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Dependence of ultrasound echo decorrelation on local tissue temperature during *ex vivo* radiofrequency ablation

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Abstract

This study investigates echo decorrelation imaging, an ultrasound method for thermal ablation monitoring. The effect of tissue temperature on the mapped echo decorrelation parameter was assessed in radiofrequency ablation experiments performed on *ex vivo* bovine liver tissue. Echo decorrelation maps were compared with corresponding tissue temperatures simulated using the finite element method. For both echo decorrelation imaging and integrated backscatter imaging, the mapped tissue parameters correlated significantly but weakly with local tissue temperature. Receiver operating characteristic (ROC) curves were used to assess the ability of echo decorrelation and integrated backscatter to predict tissue temperature greater than 40, 60, and 80°C. Significantly higher area under the ROC curve (AUROC) values were obtained for prediction of tissue temperatures greater than 40, 60, and 80°C using echo decorrelation imaging (AUROC = 0.871, 0.948 and 0.966) compared to integrated backscatter imaging (AUROC = 0.865, 0.877 and 0.832).

Keywords

Ultrasound imaging; Echo decorrelation imaging; Radiofrequency ablation; Temperature monitoring

1. Introduction

Radiofrequency ablation (RFA) is a common treatment for unresectable liver tumors (Shiina et al., 2012). RFA involves application of alternating current through a radiofrequency (RF) electrode at the tumor site. The current propagates through tissue causing ionic agitation and frictional heating, resulting in coagulative necrosis. RFA has been shown effective for the treatment of unresectable liver and other soft tissue tumors clinically (Shiina et al., 2012), offering several advantages over surgical resection, such as reduced morbidity, cost, and hospital stay duration (Livraghi et al., 2008; Shiina et al., 2012). However, presence of blood vessels near the tumor site can affect the size and shape of the thermal lesion, and can cause incomplete tumor ablation resulting in local recurrence (Goldberg et al., 2000). In addition, RFA treatments can cause damage to adjacent organs such as the diaphragm and bowel (Wong et al., 2010). Real-time treatment monitoring could help to ensure irreversible damage to the tumor and also help prevent heating of adjacent tissues and organs.

RFA procedures are often guided using sonography (Wong et al., 2010). Ultrasound imaging offers the advantage of being portable, inexpensive and non-ionizing. However, the lack of reliable temperature feedback and imprecise real-time evaluation of the extent of thermal necrosis are major limitations. Often necrosis is not visualized due to low contrast between ablated and unablated regions or artifacts caused by microbubble formation at the ablation site, resulting in over- or under-prediction of treated regions. However, changes in raw ultrasound pulse echo signals can be tracked to quantify thermal ablation.

Ultrasound echo decorrelation imaging is a pulse-echo imaging technique proposed for monitoring of RFA (Mast et al., 2008). This approach exploits the rapid fluctuation in echo signals observed during tissue heating. Echo decorrelation images are formed by spatially mapping millisecond-scale changes in echo signals occurring during thermal ablation. Echo decorrelation imaging has several advantages over other ultrasound based treatment monitoring methods such as echo strain imaging (Souchon et al., 2005), elastography (Varghese et al., 2004), acoustic radiation force imaging (Fahey et al., 2006), and harmonic motion imaging (Maleke and Konofagou, 2008). These methods rely on cross-correlation techniques to track changes in time-delay, displacement or strain, which are susceptible to non-uniform scatterer displacements caused by tissue heating and heat induced bubble activity (Kallel et al., 1997). Echo decorrelation imaging, on the other hand, exploits these changes to track ablation (Mast et al., 2008; Gudur et al., 2012; Hooi et al., 2015). Echo decorrelation imaging has previously been tested for prediction of thermal lesioning in liver tissue during *in vitro* and *in vivo* radiofrequency ablation (Mast et al., 2008; Subramanian et al., 2014) as well as HIFU (Gudur et al., 2012) procedures. For prediction of local radiofrequency ablation, areas under the ROC curve (AUROC) greater than 0.8 have been observed both *ex vivo* (Mast et al., 2008) and *in vivo* (Subramanian et al., 2014), indicating that this method is potentially useful for real-time ablation monitoring. However, physical mechanisms causing echo decorrelation still remain to be investigated.

