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***In vivo* thermal ablation monitoring using ultrasound echo decorrelation imaging**

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Abstract

Previous work has shown ultrasound echo decorrelation imaging can track and quantify changes in echo signals to predict thermal damage during *in vitro* radiofrequency ablation (RFA). In the *in vivo* studies reported here, the feasibility of using echo decorrelation imaging as a treatment monitoring tool is assessed. RFA was performed on a normal swine liver ($N = 5$) and ultrasound ablation using image-ablate arrays was performed on a rabbit liver implanted with VX2 tumors ($N = 2$). Echo decorrelation and integrated backscatter were computed from Hilbert transformed pulse-echo data acquired during RFA and ultrasound ablation treatments. Receiver operating characteristic (ROC) curves were employed to assess the ability of echo decorrelation imaging and integrated backscatter to predict ablation. Area under the ROC curves (AUROC) was determined for RFA and ultrasound ablation using echo decorrelation imaging. Ablation was predicted more accurately using echo decorrelation imaging (AUROC 0.832 and 0.776 for RFA and ultrasound ablation respectively) than using integrated backscatter (AUROC 0.734 and 0.494).

Keywords

Echo decorrelation imaging; therapy monitoring; bulk ultrasound ablation; radiofrequency ablation

INTRODUCTION

Thermal ablation is a treatment of choice for unresectable tumors within the liver, kidneys, and other organs (Dupuy et al., 2000; Gervais et al., 2005). Thermal ablation involves application of energy at the tumor site causing heating in the tissue, thereby resulting in coagulative necrosis of the tumor. Common thermal ablation methods include radiofrequency ablation (RFA), ultrasound ablation, laser ablation, and microwave ablation (Murakami et al., 1995; Rhim and Dodd, 1999; Kennedy et al., 2004; Caspani et al., 2010). RFA has been shown to be effective for the treatment of unresectable liver tumors clinically

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(Curley et al., 1999; Solbiati et al., 2001; Tateishi et al., 2005), offering several advantages over surgical resection, such as reduced morbidity, costs, and hospital stays (Livraghi et al., 2008). Ultrasound ablation methods, including high intensity focused ultrasound (HIFU) and bulk ultrasound ablation, have also shown potential for clinical applications (Yang et al., 1991; Illing et al., 2005; Mast et al., 2005, 2011).

Treatment monitoring and probe placement for thermal ablation can be performed using magnetic resonance imaging (MRI) (Hynynen and McDannold, 2004), ultrasound (Chiou et al., 2007), or x-ray computed tomography (CT) (Dupuy et al., 2000). While MRI has shown great potential for monitoring thermal ablation, being capable of accurate temperature monitoring and control (Smith et al., 2001; Hynynen and McDannold, 2004; Arora et al., 2005; McDannold, 2005), use of MRI increases treatment complexity and cost, and additionally requires use of MR-ablation compatible ablation tools (Boaz et al., 1998; Vigen et al., 2006).

Ultrasound imaging offers a real-time, portable and inexpensive alternative. Ultrasound imaging is currently used clinically in RFA for probe placement and treatment guidance (Chiou et al., 2007). However, ultrasound imaging by itself offers limited treatment monitoring capability, tracking only changes in the image brightness or tissue echogenicity. Often tissue necrosis is not visualized due to low contrast between the ablated and unablated regions or artifacts caused by microbubble formation at the ablation site, resulting in over- or under-prediction of treated regions (Solbiati et al., 1999; Cha et al., 2000; Leyendecker et al., 2002).

Methods tracking deformation of ultrasound echoes, such as echo strain imaging (Souchon et al., 2005), elastography (Varghese et al., 2002), and acoustic radiation force imaging (Fahey et al., 2006) have shown potential for treatment monitoring. However, these methods are sensitive to errors caused by the formation of microbubble clouds at the ablation site (Solbiati et al., 1999; Leyendecker et al., 2002), tissue motion (Chandrasekhar et al., 2006) and by echo decorrelation (Miller et al., 2002; Varghese et al., 2004) caused by bubble activity and other tissue changes.

Echo decorrelation imaging is a real-time pulse-echo method that potentially uses these degradations in signals to map thermal ablation. Heat-induced tissue changes during thermal ablation are monitored by tracking millisecond-scale changes in echo signals, quantified by the local signal decorrelation. These changes in the echo signals are tracked over the duration of a thermal ablation treatment to produce a cumulative echo decorrelation map. Echo decorrelation imaging has shown potential for predicting tissue damage during RFA of *ex vivo* tissue (Mast et al., 2008). However, echo decorrelation imaging is more challenging *in vivo* because of potential decorrelation artifacts due to respiratory motion, cardiac motion and perfusion.

