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● *Original Contribution*

USING PASSIVE CAVITATION IMAGES TO CLASSIFY HIGH-INTENSITY FOCUSED ULTRASOUND LESIONS

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Abstract—Passive cavitation imaging provides spatially resolved monitoring of cavitation emissions. However, the diffraction limit of a linear imaging array results in relatively poor range resolution. Poor range resolution has limited prior analyses of the spatial specificity and sensitivity of passive cavitation imaging in predicting thermal lesion formation. In this study, this limitation is overcome by orienting a linear array orthogonal to the high-intensity focused ultrasound propagation direction and performing passive imaging. Fourteen lesions were formed in *ex vivo* bovine liver samples as a result of 1.1-MHz continuous-wave ultrasound exposure. The lesions were classified as focal, "tadpole" or pre-focal based on their shape and location. Passive cavitation images were beamformed from emissions at the fundamental, harmonic, ultraharmonic and inharmonic frequencies with an established algorithm. Using the area under a receiver operating characteristic curve (AUROC), fundamental, harmonic and ultraharmonic emissions were found to be significant predictors of lesion formation for all lesion types. For both harmonic and ultraharmonic emissions, pre-focal lesions were classified most successfully (AUROC values of 0.87 and 0.88, respectively), followed by tadpole lesions (AUROC values of 0.77 and 0.64, respectively) and focal lesions (AUROC values of 0.65 and 0.60, respectively). (E-mail: kevin.haworth@uc.edu) © 2015 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Thermal ablation monitoring, Passive acoustic mapping, Cavitation, Receiver operating characteristic curve, Ultrasound-guided ablation.**

INTRODUCTION

The pace of development of clinical applications of high-intensity focused ultrasound (HIFU) thermal ablation has increased over the last 10 years. Clinical trials with successful outcomes have been reported in the treatment of cancer (Liberman et al. 2009; Ng et al. 2011; Wu et al. 2004; Xu et al. 2011), neurologic disorders (Elias et al. 2013; Jeanmonod et al. 2012) and uterine fibroids (Kim et al. 2012; Voogt et al. 2012). Concurrent with these successes have been the development and implementation of methods for predicting when and where a lesion has formed.

The inability to monitor lesion formation remains a limitation (Zhou 2011). Currently, magnetic resonance imaging (MRI) thermometry and B-mode ultrasound are used clinically to predict lesion formation (Aubry et al. 2013). MRI thermometry can accurately and quantitatively determine the temperature rise from HIFU, but necessitates the use of both an expensive MRI system and MRI-compatible HIFU arrays (Chapman and ter Haar 2007; Köhler et al. 2009; Tempany et al. 2003). Additionally, MRI thermometry in fatty tissues is difficult because of the differing response of adipose and aqueous media to temperature (Merckel et al. 2013; Rieke and Butts Pauly 2008). With the growing obesity epidemic in developed countries (Alwan 2011), this current limitation may become more problematic. B-Mode ultrasound relies on feedback from boiling bubbles in tissue, which is an indicator of overtreatment (Yu and Xu 2008). Therefore, alternate methods for image guidance of HIFU thermal ablation are desirable.

HIFU-induced acoustic cavitation accelerates tissue heating (Coussios et al. 2007). This observation has motivated the use of cavitation detection as a means of monitoring HIFU thermal ablation. One commonly used approach is single-element passive cavitation detection. Passive cavitation detectors (PCDs) monitor cavitation

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emissions induced by a separate therapy transducer. PCDs can be used to monitor the different types of cavitation, which can result in mechanistically different forms of heating (Holt and Roy 2005). Stable cavitation, often characterized by harmonic emissions (*i.e.*, multiples of the fundamental insonation frequency) or ultraharmonic emissions (*e.g.*, odd multiples of one-half the fundamental insonation frequency), can cause viscous heating. Inertial cavitation can cause heating via absorption of broadband emissions, which are observed by the PCD as energy in the inharmonic frequency bands (*i.e.*, bands that exclude the fundamental, harmonic and ultraharmonic frequencies).