A previous study has shown the mapped echo decorrelation parameter to approximate the decoherence spectrum of tissue reflectivity (Hooi et al., 2015), providing means to quantify heat induced changes in the scattering medium. These include structural changes directly related to temperature rise in the tissue. When the tissue temperature is increased to 40–45 °C, reversible cell injury occurs, which could become irreversible after prolonged exposure over several hours (Thomsen, 1991). However, irreversible tissue damage occurs almost instantaneously when temperatures exceed 60 °C from protein denaturation (Zervas and Kuwayama, 1972; Izzo, 2003). At tissue temperatures greater than 90 °C, phenomena such as microbubble formation (Kruskal et al., 2001) and tissue boiling (Nahirnyak et al., 2010) have been reported. When the tissue temperature is raised above 100 °C, boiling and vaporization occur, preventing conduction of heat. The key aim for thermal ablation is to achieve and maintain a 50–100 °C temperature range throughout the entire treatment volume, to induce irreversible damage and also to prevent heating of adjacent tissues and organs (Goldberg et al., 2000). Use of image-guided methods to monitor thermal ablation would greatly improve the quality of treatment.

In this paper, the relationship between tissue temperature and echo decorrelation is assessed through a series of RFA treatments performed on *ex vivo* bovine liver tissue. Previously

validated simulations of tissue temperature profiles (Subramanian and Mast, 2015), obtained using tissue parameters optimized to match experimental ablation outcomes, are compared to corresponding echo decorrelation images. The ability of echo decorrelation imaging to predict ablative temperatures is also assessed using receiver operating characteristic (ROC) curves. For comparison, integrated backscatter changes (Mast et al., 2008) are also computed and their ability to predict ablative temperatures is compared with echo decorrelation imaging.

2. Methods

2.1. Ablation Experiments

RFA treatments were performed in a series of experiments described previously (Subramanian and Mast, 2015). Fresh bovine livers were acquired from a local slaughterhouse, cut into samples matching dimensions of an acrylic sample holder ($85 \times 85 \times 60 \text{ mm}^3$), placed in a bag filled with phosphate buffered saline (PBS), and stored in ice at 0°C until their treatment. All treatments were performed within 12 hours postmortem. For experiments, tissue samples were placed in the acrylic sample holder and allowed to acclimate to room temperature.

The experimental setup is shown in figure 1(a). Two 1 mm diameter thermocouples and a 1.4 mm diameter needle electrode with an exposed length of 22 mm were inserted into the liver sample through a custom made guide, such that all three were all aligned parallel to one another. The guiding tracks for the thermocouples were drilled at a distance of 11 mm and 9 mm from the track for the RF electrode. A grounding pad was placed at the distal end of the tissue relative to the RFA probe as shown in figure 1(b).

A 192-element, 7-MHz ultrasound array (L7, Guided Therapy Systems, Mesa, AZ) was placed against an acoustically transparent window (Tegaderm, 3M, St Paul, MN), as shown in figure 1(b). The ultrasound array was placed on a custom-made holder to ensure that the image plane was aligned parallel to the benchtop and contained tips of both the RF needle electrode and thermocouples (figure 1(c)). Thermocouple positions within the image plane were estimated from the B-mode images as the centers of corresponding hyperechoic spots in the image plane (enclosed by red circles in figure 1(c)).

A 500 kHz sine wave was produced by a signal generator (33220A, Agilent, Santa Clara, CA) with voltage amplitude 280–320 mV_{pp}, amplified using a 50 dB gain RF power amplifier (3100L, ENI, Rochester, NY), and supplied to the needle electrode. 15 RFA treatments were performed with 31–34 V_{RMS} input voltage and treatment durations 1–6 min. The average tissue temperature at the start of the treatment was $18.87 \pm 0.27^\circ\text{C}$; higher starting temperatures were found to increase spurious gas activity. For each experiment, the treatment was stopped when electrical impedance near the RF probe increased due to tissue vaporization at very high temperatures ($> 100^\circ\text{C}$), as indicated by large fluctuations of the built-in power meter.