In this paper, echo decorrelation imaging is tested *in vivo* for both RFA and ultrasound ablation treatments. The predictive ability of echo decorrelation imaging is assessed by quantitatively comparing echo decorrelation with gross tissue histology using receiver operating characteristic (ROC) curves. For comparison, the integrated ultrasound backscatter is also computed (Arthur et al., 2005; Zhong et al., 2007) and its predictive ability is assessed in a manner similar to echo decorrelation imaging (Mast et al., 2008).

MATERIALS AND METHODS

Echo decorrelation imaging was tested using pulse-echo data recorded during *in vivo* RFA and ultrasound ablation experiments. Methods used for the experiments, image formation,

and data analysis are detailed below for RFA experiments performed in porcine liver and for ultrasound ablation experiments performed using image-ablate arrays in rabbit liver with a VX2 tumor model. All animal experiments were performed according to protocols approved by the University of Cincinnati Institutional Animal Care and Use Committee (IACUC).

Theory

The echo decorrelation imaging algorithm previously described in Mast (2008) and Mast and Subramanian (2010) is implemented here with some minor changes. Let the function $p(\mathbf{r}, t)$ represent a pulse-echo frame consisting of a collection of beamformed echo signals in complex radiofrequency (Hilbert-transformed) form acquired at time t , where $\mathbf{r}$ is the spatial position vector within the image plane. The function $p(\mathbf{r}, t + \tau)$ represents pulse-echo image frame acquired at a later time $t + \tau$, where τ is the inter-frame time.

A spatio-temporal cross-correlation function between the two sequential complex pulse-echo image frames separated by time τ is defined as

$$R_{01}(\mathbf{r}, t) = \langle p(\mathbf{r}, t) p^*(\mathbf{r}, t + \tau) \rangle, \quad (1)$$

where $\langle \cdot \rangle$ represents a two-dimensional convolution with a Gaussian mask

$$\langle f(\mathbf{r}) \rangle = f(\mathbf{r}) \otimes e^{-|\mathbf{r}|^2/2\sigma^2}, \quad (2)$$

where σ is a width parameter.

Similarly, the autocorrelation functions $R_{00}(\mathbf{r}, t)$ and $R_{11}(\mathbf{r}, t)$ are defined here as

$$R_{00}(\mathbf{r}, t) = \langle |p(\mathbf{r}, t)|^2 \rangle \text{ and } R_{11}(\mathbf{r}, t) = \langle |p(\mathbf{r}, t + \tau)|^2 \rangle \quad (3)$$

respectively, which can be regarded as maps of integrated backscattered energies at times t and $t + \tau$. A integrated backscatter term can thus be defined as

$$\beta(\mathbf{r}, t) = \sqrt{R_{00}(\mathbf{r}, t) R_{11}(\mathbf{r}, t)}. \quad (4)$$

An echo decorrelation map is then defined as

$$\Delta(\mathbf{r}, t) = 2 \frac{\beta^2(\mathbf{r}, t) - |R_{01}(\mathbf{r}, t)|^2}{\beta^2(\mathbf{r}, t) + \beta^2(t)}, \quad (5)$$

where the function $\overline{\beta^2(t)}$ represents the spatial mean value of $\beta^2(\mathbf{r}, t)$ from Eq. (4). The echo decorrelation function was normalized by this denominator because normalization by $\beta^2(\mathbf{r}, t)$ alone was found to cause artifactually high decorrelation in the regions of low echogenicity, while normalization by the function $\beta^2(\mathbf{r}, t)$ caused artifacts in regions of high echogenicity (Mast et al., 2008). The normalization in Eq. (5) results in a more uniform echo decorrelation map. The resulting echo decorrelation map is zero in regions where the image is unchanged and maximum in regions where local echo changes are greatest. Finally, because the echo decorrelation map defined by Eq. (5) also varies stochastically in time, a temporal running average was employed to provide a better estimate of local changes in the scattering medium (Mast et al., 2008). The temporal running average employed is given by

$$\overline{\Delta}(\mathbf{r}, t_i) = (1 - \varepsilon) \overline{\Delta}(\mathbf{r}, t_{i-1}) + \varepsilon \Delta(\mathbf{r}, t_i), \quad (6)$$

where t_i is the time of the current (i^{th}) echo decorrelation image frame and ε is a user-defined parameter ($0 < \varepsilon < 1$) that determines the effective length of temporal averaging.