Single-element PCDs are limited by the trade-off between spatial sensitivity and specificity. A focused single-element transducer has a relatively small detection region over which it is sensitive. Cavitation emissions that occur outside of the sensitive region will not be detected. Focused single-element PCDs thus exhibit good spatial specificity, but poor spatial sensitivity. Unfocused, single-element PCDs suffer from the opposite limitation. The detection region is relatively large, making them sensitive to a large spatial volume. However, the precise origin of the detected cavitation emissions is unknown, and thus, unfocused single-element PCDs exhibit poor spatial specificity. This limitation is problematic because the HIFU pressure varies substantially as a function of location. Similarly, large temperature gradients are observed in the ablated medium. Hence, the concomitant bubble activity exhibits significant spatial variations.

Passive cavitation detection using ultrasound imaging arrays has been described as a means of overcoming the limitations of single-element PCDs. Array-based PCDs allow cavitation emissions recorded by individual elements of the array to be beamformed. This beamforming enables spatial specificity and sensitivity. In many ways, the advantages of array-based PCDs over single-element PCDs are analogous to those of array-based B-mode ultrasound imaging over single-element A-mode detection. Gyöngy et al. (2008), Salgaonkar et al. (2009) and Farny et al. (2009) all described similar time-domain approaches to forming passive cavitation images (alternatively referred to as passive acoustic maps). The differences in their techniques derived in large part from the capabilities of the ultrasound imaging array systems they employed. More recently, Haworth et al. (2012) used a Fourier-domain approach to demonstrate that the imaging resolution is determined by diffraction and not the ultrasound pulse shape and duration.

Jensen et al. (2012) have reported on the use of passive cavitation images and B-mode images to predict the formation of thermal lesions in *ex vivo* bovine liver. Passive cavitation images were used to monitor cavitation energy (either broadband or harmonic) in a 10×10 mm^2 window centered about the HIFU focus. The total energy was used to predict whether a lesion formed. However, the location of the lesion within the window was not determined. Jensen et al. (2012) found that at peak negative insonation pressures above 5.4 MPa, passive cavitation imaging was superior to B-mode imaging for the rate of correctly predicting whether a lesion was formed (accuracy of 84% vs. 53%), the proportion of lesions that were correctly predicted (sensitivity of 85% vs. 48%) and the proportion of negative predictions that were correct (negative predictive value of 53% vs. 24%). These results support the feasibility of passive cavitation imaging for monitoring if a lesion forms, but they do not address whether passive cavitation imaging can be used to resolve where a lesion forms.

The objective of this study was to assess the ability of passive cavitation imaging to predict HIFU thermal ablation lesion formation quantitatively. This objective was pursued using an established passive cavitation imaging algorithm (Salgaonkar et al. 2009) and modifying the transducer arrangement of Jensen et al. (2012). Passive cavitation images were compared with optical images after exposure to HIFU. The ability to use passive cavitation imaging to predict where a lesion formed was assessed using receiver operating characteristic (ROC) curves. The sensitivity and specificity of predicting both the presence and spatial extent of HIFU lesions were determined. This analysis is a crucial step toward the development of cavitation-based non-invasive image-guided feedback for HIFU therapies.

METHODS

Ablation procedure

The overall experimental setup can be seen in Figure 1 and has been described in detail by Salgaonkar (2009). As highlighted in previous studies, passive cavitation images obtained with diagnostic linear arrays provide millimeter to sub-millimeter resolution in the azimuthal direction, but significantly poorer resolution along the range direction (Gyöngy and Coussios 2010; Haworth et al. 2012; Salgaonkar et al. 2009). Therefore, an orthogonal orientation between the HIFU therapy transducer and passive imaging array was implemented. Although this geometry is not practical for some clinical applications because of the available acoustic windows, the geometry allowed for good passive cavitation imaging resolution along the axial length of the thermal ablation lesion. For the L7 linear array (Ardent Sound, Mesa, AZ, USA) used in this study, the azimuthal and range resolutions based on the diffraction pattern of the linear array at the center of the passive cavitation images at 1.1 MHz were 1.5 and 9.7 mm, respectively (Chen and McGough 2008; Haworth et al. 2012; McGough 2004).