After completion of each treatment, the liver specimen was placed in an acrylic box with dimensions identical to the sample holder and frozen in a -80°C freezer to retain shape for

the purpose of accurate image registration (Mast et al., 2008). The tissue was then sectioned parallel to the image plane and scanned using a flatbed scanner (V600, Epson, Long Beach, CA) at 600 dpi. For direct comparison of temperature profiles and echo decorrelation images, the tissue section closest to the ultrasound image plane was registered to the ultrasound image using visible probe tracks as landmarks. The lesion area was manually segmented based on gross discoloration of the tissue, with pixels within the lesion boundary defined as ablated. The ablated area was then quantified as the total area of all pixels within the segmented lesion boundaries (Mast et al., 2008).

2.2. Echo Decorrelation Imaging

The echo decorrelation imaging algorithm previously introduced by Mast et al. (2008) was implemented on the pulse-echo ultrasound signals acquired during the RFA treatments, using methods similar to Subramanian et al. (2014). Ultrasound imaging was performed by the Iris 2 ultrasound imaging and ablation system (Guided Therapy Systems, Mesa, AZ) using the 192-element, 7 MHz linear ultrasound array (L7, 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. Throughout each treatment, pulse-echo image frame pairs comprising 384 beamformed echo signals were acquired at intervals of ~ 0.117 s. Each pair comprised two consecutive pulse-echo frames $p(\mathbf{r}, t)$ and $p(\mathbf{r}, t + \tau)$ acquired at time t , where $\mathbf{r}$ is the spatial position vector within the image plane and τ is the inter-frame time interval, here equal to 19.6 ms (inverse of the system frame rate, 51 Hz). Echo signals were filtered using a Gaussian bandpass filter with a 7.36 MHz center frequency and 1 MHz bandwidth. This filter also implicitly performed a Hilbert transform to form complex analytic pulse-echo image frames. B-mode (brightness mode) images were obtained by logarithmically scaling echo envelopes (absolute value $|p(\mathbf{r}, t)|$ of the complex analytic echo signals) with a displayed dynamic range of 60 dB.

To compute echo decorrelation images, the spatio-temporal cross-correlation and autocorrelation functions are defined as $R_{01}(\mathbf{r}, t) = \langle p(\mathbf{r}, t) p^*(\mathbf{r}, t + \tau) \rangle$, $R_{00}(\mathbf{r}, t) = \langle |p(\mathbf{r}, t)|^2 \rangle$, and $R_{11}(\mathbf{r}, t) = \langle |p(\mathbf{r}, t + \tau)|^2 \rangle$, where $\langle \rangle$ represents two-dimensional convolution with a Gaussian mask

$$\langle f(\mathbf{r}) \rangle = f(\mathbf{r}) \otimes e^{-|\mathbf{r}|^2/2\delta^2}, \quad (1)$$

with a width parameter δ (Mast et al., 2008), defined here as 1.5 mm. This window width is consistent with previous simulation results that showed minimum error between the mapped echo decorrelation and scattering medium decoherence for correlation window sizes on the order of $1/6$ – $1/2$ the thermal lesion size (Hooi et al., 2015).

The time- and position-dependent echo decorrelation was then computed as (Subramanian et al., 2014)

$$\Delta(\mathbf{r}, t) = 2 \frac{R_{00}(\mathbf{r}, t)R_{11}(\mathbf{r}, t) - |\overline{R_{01}(\mathbf{r}, t)}|^2}{R_{00}(\mathbf{r}, t)R_{11}(\mathbf{r}, t) + \overline{R_{00}R_{11}}}, \text{ where } \quad (2)$$

$\overline{R_{00}R_{11}}$ represents the spatial mean value of $R_{00}(\mathbf{r}, t)R_{11}(\mathbf{r}, t)$. 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 equation 2 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 echo decorrelation maps were temporally smoothed using (Mast et al., 2008)

$$\overline{\Delta}(\mathbf{r}, t_i) = (1 - \varepsilon)\overline{\Delta}(\mathbf{r}, t_{i-1}) + \varepsilon\Delta(\mathbf{r}, t_i), \quad (3)$$

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 (Mast et al., 2008), taken here to be 0.02. To form cumulative echo decorrelation maps, the temporal maximum of the resulting echo decorrelation was recorded at each pixel location. Hybrid echo decorrelation images were formed for display by overlaying logarithmically scaled cumulative echo decorrelation maps onto the corresponding B-mode image frames.