Echo Decorrelation Imaging Implementation

Echo decorrelation algorithm described above was implemented on the pulse-echo data acquired during RFA and ultrasound ablation. Ultrasound imaging was performed by the Iris 2 ultrasound imaging and ablation system (Guided Therapy Systems, Mesa, AZ) (Barthe et al., 2004). Throughout each treatment, echo signals were recorded from the Iris system using a 14-bit, PC-based A/D converter (CompuScope CS 14200, Gage Applied Technologies, Montreal, Quebec, Canada) at a sampling rate of 33.3 MHz and stored. The acquired echoes were then processed in MATLAB (MathWorks, Natick, MA) to form B-mode, integrated backscatter, and echo decorrelation images as described below. For each recorded pulse-echo frame pair, echo signals were bandpass filtered using the Gaussian filter defined by

$$G(f) = e^{-\frac{(f-f_0)^2}{2\alpha^2}}, \quad (7)$$

where f_0 is the center frequency and α is the bandwidth. This filter also implicitly performs a Hilbert transform to form analytic echo signals. B-mode (brightness mode) images were obtained by logarithmically scaling the echo envelopes (absolute value of the complex analytic echo signals) $|p(\mathbf{r}, t)|$ with a displayed dynamic range of 60 dB.

To compute echo decorrelation and integrated backscatter images, the cross-correlation and autocorrelation functions $R_{01}(\mathbf{r}, t)$, $R_{00}(\mathbf{r}, t)$, and $R_{11}(\mathbf{r}, t)$ were computed using Eqs. (1) and (3). Spatial integration was implemented by Eq. (2), using a Gaussian window with width parameter $\sigma = 2.5$ mm. The time- and position-dependent echo decorrelation was then computed using Eq. (5) and smoothed by the running average of Eq. (6) with $\varepsilon = 0.05$. To form cumulative echo decorrelation maps, the temporal maximum of the resulting echo decorrelation was recorded at each pixel location.

To form integrated backscattered images, the integrated backscatter computed using Eq. (4) was smoothed temporally using a running-average smoothing filter similar to Eq. (6). The relative integrated backscatter was defined as the decibel-scaled ratio between the cumulative integrated backscatter and the integrated backscatter computed before treatment (Mast et al., 2008):

$$\text{IBS}(\mathbf{r}, t) = 10 \cdot \log_{10} \left(\frac{\beta(\mathbf{r}, t)}{\beta(\mathbf{r}, 0)} \right), \quad (8)$$

where β is the integrated backscatter function defined by Eq. (4). Relative integrated backscatter maps were formed from the temporal maxima of $\text{IBS}(\mathbf{r}, t)$ at each pixel location. Hybrid integrated backscatter maps were formed for display by overlaying these relative integrated backscatter maps over the B-mode image frames.

Radiofrequency Ablation

RFA experiments were performed within a normal porcine liver *in vivo* for $N = 5$ treatments. The experimental setup for the treatments is shown in Fig. 1(a). The swine was anesthetized and its liver was exposed via laparotomy. RFA was performed using a 2.0 cm RF needle electrode (LaVeen, Boston Scientific, Boston, MA), which was inserted into the liver. Treatments were performed in left, medial, and right lobes of the liver. Two grounding pads were placed on the back of the pig. A low noise 1 mm thermocouple (GKMQSS, Omega Engineering, Stamford, CT) was also inserted near the RF needle electrode to record local tissue temperature during treatment. For each treatment, the RF needle electrode was driven

by an RF generator (RF 2000B, Radio Therapeutics, Mountain View, CA). The power supplied and time duration used for all RFA treatments are shown in Table 1.

A 192-element, 7 MHz linear ultrasound array (L7, Guided Therapy Systems, Mesa, AZ) was positioned on the porcine liver such that its image plane included the RF needle electrode and the thermocouple. The ultrasound array position on the liver was marked using an electrocautery device. In each acquisition, 384 echo signals, comprising a pulse-echo image frame pair, were acquired at intervals of 0.85 ± 0.05 s. These echoes were then filtered by the Gaussian bandpass filter from Eq. (7) with a center frequency 7.36 MHz and a bandwidth of 1 MHz, resulting in a pair of complex analytic pulse-echo image frames with dimensions $42.2 \times 30.5 \text{ mm}^2$, separated by an inter-frame time of 19.6 ms (inverse of the system frame rate, 51 Hz). For treatment 1, pre-treatment data (ultrasound imaging only) were acquired immediately before RFA treatment at the same position. To compare echo decorrelation images with and without ablation treatment, the pre-treatment data were analyzed over a duration equal to the subsequent RFA treatment.

After all the treatments were performed, the liver was excised and the animal was sacrificed. To maintain tissue shape for accurate registration with B-mode images, the excised liver lobes were frozen in a -80°C freezer and then sliced parallel to the image plane as indicated by the electrocautery marks. Tissue sections were scanned on a flatbed scanner (CanoScan 8800F, Canon, Tokyo, Japan) at 800 dpi ($32 \mu\text{m}$) resolution. For direct comparison with echo decorrelation and integrated backscatter images in each case, scanned tissue sections were oriented and registered to ultrasound images using tissue boundaries and visible probe tracks as spatial references. To test the utility of echo decorrelation and integrated backscatter imaging in predicting ablation, the treated region was segmented based on gross discoloration of the tissue (ImageJ, National Institute of Health, Bethesda, MD), with all pixels within the lesion boundary defined as ablated and the rest defined as unablated.

