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● *Original Contribution*

REAL-TIME SPATIOTEMPORAL CONTROL OF HIGH-INTENSITY FOCUSED ULTRASOUND THERMAL ABLATION USING ECHO DECORRELATION IMAGING IN *EX VIVO* BOVINE LIVER

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Abstract—The ability to control high-intensity focused ultrasound (HIFU) thermal ablation using echo decorrelation imaging feedback was evaluated in *ex vivo* bovine liver. Sonications were automatically ceased when the minimum cumulative echo decorrelation within the region of interest exceeded an ablation control threshold, determined from preliminary experiments as –2.7 (log-scaled decorrelation per millisecond), corresponding to 90% specificity for local ablation prediction. Controlled HIFU thermal ablation experiments were compared with uncontrolled experiments employing two, five or nine sonication cycles. Means and standard errors of the lesion width, area and depth, as well as receiver operating characteristic curves testing ablation prediction performance, were computed for each group. Controlled trials exhibited significantly smaller average lesion area, width and treatment time than five-cycle or nine-cycle uncontrolled trials and also had significantly greater prediction capability than two-cycle uncontrolled trials. These results suggest echo decorrelation imaging is an effective approach to real-time HIFU ablation control. (E-mail: doug.mast@uc.edu) © 2017 World Federation for Ultrasound in Medicine & Biology. All rights reserved.

Key Words: **Echo decorrelation imaging, High-intensity focused ultrasound, Thermal ablation, Real-time control.**

INTRODUCTION

Local thermal ablative techniques have been reported to be an effective treatment for nonresectable hepatocellular carcinoma and colorectal metastases in liver (van Sonnenberg et al. 2005), offering potential tumor control and, in some cases, long-term, disease-free survival. However, use of these techniques to treat tumors located near major blood vessels while avoiding blood vessel injury remains difficult (Ng et al. 2004). High-intensity focused ultrasound (HIFU) can cause coagulative necrosis at a precise focal point within the tissue without harming overlying and adjacent structures, even those within the beam path (Zhang et al. 2009), providing sufficient residual liver tissue for patient survival (Aubry et al. 2013). HIFU has been employed to treat unresectable liver cancer in thousands of cases in China (Luo et al. 2015).

Imaging modalities are needed for real-time monitoring of tissue changes during HIFU thermal ablation. Magnetic resonance-guided HIFU (MRg-HIFU) and ultrasound-guided HIFU (USg-HIFU) are the most commonly used platforms for HIFU treatment guidance and control. MRg-HIFU has been used for monitoring and control of thermal ablation using real-time MR thermometry (Bohris et al. 1999; Bour et al 2017; Darkazanli et al. 1993; Hynynen and McDannold 2004; Hynynen et al. 1993). However, MR imaging increases treatment complexity and cost (Napoli et al. 2013; Zhou 2011). USg-HIFU is more portable and inexpensive, and its high frame rate and real-time capability potentially make it more capable of ablating moving organs (e.g. liver (Kennedy et al. 2004; Wu et al. 2004) and kidney (Illing et al. 2005; Klingler et al. 2008)).

Various monitoring algorithms have been developed to detect HIFU-induced thermal lesioning based on ultrasound pulse-echo imaging, including B-mode (Gudur et al. 2012; Vaezy et al. 2001), M-mode (Kumon et al. 2012), backscatter (Chen et al. 2011; Seip et al. 2002; Shishitani et al. 2013), echo strain imaging (Souchon et al. 2005), harmonic motion imaging (HMI) (Grondin et al. 2015; Han et al. 2015; Yang et al. 2017), elastography (Iwasaki et al. 2016) and acoustic radiation force imaging

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(Lizzi et al. 2003). All these methods aim to provide feedback on the progress of thermal treatment and to confirm the completeness of ablation. However, these methods are sensitive to errors caused by the formation of microbubble clouds at the ablation site (Varghese et al. 2004), the complex non-linear dependence of tissue acoustic and viscoelastic properties on temperature (Suomi et al. 2016) and decorrelation of the backscattered signal caused by tissue motion (Curiel et al. 2009), bubble activity (Casper et al. 2013; Kumon et al. 2012) and heat-induced changes in tissue structure (Hooi et al. 2015; Kruskal et al. 2001; Majaron et al. 1999).