An integrated backscatter term can be defined as $\sqrt{R_{00}(\mathbf{r}, t)R_{11}(\mathbf{r}, t)}$. Integrated backscatter images were defined as the integrated backscatter in dB relative to the the integrated backscatter term computed before treatment,

$$\text{IBS}(\mathbf{r}, t) = 10 \cdot \log_{10} \left(\frac{\sqrt{R_{00}(\mathbf{r}, t)R_{11}(\mathbf{r}, t)}}{\sqrt{R_{00}(\mathbf{r}, 0)R_{11}(\mathbf{r}, 0)}} \right). \quad (4)$$

Integrated backscatter maps were temporally averaged using the running average of equation 3, similar to the echo decorrelation maps. Cumulative integrated backscatter maps were formed from the temporal maxima of $\text{IBS}(\mathbf{r}, t)$ at each pixel location. Hybrid integrated backscatter images were formed for display by overlaying maps of the decibel-scaled integrated backscatter onto corresponding B-mode image frames.

2.3. Temperature Simulations

Temperature simulations of the RFA experiments described above were performed by solving the bioheat transfer equation using finite element analysis, as described in detail by Subramanian and Mast (2015). For each treatment, 3D models of the needle electrode and liver tissue were constructed using Abaqus software (Hibbit, Karlsson and Sorenson Inc., Pawtucket, RI). Thermocouple locations for finite element simulations were determined from the positions of corresponding bright spots in the ultrasound image, as shown in figure

1(c). Estimated distances between the thermocouples and RF electrode were 9.93 ± 0.883 mm and 8.400 ± 0.736 mm (mean $\pm$ standard deviation) respectively. A fine mesh was created near the RF electrode and a coarser mesh was created at the tissue boundaries. The simulations were performed using tissue properties (thermal conductivity, specific heat and electrical conductivity) individually optimized such that simulated ablated tissue areas matched measured areas for each experiment. As the treatments were performed ex vivo, the effect of blood perfusion was not modeled.

To optimize tissue physical parameter values, the unscented transform was used to approximate the mean and variance of the ablated area through a nonlinear transformation of known mean and variance of tissue parameters (dos Santos et al., 2009). The mean-square error between simulated and measured ablated areas was then minimized using the unscented Kalman filter (UKF) to recover a set of tissue parameters for accurate temperature simulation. The mean and standard deviation of UKF-estimated thermal conductivity, specific heat and electrical conductivity values used were 0.4 ± 0.038 W/m²/°C, 3005 ± 149 J/Kg/°C and 0.465 ± 0.073 S/m respectively. Estimated tissue parameters were then propagated through the finite element model to generate a temperature profile in the image plane for each RFA treatment. In validation of the generated temperature profiles, RMS error of 3.75 °C was obtained between measured and simulated tissue temperatures at the two thermocouple locations, comparable to the experimental uncertainty of 3.36 °C (Subramanian and Mast, 2015).

2.4. Data Analysis

For comparison of ultrasound echo decorrelation with tissue temperature, both the mapped echo decorrelation and simulated temperature profiles were interpolated spatially and temporally. In this analysis, the spatial sampling interval was chosen to ensure the independence of echo decorrelation values for each sampled location, based on the Gaussian window size used for the computation of echo decorrelation. For this calculation, two Gaussian spatial windows defined in equation 1 were considered independent when their spatial cross-correlation coefficient $r < 0.5$. This corresponds to a distance $2\sqrt{2 \log(2)}\delta$ between window centers, where $\delta = 1.5$ mm is the Gaussian window width parameter (Subramanian et al., 2014). Similarly, the temporal sampling interval was defined as $1/(\epsilon F)$, where $\epsilon = 0.02$ is the running average parameter from equation 3 and $F = 9$ fps is the nominal frame rate for acquisition of pulse-echo frame pairs. The same temporal and spatial sampling was performed for the corresponding temperature profiles and integrated backscatter maps.

To test the dependence of echo decorrelation on tissue temperature, Pearson correlation coefficients were determined between log₁₀-scaled echo decorrelation and simulated tissue temperature values from all sampled spatial points in the image plane and all sampled temporal points throughout all treatments. To test the ability of echo decorrelation to map tissue temperature, linear regression was performed between the tissue temperature and the log₁₀-scaled echo decorrelation. To determine the accuracy of temperature predictions made using this linear fit, the standard deviation of the prediction error was determined. For comparison, this analysis was repeated using the integrated backscatter maps to test the

ability of integrated backscatter imaging to map tissue temperature. To assess the significance of the difference between correlation coefficients obtained for integrated backscatter and echo decorrelation, the Fisher r -to- z transformation was applied to compute normalized z -scores. The difference between these z values was normalized using the RMS value of the two individual standard errors. The significance of this difference was then assessed based on the cumulative distribution function of the normal distribution.