To assess the effect of tissue motion on echo decorrelation imaging, echo decorrelation images were recomputed using motion gating. To this end, a $5 \pm 5 \text{ mm}^2$ region of interest (ROI) was selected for each trial from an unablated region where minimal echo decorrelation was observed. The first frames within all acquired frame pairs were selected for analysis. The Pearson product moment correlation was used to compute the correlation coefficient of the echo signals within the ROI for all the selected frames sequentially. Fig. 2 shows a representative plot of Pearson product moment correlation performed between echoes within the ROI for sequentially selected frames separated by 0.85 ± 0.05 s. The temporal interval between two peaks of the correlation coefficient plot was found to be ~ 6 s. The correlation coefficient plot suggests that the pulse-echo frames are correlated for a portion of the respiratory cycle and severely uncorrelated for the remainder.

To perform motion gating, echo decorrelation was computed using only frame pairs containing selected frames with correlation coefficients greater than 0.6. This threshold choice omitted only the frames which were severely uncorrelated, due to substantial tissue motion. Similar to the computations of echo decorrelation without motion gating, a temporal running average was performed using Eq. (6) and cumulative echo decorrelation maps were formed from the temporal-maximum echo decorrelation at each pixel location.

To assess the ability of echo decorrelation to delineate between ablated and unablated region, paired *t*-tests was performed between the mean (spatially averaged) cumulative echo decorrelation within the ablated and unablated regions at the end of treatment, with and without motion gating. Differences in echo decorrelation were assessed for statistical significance using the criterion $p < 0.05$. One-tailed *p*-values were employed to assess the

significance of any increase in echo decorrelation caused by tissue ablation, as well as any decrease in echo decorrelation caused by motion gating.

The time-dependent measured echo decorrelation during the RFA treatments was also compared with the temperature simultaneously measured by thermocouple. As the precise location of the thermocouple was not known in all cases, for comparison of tissue temperature with echo decorrelation, the spatial maximum of the running-average echo decorrelation was determined at each time point. The spatial maximum of the echo decorrelation was then temporally interpolated to synchronize with the temperature recordings from the thermocouple. To determine if echo decorrelation is correlated with tissue temperature, the Pearson correlation coefficient was computed between the measured temperature and the log-scaled, spatial-maximum echo decorrelation, using all temporal data points from the five trials. When testing statistical significance of the correlation between echo decorrelation and tissue temperature, the number of independent samples was conservatively estimated as the number of temporal data points multiplied by the running-average parameter $\varepsilon = 0.05$ from Eq. (6).

Ultrasound Ablation

Ultrasound ablation and imaging were performed using a 3 mm diameter, 32 element miniaturized image-ablate array probe on a rabbit liver with implanted VX2 tumors for $N = 2$ treatments, within a series of *in vivo* experiments described previously (Mast et al., 2011). VX2 tumor fragments were implanted in separate liver lobes 11 days before the experiment was performed. At the time of the ablation experiments, the tumors had grown to about 1 cm diameter.

For the ablation experiments, the rabbit was anesthetized and its liver exposed. The image-ablate array was inserted into a balloon through which cooling water was circulated. The probe assembly was placed on the liver lobe surface proximal to the VX2 tumor and fixed by a 3D positioning arm, as shown in Fig. 1(b). Acoustic coupling was implemented between the probe and liver surface using phosphate buffered saline (PBS) and confirmed using ultrasound imaging from the image-ablate array. Continuous-wave, 4.8 MHz ultrasound was fired from the entire 32-element array in an unfocused beam with spatial-average, temporal-average intensity 38.5 W/cm^2 . Treatment cycles, consisting of 8.5 s continuous-wave sonication followed by 1.5 s of imaging by the same array, were repeated for exposure durations of 1.5–2.0 min. The exposure conditions used for the ultrasound ablation treatments are shown in Table 2.

In each acquisition 32 echo signals were acquired at a frame rate of 16 Hz. The echoes were then filtered by the Gaussian bandpass filter from Eq. (7) with a center frequency 4.8 MHz and a bandwidth of 0.3 MHz to form complex analytic echo signals. To assess the effect of disturbances such as tissue motion on echo decorrelation imaging, pre-treatment pulse-echo data were similarly acquired immediately before each ablation treatment, at the same probe position. Cumulative echo decorrelation images were computed from pre-treatment data with durations matching the corresponding ablation treatments.

