresis (Tang *et al.*, 2002; Tezel *et al.*, 2002; Tezel and Mitragotri, 2003), drug and gene release and delivery (Newman and

Bettinger, 2007; Hernot and Klibanov, 2008; Zhou *et al.*, 2008; Wu and Nyborg, 2008; Evjen *et al.*, 2011), thermal ablation (ter Haar and Coussios, 2007; Mast *et al.*, 2008; Nandlall *et al.*, 2011), and hemostasis (Poliachik *et al.*, 2004). However, the single-element PCD approach is limited by the necessary trade-off between good spatial specificity (i.e., knowing where emissions originate) and spatial sensitivity (i.e., being able to detect over a large area). Focused single-element PCDs provide good spatial specificity, whereas unfocused single-element PCDs have a larger region over which they are sensitive. To overcome this limitation, several recent investigators have developed and implemented passive cavitation imaging (Gyöngy *et al.*, 2008; Farny *et al.*, 2009; Salgaonkar *et al.*, 2009; Haworth *et al.*, 2012; Jensen *et al.*, 2012).

Passive cavitation images (PCIs) play an analogous role to single-element passive cavitation detection as B-mode ultrasound images are to A-line ultrasound. To form PCIs, an array passively records cavitation emissions with each element of the array. The emissions are beamformed to create an image. The basic beamforming algorithm is delay-and-sum using the time-of-flight from the spatial coordinates of a pixel to each element in the array. The resulting signal is processed in the temporal or Fourier domain to obtain a value that is used as the pixel amplitude. Gyöngy *et al.* (2008) and Salgaonkar *et al.* (2009) both provide a more detailed explanation of the algorithm in the time-domain and single-frequency domain, respectively. Haworth *et al.* (2012) used a Fourier-domain approach to investigate how the therapeutic ultrasound pulse shape affects image resolution and found minimal dependence. All PCI studies have shown relatively poor axial resolution compare to B-mode ultrasound.

Jensen *et al.* (2012) demonstrated the feasibility of monitoring the presence of lesions in *ex vivo* bovine livers formed by high-intensity focused ultrasound (HIFU) thermal ablation. The authors placed the passive cavitation array inline with the HIFU array. This arrangement provided a very practical geometry for future *in vivo* measurements. However, in this geometry the long axial spatial extent of the HIFU focus was concomitant with the poor axial PCI resolution. This overlap limited the ability to study the spatially resolved prediction of HIFU lesions. The present study was designed to test the hypothesis that PCIs can predict the spatial extent of HIFU lesions in the azimuthal direction of the PCI.

Materials & Methods

Fourteen HIFU lesions were formed in fresh *ex vivo* bovine liver samples, each measuring $6 \times 6 \times 10 \text{ cm}^3$. Lesions were formed by 40 W HIFU exposures with a 30 s duration. The exposures were continuous-wave with a center frequency of 1.1 MHz (H101, Sonic Concepts, Woodenville, WA, USA). Aligned confocally but perpendicularly to the HIFU transducer was an L7 imaging array connected to an Iris 2 imaging system (Arden Sound, Mesa, AZ, USA) (figure 1). Care was taken to align the face of the bovine liver sample 5 mm closer to the HIFU transducer than the edge of the L7 array. This configuration placed the HIFU focus approximately 6 mm proximal to the center of both the liver sample and space over which the passive cavitation images would be formed (figure 1). Careful alignment also allowed for co-registration of the PCI and HIFU lesion. The ultrasound transducers and tissue container were placed in degassed and deionized water with a dissolved oxygen content below 25%. The water was maintained at room temperature

(22°C). All liver samples were used within 4 hours *post mortem*. Prior to exposure, samples were kept on ice. Just prior to exposure, each sample was excised from the liver and placed in an acrylic container with Tegaderm windows facing both the HIFU transducer and imaging array. The bottom of the container was flat and care was taken to orient the bottom of the container to be parallel to the L7 imaging plane (i.e., in the plane of the page in figure 1). Air bubbles between the sample and container walls were minimized by adding a small amount of degassed phosphate-buffered saline and gently tapping the container. The saline was degassed to approximately 40% of saturation to minimize the likelihood of cavitation in the saline.