In order to test prediction of clinically significant temperature elevations using echo decorrelation and integrated backscatter imaging, receiver operating characteristic (ROC) curves (Mast et al., 2008; Krzanowski and Hand, 2009) were employed to test prediction of temperature elevation above 40, 60, and 80 °C. These temperature thresholds were chosen because temperature elevation to 40 °C does not result in irreversible tissue damage, while at 60 °C, irreversible cell death occurs (Thomsen, 1991) and at 80 °C, most biological proteins have denatured (Bischof and He, 2006). While accurate prediction of tissue temperatures above 60 °C would be sufficient to predict cell death, confirmation of temperatures above 80 °C would provide more reliable assurance of tissue ablation. In current RFA procedures, tissue temperatures are routinely elevated above 80 °C, and typically exceed 100 °C near the tip of the RF electrode (Goldberg et al., 1999).

In this analysis, using pixel-by-pixel comparison of time-dependent echo decorrelation and integrated backscatter images with corresponding simulated temperature profiles, spatio-temporal points exceeding a given echo decorrelation or integrated backscatter threshold were predicted to have exceeded 40, 60, or 80 °C. Temperature prediction success was determined for each spatio-temporal point as a function of the predicting parameter threshold; ROC curves were then created by plotting the true-positive rate (sensitivity) against the false-positive rate (1–specificity). Areas under the ROC curve (AUROC) were determined to assess the utility of echo decorrelation and integrated backscatter to predict temperature elevations.

Assessment of temperature prediction success was performed by testing significance of the AUROC statistic using a general model for the AUROC standard error (Hanley and McNeil, 1982). 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 the three temperature thresholds using DeLong's method of comparing two correlated ROC curves (Hanley and McNeil, 1983; DeLong et al., 1988). Reference echo decorrelation and integrated backscatter thresholds for temperature prediction were defined as the thresholds yielding equal numbers of false-positive and false-negative predictions, so that the average area enclosed within the 40, 60, or 80 °C contours matched between predictions and simulations. Sensitivity and specificity values were computed at these thresholds for prediction of tissue temperatures exceeding 40, 60, and 80° C.

To assess the ability of echo decorrelation and integrated backscatter imaging methods to predict thermal ablation in tissue, ROC curves were also computed using pixel-by-pixel comparison of cumulative echo decorrelation and integrated backscatter images with corresponding segmented histologic maps of thermal lesions, similar to previous analyses

(Mast et al., 2008; Subramanian et al., 2014). To compute these ROC curves, prediction of local ablation was tested for each spatial point as a function of the predicting decorrelation or backscatter threshold. Similar to the temperature predictions, decorrelation backscatter thresholds for prediction of thermal ablation were defined as those yielding equal numbers of false-positive and false-negative predictions. This selection of thresholds resulted in unbiased prediction of the thermal lesion area. Sensitivity and specificity values were computed for prediction of tissue ablation at these thresholds. Absolute RMS error, expressed in mm^2 , and normalized RMS error, expressed in percent, were computed between the predicted and measured ablated areas.

3. Results

A representative comparison of time-dependent echo decorrelation with temperature is shown in figure 2. Figure 2(a) shows the instantaneous echo decorrelation computed using equation 2 for an RFA treatment, sampled at a spatial location ~ 1 mm from the RF electrode. Figure 2(b) shows the corresponding running-average echo decorrelation computed using equation 3, as well as the cumulative $\log_{10}$ -scaled echo decorrelation. Shown in figure 2(c) is the simulated tissue temperature at the same location. Qualitatively, an increase in decorrelation is observed as the local tissue temperature rises from 20 to 100 °C.

The spatio-temporal progress of echo decorrelation and temperature elevation is shown in figure 3 for the same representative treatment. Hybrid echo decorrelation images, comprising B-mode and echo decorrelation maps, show the $\log_{10}$ -scaled echo decorrelation superimposed on B-mode ultrasound images after 15 s, 20 s, and 60 s of treatment. Corresponding simulated tissue temperatures within the image plane are shown at the same times. Echo decorrelation is seen to increase in magnitude and to spread spatially as the treatment progressed, with corresponding increases in tissue temperature. Some elevated decorrelation is observed outside the primary heated region near the RFA probe tip, but does not coincide with the marked thermocouple locations. These decorrelation artifacts may be caused by gas or vapor motion through large blood vessels.