Echo decorrelation and integrated backscatter were computed using Eqs. (4) and (5) from consecutive frames of pulse-echo data, with an inter-frame time of 60 ms, obtained during the 1.5 s quiescent periods between each sonication cycle. A temporal running average was performed using Eq. (6).

After the treatments were completed, the animal was sacrificed. The liver was then excised, sectioned along the image plane at the array location, and stained with triphenyl tetrazolium chloride (TTC) vital stain. Tissue sections were scanned and registered in a manner similar

to the RFA treatments. Tissue sections were segmented, mapping regions of treatment based on the local TTC uptake and registered to ultrasound images using visible tissue boundaries and anatomic landmarks.

To test whether echo decorrelation imaging could delineate between the ablated and unablated regions in the ultrasound ablation experiments, a paired *t*-test was performed between mean cumulative echo decorrelation values for the ablated and unablated regions ($N=2$ trials).

Receiver operating curve analysis

In order to test prediction of ablation by echo decorrelation imaging and integrated backscatter, for both RFA and ultrasound ablation, receiver operating characteristic (ROC) curves were employed (Mast et al., 2008; Krzanowski and Hand, 2009). In this analysis, treatment outcomes were predicted using echo decorrelation and integrated backscatter thresholds, so that all the spatial points exceeding a threshold were predicted to be ablated, and the rest unablated. Using pixel-by-pixel comparison of cumulative echo decorrelation and integrated backscatter images with corresponding segmented tissue maps, prediction success was determined for each pixel as a function of the threshold. ROC curves, defined as the true-positive rate (sensitivity) vs. the false-positive rate ($1 - \text{specificity}$), were then plotted for prediction of ablation. Area under the ROC curve (AUROC) was determined to assess the utility of echo decorrelation and integrated backscatter to predict ablation. An AUROC of 1 indicates that the treated region was classified perfectly, while an AUROC of 0.5 means that the classification was no better than chance.

The positive and negative predictive values (PPV and NPV) were computed for all decorrelation and integrated backscatter thresholds. The PPV indicates the proportion of positive outcomes (local tissue ablation) that were correctly classified, while the NPV indicates the proportion of negative outcomes (tissue locally unablated) that were correctly classified. Optimal decorrelation and integrated backscatter thresholds for prediction of local ablation were selected by using the thresholds yielding equal PPV and NPV.

Assessment of prediction success was performed for both RFA and ultrasound ablation by testing significance of the AUROC statistic using a general model for the AUROC standard error (Hanley and McNeil, 1982). In this analysis, effective sample sizes for each treatment outcome were conservatively estimated from the Gaussian window size used for the computation of echo decorrelation and integrated backscatter. For this calculation, the windows were considered independent when the spatial cross-correlation coefficient of two Gaussian windows, as defined in Eq. (2), was below 0.5. The distance between window centers for a correlation coefficient of 0.5 is $2\sqrt{2\log(2)}\sigma$. The effective number of treatment outcomes in each spatial region (ablated and unablated) was determined based on the maximum hexagonal packing density, which is given by $\pi/\sqrt{12}$ unit-diameter circles per unit-area rectangle. Similarly, to compare predictions using echo decorrelation with those using integrated backscatter, the significance of AUROC differences between echo decorrelation and integrated backscatter was also computed for both RFA and ultrasound ablation.

RESULTS

Figure 3 shows hybrid echo decorrelation maps, comprising echo decorrelation and B-mode images, for all ($N = 5$) *in vivo* RFA treatments. For each case, hybrid echo decorrelation maps are shown at the end of RFA treatment at the same location. Similar hybrid images are also shown for integrated backscatter at the end of RFA treatment. Also shown are the

corresponding segmented tissue sections, with the segmented ablated regions enclosed by dashed black lines. Qualitatively, higher echo decorrelation and integrated backscatter is observed in the ablated regions, while relatively lower echo decorrelation and integrated backscatter is observed in the unablated regions.

The temporal evolution of echo decorrelation during RFA treatment is illustrated by Fig. 4. Panel 4(a) shows the hybrid echo decorrelation maps plotted at 40 s into pretreatment, matching the duration of RFA treatment 1. Panels 4(b)–(f) show the hybrid echo decorrelation maps plotted after 20, 25, 30, 35 and 40 s RFA treatment, in the same image plane where the pretreatment data were acquired. While echo decorrelation was minimal in the ablated region, echo decorrelation due to tissue motion was elevated near the liver lobe boundaries during pretreatment. As the RFA treatment progressed, echo decorrelation increased in the ablated region. Echo decorrelation due to tissue motion similarly increased, however it was largely concentrated at the liver lobe boundaries.