After exposure, the samples were transferred to an acrylic box without windows to maintain the tissue shape and placed in a -80 °C freezer. After freezing overnight, the samples were sliced parallel to the bottom of the container, which should be parallel to the image plane. Slices were $6 \times 6 \text{ cm}^2$ and 1.2–1.5 mm thick. The slicing was performed rapidly enough for the samples to remain frozen and maintain their geometry. The frozen slices were placed on the bed of an optical scanner. Samples were allowed to thaw. After thawing, images of the slices were taken at a resolution of 1500 dpi (pixel size $16.9 \mu\text{m}$). Lesions were automatically segmented based on a grayscale pixel amplitude threshold. The threshold was determined by manually segmenting a subset of the lesions and finding the pixel amplitude threshold that best replicated the area of the manually segmented lesions. The edges of the liver were also noted on the image to determine the location of the lesion relative to the ultrasound transducers.

Acoustic emissions from the liver tissue were passively recorded throughout each exposure by the L7 imaging array and Iris 2 system. The L7 imaging array parameters and passive cavitation imaging algorithms have been previously described by Salgaonkar *et al.* (2009). A uniform time-gain compensation was applied across the image depth. Beamformed radiofrequency A-lines were formed by the Iris 2 system by synthetically focusing acoustic emissions received by 64-element subapertures of the L7 array. Emissions synthetically focused at 9 discrete depths, covering the range 0–56 mm, were concatenated to synthesize 192 A-line signals per image with a line spacing equal to the array element pitch (0.22 mm). Each A-line was recorded at a 33.3 MHz sampling rate by a PC-based data acquisition system (Compuscope CS 14100, Gage Applied Technologies, Lachine, Quebec, Canada). At this sampling rate, the beamformed signal from each focal zone comprised 276 time-points. Each data set included 9 consecutive frames captured at a 28-Hz frame rate. Approximately 3 s was required for each data set to be transferred to memory before the next data set could be recorded. Therefore, during each 30 s HIFU exposure, 10 data sets were recorded.

To form PCIs, power spectra of the beamformed acoustic emissions from each focal zone, separated by approximately 7 mm, were estimated. For each PCI pixel location, the 276-point waveforms from the corresponding focal zone were windowed. The temporal window was designed to ensure that spectral leakage half-way between neighboring ultraharmonics and harmonics would be 85 dB below the signal peaks at the neighboring ultraharmonics and harmonics. The windowed signals were Fourier transformed using a 3333-point fast Fourier transform (FFT) for each of the 9 frames in a data set. The magnitude-squared FFTs of these 9 frames were averaged to produce a single power spectrum for each pixel location.

The power spectra for the 10 data sets per liver sample were summed to obtain the cumulative cavitation dose.