Hybrid post-treatment echo decorrelation images are shown in figure 4(a) for three representative treatments. The dashed lines show boundaries of regions predicted by the optimal decorrelation thresholds to have tissue temperatures greater than 40, 60, and 80 °C. Figure 4(b) shows corresponding hybrid integrated backscatter images for the same three treatments, with dashed lines depicting the ablation boundaries predicted by the optimal integrated backscatter thresholds for 40, 60, and 80 °C. Figures 4(c) and (d) show temperature profiles simulated using the UKF estimated tissue parameters and scanned tissue sections for the same treatments. The dashed black lines in figure 4(d) represent the segmented ablation boundary, determined from gross discoloration of tissue. Qualitatively, higher echo decorrelation is observed in ablated regions and in regions with greater temperature elevations, compared to unablated regions.

Scatter plots showing relationships between time-dependent simulated temperature, echo decorrelation, and integrated backscatter are shown in figure 5. Figure 5(a) shows the $\log_{10}$ -

scaled, running-average echo decorrelation plotted against the temperature simulated using UKF-estimated tissue parameters for all spatiotemporal points sampled in the 15 RFA experiments. Also shown is the best linear regression fit between $\log_{10}$ -scaled echo decorrelation and tissue temperature, given by

$$T = 7.018 \cdot \log_{10}(\Delta) + 55.92. \quad (5)$$

Echo decorrelation was significantly correlated with tissue temperature with a Pearson correlation coefficient of 0.516 ($p \ll 10^{-14}$, $N = 60580$). The standard deviation of the difference between the simulated tissue temperature and the temperature estimated from the linear fit defined in equation 5 is 12.23 °C. Similarly, figure 5(b) shows the dB-scaled, running-average integrated backscatter plotted against the temperature simulated using UKF-estimated tissue parameters, as well as the line of best fit, defined as

$$T = 2.524 \cdot \text{IBS} + 24.01. \quad (6)$$

The correlation coefficient between integrated backscatter and simulated tissue temperature was 0.567 ($p \ll 10^{-14}$, $N = 60580$). The standard deviation of the difference between the simulated tissue temperature and the tissue temperature estimated from the linear fit defined in equation 6 is 11.76 °C. These results indicate that both echo decorrelation and integrated backscatter map tissue temperature with poor accuracy. However, integrated backscatter performed significantly better as a linear predictor of tissue temperature compared to echo decorrelation ($z = -12.57$, $p \ll 10^{-14}$, $N = 60580$).

Accuracy of echo decorrelation and integrated backscattering imaging for prediction of tissue temperatures greater than 40, 60, and 80 °C are summarized in figure 6(a,b) and table 1. Figures 6(a) and 6(b) show ROC curves for prediction of temperatures exceeding these thresholds by echo decorrelation and integrated backscatter imaging, while numerical results of the ROC analysis are listed in table 1. Echo decorrelation imaging performed significantly better than integrated backscatter for prediction of tissue temperatures greater than 40 °C ($p = 0.019$), 60 °C ($p < 10^{-14}$), and 80 °C ($p < 10^{-14}$) over all spatiotemporal points from the 15 RFA experiments ($N = 60580$). Echo decorrelation imaging also had better sensitivity and specificity values for prediction of tissue temperatures greater than 40, 60, and 80 °C compared to integrated backscatter imaging, implying that echo decorrelation performed better than integrated backscatter for prediction of ablative temperatures.

Figure 6(c) shows ROC curves computed for prediction of thermal lesioning using echo decorrelation and integrated backscatter imaging, over all spatial points sampled in the 15 RFA experiments. AUROC values for prediction of thermal lesioning using echo decorrelation and integrated backscatter imaging were 0.919 and 0.893 respectively. The optimal $\log_{10}$ -scaled decorrelation threshold for prediction of thermal lesioning was -1.604. The optimal integrated backscatter threshold for prediction of thermal lesioning was 9.408

dB. Echo decorrelation performed better than integrated backscatter for prediction of ablation, with a significantly higher AUROC value ($p = 0.03$, $N = 495$).