For the ultrasound ablation trials, Fig. 5 shows hybrid echo decorrelation maps formed during at the end of pre-treatment imaging and at the end of ultrasound ablation treatment. Also shown are the corresponding segmented tissue sections, with segmented ablated regions enclosed by dashed black lines. The B-mode ultrasound images, produced during ultrasound ablation using the 32 element image-ablate array, were of low resolution compared to those produced using the 192 element L7 diagnostic array used for RFA experiments. At the end of pre-treatment imaging, some echo decorrelation is observed in the echo decorrelation images, possibly due to tissue motion. Similarly, Fig. 6 shows the hybrid integrated backscatter maps formed at the end of pre-treatment imaging and at the end of each ultrasound ablation treatment, along with corresponding segmented tissue sections.

Mean cumulative echo decorrelations in the ablated and unablated regions for all RFA treatments are given in Table 3. Figure 7(a) shows the mean and standard deviation of the cumulative echo decorrelation in the ablated and unablated regions of the tissue at the end of RFA treatment, with and without motion gating. For RFA, the mean cumulative echo decorrelation in the ablated region (0.1032 ± 0.0624) was significantly greater than the unablated region (0.0231 ± 0.0198) at the end of treatment ($t = 3.3497$, $p = 0.0143$). With motion gating, the mean echo decorrelation in the unablated region (0.0129 ± 0.0109) at the end of treatment was significantly reduced ($t = 2.5249$, $p = 0.0325$). The mean cumulative echo decorrelation in the ablated region at the end of treatment was also significantly reduced ($t = 2.7072$, $p = 0.0268$) relative to the ungated case (0.0545 ± 0.0308). Still, after motion gating, the mean cumulative echo decorrelation in the ablated region was significantly greater than in the unablated region ($t = 4.0148$, $p = 0.008$), with a greater relative difference compared to the non-gated case.

For the RFA case where pre-treatment images were available, the mean cumulative echo decorrelation in the ablated region at the end of treatment (0.0654) was substantially greater than the mean cumulative echo decorrelation (0.0209) in the same region after 40 s pre-treatment imaging. The mean cumulative echo decorrelation in the unablated region at the end of treatment (0.0174) was only marginally greater than the mean cumulative echo decorrelation (0.0161) after pre-treatment imaging of the same 40 s duration.

For ultrasound ablation, Fig. 7(b) shows the mean and standard deviation of the cumulative echo decorrelation in the ablated and unablated tissue regions at the end of pre-treatment imaging and at the end of ablation treatment for each case. The mean cumulative echo decorrelation in the ablated and unablated regions of the tissue for all treatments are given in Table 4. Similar to the RFA trials, the mean cumulative echo decorrelation at the end of

ablation treatment was greater in the ablated region (0.0637 ± 0.0048) than in the unablated region (0.0333 ± 0.0026), a statistically significant difference ($t = 19.46$, $p = 0.0163$). At the end of pre-treatment imaging, the mean cumulative echo decorrelation within the ablated region (0.0445 ± 0.0300) was greater than in the unablated region (0.0176 ± 0.0079), a statistically insignificant difference ($t = 1.7228$, $p = 0.1674$). The mean cumulative echo decorrelation at the end of treatment was greater in the ablated region when compared to the mean cumulative echo decorrelation in the same region after pre-treatment imaging of matching duration, but this difference was not statistically significant ($t = 1.0743$, $p = 0.2386$). Similarly, the mean echo decorrelation in the unablated region at the end of treatment was not significantly higher than at the end of pre-treatment imaging ($t = 4.2015$, $p = 0.0744$).

Computed ROC curves for the prediction of ablation are shown for both the RFA and ultrasound ablation experiments in Fig. 8. AUROC for RFA exposures was 0.8328 for prediction of ablation using echo decorrelation ($p \ll 10^{-13}$) and 0.7336 using integrated backscatter ($p = 4.7 \times 10^{-9}$). AUROC for ultrasound exposures was 0.7761 using echo decorrelation ($p = 0.0047$) and 0.4944 using integrated backscatter ($p = 0.5156$) for prediction of ablation. Although these AUROC statistics show comparable prediction performance for both sets of experiments for echo decorrelation imaging, statistical significance for the ultrasound exposures is lower because of the smaller effective sample size, with a conservative estimate of 19 independent predictions of treatment outcome, compared to 214 independent predictions for RFA exposures. AUROC values were significantly higher for ablation prediction using echo decorrelation imaging, compared to prediction using integrated backscatter, for both RFA ($p = 0.0020$) and ultrasound ablation ($p = 0.0041$) cases.

Optimal echo decorrelation thresholds for ablation prediction, corresponding to equal positive predictive value (PPV) and negative predictive value (NPV), were 0.1555 for RFA and 0.0096 for ultrasound ablation. PPV and NPV at the optimum decorrelation threshold were 0.750 for RFA and 0.730 for ultrasound ablation. Optimal integrated backscatter thresholds for ablation prediction were 14.80 dB for RFA and 7.9228 dB for ultrasound ablation respectively. The corresponding PPV and NPV at the optimal integrated backscatter thresholds were 0.730 for RFA and 0.318 for ultrasound ablation.