Because the fifth focal zone of the PCI contained the focus of the HIFU array, PCI cross sections at this depth were compared with the segmented tissue lesions. One-dimensional PCIs were formed by summing energy in bands 330-kHz wide and centered at the fundamental, harmonics, ultraharmonics, or inharmonics (e.g., broadband components not in a previously mentioned frequency band). The inharmonic bands were centered about the point halfway between an ultraharmonic and the nearest harmonic located at a frequency less than the ultraharmonic. The energy in the first 13 inharmonic, harmonic, and ultraharmonic bands were summed, respectively, to obtain a representation of each of these types of emission. One-dimensional lesion maps were formed as projections of the segmented tissue maps described above. Receiver operating characteristic (ROC) curves were computed to assess prediction of local tissue lesioning from the local magnitude of PCIs formed from each frequency band. ROC curves are a means for assessing the ability of a binary classification system. In this study, the PCI pixel amplitudes were used to predict normal or lesioned tissue based on a pixel amplitude threshold value. A positive prediction (i.e. prediction of lesion formation) at a given location was based on the pixel amplitude for a given location being larger than the threshold value. Conversely a negative prediction (i.e. prediction of no lesion formation) was made when the pixel amplitude at a location was less than the threshold value. The true positive rate and true negative rate were computed as the fraction of predictions that were confirmed to be correct by the optical scan data. The threshold was varied from the lowest to highest PCI pixel amplitudes and the true positive rate was plotted against the true negative rate for all threshold values to form the ROC curve. ROC curves were computed from all fourteen exposures grouped together, as well as exposures classified by lesion type. The lesion types were classified based on the common HIFU lesion descriptions of focal, tadpole, and prefocal (Watkin *et al.*, 1996; Kennedy *et al.*, 2003; Coussios *et al.*, 2007). Figure 2 shows typical examples of each lesion type. Note that each lesion type can be classified based on its location and spatial extent in the HIFU axial direction. Focal lesions are nominally centered about the HIFU focus. Tadpole lesions typically have their most distal point near the HIFU focus and extend towards the HIFU transducer. Prefocal lesions are entirely proximal to the HIFU focus.

Results

Six focal lesions, five tadpole lesions and three prefocal lesions were observed. Two vertical lines are shown in each panel, demarcating the axial -3 dB beamwidth of the HIFU array. Focal lesions consistently had a smaller area than tadpole or prefocal lesions.

Figure 3 shows typical spectra for the three emission cases observed. The first case was composed only of the fundamental and its harmonics. The second case had ultraharmonics, in addition to the fundamental and harmonics, but did not have inharmonics. These emissions are associated with stable cavitation. The third case included fundamental, harmonic, ultraharmonic, and inharmonic emissions. The increase at the inharmonics in the red line in figure 3 is due to broadband emissions, indicating inertial cavitation occurred.

Table 1 lists the area under the ROC curve for each emission type. The results are shown for all 14 trials combined (i.e. not classifying by lesion type) and for each individual lesion type. The null hypothesis that the area under the ROC curve is not different than 0.5 was tested using the equation for the standard error given by Hanley and McNeil (1982) and computing a Z-score from the standard error using the equation given by Krzanowski and Hand (2009). The p-values are shown in Table 2. In all cases the area under the ROC is greater than 0.5, demonstrating that the PCIs positively predicted the spatial extent of the lesion. However, for the focal lesion, only the fundamental and harmonic emissions are significant at an α of 0.001. Focal lesions were best predicted by harmonic and fundamental emissions. Tadpole lesions were predicted with approximately equal quality by all emission types. Prefocal lesions were best predicted by harmonic and ultraharmonic emissions.

Discussion

Differences in the ability of PCIs to predict the location of HIFU lesion formation is likely due to the nature of lesion formation. Focal lesions have been described as forming through absorption of ultrasound energy due to the intrinsic absorption coefficient of the tissue (Kennedy *et al.*, 2003). This mechanism does not rely on or postulate the presence of cavitation. Correspondingly, we note that PCIs of the fundamental and harmonic emissions best predicted focal lesion formation. These PCIs, may not have been cavitation images, but rather passive scattering images, as noted by Haworth *et al.* (2012). The scattered fundamental and harmonic emissions can arise from inhomogeneities in the tissue and the nonlinearity of the tissue for both propagation and scattering.

In contrast, tadpole and prefocal lesions are postulated to form in the presence of bubble activity (Watkin *et al.*, 1996; Coussios *et al.*, 2007). Tadpole lesions begin as focal lesions that form microbubbles or vapor cavities, which strongly reflect the incident ultrasound, shadowing the distal tissue and increasing acoustic energy deposition in the proximal tissue. The reflection of incident ultrasound energy results in the lesion growing towards the HIFU source. We postulate that the prefocal lesions observed in this study were the result of pre-existing microbubbles in the tissue. As the microbubbles were insonified, they both scattered and absorbed ultrasound energy, again shadowing distal tissue. The PCI results are consistent with this premise. The spatial extent of tadpole lesions is better predicted by PCIs than the spatial extent of focal lesions. PCIs predicted the spatial extent of prefocal lesions better than the spatial extent of either tadpole lesions or focal lesions. The spatial extent of tadpole lesions may not have been predicted as well as for prefocal lesions because some of the lesion formation occurred without cavitation.