Echo decorrelation imaging (Fosnight et al. 2017; Mast et al. 2008; Matsuzawa et al. 2012; Sasaki et al. 2014; Subramanian et al. 2014) potentially overcomes these errors by using heat-induced, millisecond-scale echo variations to spatially map thermal lesioning during HIFU thermal ablation. Echo decorrelation imaging has been successfully validated for prediction of *in vivo* HIFU thermal lesioning in normal and VX2 rabbit tumor liver tissue (Fosnight et al. 2014, 2017).

Real-time feedback control algorithms for HIFU therapy based on pulse-echo ultrasound imaging have been tested in previous research (Curiel et al. 2009; Seip et al. 2002; Sugiyama et al. 2015; Takagi et al. 2016), to reduce treatment time and to enhance ablation accuracy (Al-Bataineh et al. 2012). Curiel et al. (2009) evaluated the feasibility of using localized HMI to monitor and control HIFU ablation in VX2 rabbit tumors *in vivo*. Treatments were automatically stopped if the localized harmonic motion amplitude at the focus dropped below a specified amplitude threshold in two consecutive measurements. This algorithm was able to successfully control ablation in 69% of the trials; echo decorrelation associated with tissue state changes and motion was considered a source of error. Similarly, Sugiyama et al. (2015) used real-time localized motion imaging (LMI) as a feedback method to control HIFU thermal lesion length in porcine liver. Their feedback control system successfully provided lesion lengths close to their target (8–12 mm) with a root-mean-square error (RMSE) of 2.51 mm. However, errors were found in the estimated lesions' size, and overtreatment occurred because of system delay after ceasing the HIFU sonication. Qu et al. (2016) improved the LMI method by employing a dynamic cross-correlation window, which decreased the RMSE of the estimated coagulation length to 1.69 mm during porcine liver ablation ($N = 49$), but increased processing time for displacement estimation from 2.05 ± 0.05 to 2.64 ± 0.36 s for 28 A-mode scan lines.

Recently, Takagi et al. (2016) developed an approach for real-time monitoring and control of HIFU treatment based on cross-correlation of ultrasound signals, similar to echo decorrelation imaging. The cross-correlation coefficient between echo signals, calculated between the target frame and the first (reference) frame, was used to detect thermal coagulation during HIFU treatments in chicken breast. HIFU exposures were automatically terminated when the average cross-correlation coefficient within a focal region of interest (ROI) fell below a predetermined threshold. Feedback-controlled, HIFU-treated samples were found to be more homogeneously coagulated compared with uncontrolled cases. However, they noted that further investigation is needed to determine the optimum coagulation threshold and to increase the monitoring frame rate for better detection of tissue changes in the presence of motion, boiling and cavitation. In addition, their approach of cross-correlating with a fixed, pretreatment reference frame may not be amenable to control of *in vivo* HIFU ablation, where motion-induced decorrelation can be large (Fosnight et al. 2017; Subramanian et al. 2014).

In the research reported here, the feasibility of controlling HIFU thermal ablation using 2-D echo decorrelation imaging was assessed with a view toward *in vivo* implementation. The echo decorrelation imaging approach employed here tracks changes in echo signals over millisecond-scale intervals, potentially providing more robust control than cross-correlation with a fixed reference frame. The main goals of this research were to (i) implement an automated control algorithm based on realtime echo decorrelation imaging, (ii) determine the optimum echo decorrelation threshold for HIFU control, (iii) test the algorithm in *ex vivo* bovine liver experiments and (iv) statistically assess the effect of control on thermal lesioning results.

METHODS

In this section, the materials and methods for a series of experiments on controlled ablation of *ex vivo* liver tissue are discussed. In these experiments, both HIFU ablation and echo decorrelation imaging were performed using a linear, 5-MHz image-treat array, with treatments ceased after echo decorrelation exceeded a pre-determined threshold throughout the focal region of interest. Figure 1 (a, b) provides an overview of the experimental setup.

Echo decorrelation feedback control algorithm

To control HIFU ablation using echo decorrelation imaging, a real-time, closed-loop control algorithm was developed. This algorithm was integrated with a realtime imaging application used to compute B-mode and echo decorrelation images from beamformed radiofrequency (RF) echo signals acquired immediately after each sonication pulse, during the rest period of the HIFU transducer, as illustrated in Figure 1 (d).

Figure 1 (c) is a flowchart of the control algorithm. Echo decorrelation images, comprising maps of the local