Fig. 9 shows a scatter plot of the thermocouple-measured tissue temperature vs. the spatial-maximum, running-average, log-scaled echo decorrelation, measured simultaneously throughout the RFA treatments. This scatter plot indicates a nonlinear relationship between echo decorrelation and tissue temperature. Although there is an apparent monotonically increasing relationship between echo decorrelation and tissue temperature, the rate of increase in echo decorrelation is not the same for all treatments. However, the instantaneous tissue temperature and echo decorrelation were correlated across all treatments with high statistical significance ($r = 0.3227$, $p = 5.19 \times 10^{-23}$). The modest correlation between echo decorrelation and temperature may be partially due to the lack of precise knowledge of the thermocouple location. Also, nonthermal factors such as gas activity and tissue motion may cause substantial echo decorrelation, complicating any relationship between local echo decorrelation and tissue temperature.

DISCUSSION

Echo decorrelation imaging has previously shown potential for monitoring thermal ablation *in vitro* (Mast et al., 2008). The feasibility of ultrasound echo decorrelation imaging as a treatment monitoring tool for *in vivo* thermal ablation and its possible limitations are discussed below.

Possible causes of echo decorrelation during thermal ablation may include structural changes, vaporization, and dissolution of gas that occur in tissue during coagulative necrosis. In the case of ultrasound ablation, another possible source of echo decorrelation is bubble activity associated with acoustic cavitation. Performing thermal ablation *in vivo* introduces possible sources of artifactual echo decorrelation, including unsteady perfusion, tissue motion and respiration-induced tissue motion.

Respiratory tissue motion is an important source of error for ultrasound-based treatment monitoring methods, including echo decorrelation imaging. The relative importance of tissue motion as a source of artifactual echo decorrelation can be assessed from the motion gating test reported here. For thermal monitoring of *in vivo* RFA, motion gating significantly reduced the mean cumulative echo decorrelation in both ablated and unablated regions. However, with or without motion gating, the mean cumulative echo decorrelation in the ablated region was significantly greater than in the unablated region. This suggests that for the imaging configuration employed here, with pulse-echo image frames separated by about 20 ms, ablation-induced echo decorrelation dominated any artifactual decorrelation caused by tissue motion alone. Uncertainty caused by tissue motion could be reduced by use of a higher imaging frame rate, potentially eliminating the need for motion gating.

The ROC curves (Fig. 8) plotted for both RFA and ultrasound ablation are indicative of the ability of echo decorrelation imaging to classify ablated and unablated tissue regions. The relatively high AUROC values found for both ultrasound ablation and RFA, together with the high positive and negative predictive values obtained at optimum echo decorrelation thresholds, indicate the utility of echo decorrelation for prediction of local ablation. AUROC values for ultrasound ablation, while statistically significant for RFA, showed less predictive power than echo decorrelation. In the case of ultrasound ablation, integrated backscatter predicted ablation no better than chance. In both RFA and ultrasound cases, AUROC values for echo decorrelation imaging were significantly greater than those for integrated backscatter. This is consistent with previous results on prediction of *ex vivo* tissue ablation by RFA (Mast et al., 2008).

An important future step toward clinical thermal ablation monitoring is implementation of echo decorrelation imaging in real time. The high positive and negative predictive values obtained for both RFA and ultrasound ablation show the potential of echo decorrelation imaging for real-time prediction of heat-induced thermal damage, with applications in thermal ablation monitoring and control. Computation of echo decorrelation images requires only a few arithmetic and filtering operations applied to beamformed ultrasound echo signals, comparable to processing performed by current imaging systems for conventional B-mode and color Doppler imaging. Thus, implementation of real-time echo decorrelation imaging on clinical pulse-echo scanners would require no additional hardware and relatively modest software modifications.

As thermal ablation is an intrinsically three-dimensional problem requiring precision for the destruction of a tumor in its entirety, a 3D treatment guidance and monitoring modality is desirable. Since echo decorrelation images are computed directly from the same pulse-echo data used for 3D B-mode imaging, this method can potentially be implemented on any 3D ultrasound imaging system with sufficiently high frame rate with low computational cost. This would ultimately allow detailed real-time, 3D monitoring and control of any clinical thermal ablation procedure.