While these results confirm the hypothesis of this study, that PCIs can predict the spatially resolved formation of HIFU lesions, there are several limitations relevant to future implementations. First, unlike Jensen *et al.* (2012) the geometry of the arrays used here is not practical for *in situ* monitoring of clinical HIFU applications. However, clinical use of a geometry similar to Jensen *et al.* (2012) would require passive cavitation imaging algorithms with improved axial resolution. Another limitation of this study is that no temporal analysis of the data was performed. The lack of temporal analysis was due to the fact that lesion formation could only be observed after treatment and not during. To use PCIs for image-

guided therapy, it will be necessary to test the real-time ability of PCIs to predict lesion formation and indicate when sufficient treatment has been applied. To test the temporally-resolved predictive ability of PCIs, experimental approaches will need to be developed that allow for real-time temporal monitoring of the lesions using a “gold standard” such as optical observation of a lesion in transparent tissue phantoms (Zhang *et al.*, 2011) or magnetic resonance thermometry (Bohris *et al.*, 1999). Ideally these experiments will be performed *in vivo* to minimize changes in tissue properties that affect ultrasound and cavitation.

Conclusion

We investigated the ability of passive cavitation images to predict lesion formation in *ex vivo* bovine liver samples. Lesions were formed by a 30 s HIFU exposure at 1.1 MHz. Cavitation emissions were recorded with an imaging array and beamformed using established procedures (Salgaonkar *et al.*, 2009). Comparison of the lesion location, as assessed optically, and the location of cavitation emissions, as assessed from PCIs, was performed using ROC curves. The area under the ROC curve was used to assess whether PCIs could predict the location of lesion formation. Prefocal and tadpole shaped lesions were best predicted using PCIs formed from harmonic and ultraharmonic emissions.

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Figure 1.

Diagram of experimental HIFU ablation and passive cavitation imaging setup as viewed from above.

Figure 2.

Images of bovine liver sample with representative lesions of the three classified types. Vertical black lines indicate the axial -3 dB beamwidth of the HIFU transducer. Left: focal lesion; center: tadpole lesion; right: prefocal lesion.

Figure 3.

Three power spectra observed for a given pixel. One spectra (black dashed line) is typical of fundamental and harmonic emission only. A second spectra (blue dotted line) shows a typically spectra when ultraharmonics are additionally observed. The third spectra (solid red line) shows a typical spectra with broadband, ultraharmonics, harmonics, and fundamental emissions.

Table 1

Area under the ROC curve by lesion type and cavitation emission type.

Emission Type	All Lesions	Focal Lesions	Tadpole Lesions	Prefocal Lesions
Fundamental	0.72	0.65	0.72	0.78
Harmonic	0.73	0.67	0.77	0.87
Ultraharmonic	0.63	0.55	0.66	0.86
Inharmonic	0.68	0.60	0.70	0.71

Table 2

p-values for the null hypothesis that the area under the ROC curve is not different from 0.5. p-values are listed by lesion type and cavitation emission type.

Emission Type	All Lesions	Focal Lesions	Tadpole Lesions	Prefocal Lesions
Fundamental	$p \ll 0.001$	$p = 0.0008$	$p \ll 0.001$	$p \ll 0.001$
Harmonic	$p \ll 0.001$	$p \ll 0.001$	$p \ll 0.001$	$p \ll 0.001$
Ultraharmonic	$p \ll 0.001$	$p = 0.0755$	$p \ll 0.001$	$p \ll 0.001$
Inharmonic	$p \ll 0.001$	$p = 0.0022$	$p \ll 0.001$	$p \ll 0.001$