CONCLUSION

The results shown demonstrate the utility of echo decorrelation imaging for predicting tissue thermal damage during *in vivo* thermal ablation. Significantly higher mean cumulative echo decorrelation was observed in ablated tissue regions compared to unablated regions for both RFA and ultrasound ablation treatments, indicating the ability of echo decorrelation to delineate between ablated and unablated regions. For *in vivo* RFA, motion gating reduced the mean echo decorrelation significantly. However, with or without motion gating, the mean cumulative echo decorrelation was significantly greater in the ablated than in the unablated region. This result suggests that echo decorrelation can delineate between ablated and unablated regions in presence of motion related artifacts. Higher AUROC values were obtained for both RFA and ultrasound ablation using echo decorrelation imaging than using relative integrated backscatter, despite limitations including tissue motion and the low resolution of the image-ablate array used for ultrasound ablation. Together, these results indicate the feasibility of echo decorrelation imaging as a tool for monitoring *in vivo* thermal ablation.

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(a)

(b)

Fig. 1. Experimental configurations. (a) Radiofrequency ablation of porcine liver. The ultrasound probe is shown resting on the liver, with the thermocouple and RF probe inserted into the liver in the ultrasound image. (b) Ultrasound ablation of rabbit liver, with the probe assembly resting on the liver.

Fig. 2.
Representative Pearson product moment correlation coefficient of the RF echo data within the ROI for treatment number 3.

Fig. 3. Hybrid echo decorrelation and integrated backscatter images for all RFA treatments. (a) Echo decorrelation at end of treatment. (b) Integrated backscatter at end of treatment. (c) Tissue sections corresponding to the ultrasound image plane, with the ablated region enclosed by dashed black lines. Results for treatment numbers 1 through 5 are shown in rows (1) through (5), respectively.

Fig. 4.

Hybrid echo decorrelation images for RFA treatment 1. (a) After 40 s pretreatment. (b) After 20 s treatment. (c) After 25 s treatment. (d) After 30 s treatment. (e) After 35 s treatment. (f) After 40 s treatment.

Fig. 5. Echo decorrelation images for all ultrasound treatments. (a) End of pre-treatment imaging. (b) End of the ultrasound ablation treatment. (c) Tissue sections corresponding to the ultrasound image plane, with the ablated region enclosed by dashed black lines. Results for treatment numbers 4 and 6 are shown in rows (1) and (2), respectively.

Fig. 6. Integrated backscatter images for all ultrasound treatments. (a) End of pre-treatment imaging. (b) End of the ultrasound treatment. (c) Tissue sections corresponding to the ultrasound image plane, with the ablated region enclosed by dashed black lines. Results for treatment numbers 4 and 6 are shown in rows (1) and (2), respectively.

(a)

(b)

Fig. 7.

Bar graphs showing the mean and standard deviation of cumulative echo decorrelation in ablated and unablated regions. (a) Decorrelation at the end of RFA treatment, with and without motion gating. (b) Decorrelation for ultrasound ablation, at the end of pre-treatment imaging and at the end of ultrasound ablation treatment.

(a)

(b)

Fig. 8. Receiver operating characteristic curves for accuracy of ablation prediction. (a) RFA. (b) Ultrasound ablation.

Fig. 9. Scatter plot of spatial maximum, temporal running-average echo decorrelation map vs. simultaneous thermocouple-measured tissue temperature for all time points from 5 RFA trials.

Table 1

Exposure conditions for $N = 5$ *in vivo* RFA treatments performed in porcine liver.

Treatment number	Liver lobe	Power (W)	Duration (s)
1	Left	60	40
2	Medial	31	170
3	Right	25	175
4	Left	25	343
5	Right	26	165

Table 2

Exposure conditions for $N = 2$ *in vivo* ultrasound ablation experiments performed in rabbit liver with VX2 tumor.

Treatment number	Liver lobe	Intensity (W/cm ²)	Duration (s)
4	Left	38.5	95
6	Right	38.5	120

Table 3

Results summary for $N = 5$ *in vivo* RFA treatments in porcine liver.

Treatment	Mean cumulative echo decorrelation			
	End treatment		End treatment (gated)	
number	Unablated	Ablated	Unablated	Ablated
1	0.0174	0.0654	0.0096	0.0407
2	0.0511	0.1054	0.0269	0.0705
3	0.0026	0.0550	0.0017	0.0457
4	0.0094	0.0808	0.0045	0.0175
5	0.0351	0.2095	0.0217	0.0979
Mean	0.0231	0.1032	0.0129	0.0545
Std. dev.	0.0198	0.0624	0.0109	0.0308

Table 4

Results summary for $N = 2$ *in vivo* ultrasound ablation treatments in rabbit liver with VX2 tumor.

Treatment	Mean cumulative echo decorrelation			
	Pre-treatment		End treatment	
Number	Unablated	Ablated	Unablated	Ablated
1	0.0231	0.0657	0.0352	0.0670
2	0.0120	0.0233	0.0315	0.0603
Mean	0.0176	0.0445	0.0333	0.0637
Std. dev.	0.0079	0.0300	0.0026	0.0048