Figure 7(a) and (b) show scatter plots of ablated areas predicted by the optimum echo decorrelation and integrated backscatter thresholds vs. ablated areas estimated using gross tissue histology for all 15 RFA experiments. The mean and standard deviation of ablated area for 15 RFA treatments was $131.67 \pm 77.85 \text{ mm}^2$. The absolute RMS error for prediction of ablated area using the optimum echo decorrelation threshold was 96.42 mm^2 . The normalized RMS error between ablated area predicted by the optimum decorrelation threshold and measured ablated area was 63.40%. The absolute and normalized RMS errors for prediction of ablated area using the optimum integrated backscatter threshold were smaller, at 48.34 mm^2 and 31.78% respectively.

4. Discussion

The temperature dependence and temperature prediction utility of ultrasound echo decorrelation were assessed in this study. Echo decorrelation maps estimated during RFA were compared to simulated temperature maps, obtained using tissue parameters estimated to match experimentally measured ablation and reproducing thermocouple-measured temperatures with RMS error $< 4^\circ\text{C}$ (Subramanian and Mast, 2015). In general, increased echo decorrelation was observed in the presence of ablative tissue temperatures, while relatively little echo decorrelation was seen at sub-ablative tissue temperatures, as illustrated in figures 2–4. However, no clear one-to-one relationship was observed between tissue temperature and echo decorrelation. Although echo decorrelation was correlated with tissue temperature with high statistical significance, this correlation was relatively weak ($r = 0.51$). Integrated backscatter imaging, which maps local changes in tissue reflectivity, had marginally higher correlation with tissue temperature ($r = 0.567$) and also marginally lower error as a linear predictor of tissue temperature (RMS error 11.76°C , compared to 12.23°C for echo decorrelation) but poorer spatial correspondence with large temperature elevations, as seen in figure 4. As illustrated in the scatter plots of figure 5, echo decorrelation was almost always elevated at spatiotemporal points incurring high ablative temperatures $> 80^\circ\text{C}$. In contrast, integrated backscatter spanned a large range of values for the same spatiotemporal points, from about -5 dB (corresponding to a decrease in apparent reflectivity) to about $+15 \text{ dB}$.

One important reason for these differences is the influence of gas activity and vaporization on both echo decorrelation and integrated backscatter imaging. In general, ablated regions become increasingly hyperechoic near the end of RFA treatments, due to the formation of microbubbles at high tissue temperatures (Kruskal et al., 2001). Such bubble activity causes increased tissue brightness proximal to the ultrasound array due to the high reflectivity of gas bubbles, but decreased brightness distally due to acoustic shadowing, as seen in figure 3. Here, echo decorrelation was seen to increase for tissue temperatures above thresholds for thermal ablation ($> 60^\circ\text{C}$) but below thresholds for tissue boiling and vaporization ($> 90^\circ\text{C}$) (Nahirnyak et al., 2010), as illustrated in figures 3 and 5. In addition, the formation and motion of vapor and gas bubbles at higher temperatures can cause rapid changes in echo signals, corresponding to large echo signal decorrelation. Thus, echo decorrelation can map

tissue ablation throughout the ablative temperature range, including larger temperatures causing bubble activity and acoustic shadowing. In contrast, integrated backscatter imaging is adversely affected by microbubble activity at large temperature elevations. Figure 3(b) shows that, although integrated backscatter showed a general trend of increasing with tissue temperature, backscatter also tended to decrease over the ablative tissue temperature range of 60–100 °C. This can be attributed to shadowing, as seen in the hybrid integrated backscatter images shown in figure 4.

Both echo decorrelation imaging and integrated backscatter imaging are also susceptible to artifacts caused by bubble activity, including motion of gas and vapor bubbles. Since the liver is highly vascularized, thermally generated bubbles can move along large vessels, due to convection or, for *in vivo* ablation, due to normal blood flow. Such bubble motion can potentially cause both high echo decorrelation and integrated backscatter changes in unablated tissue regions. Hence, for future development of echo decorrelation as a treatment monitoring tool, the effect of gas and vapor bubble formation in tissue should be further characterized.

In the RFA experiments described in this paper, thermocouples were used to measure local tissue temperature for validation of temperature obtained using finite element analysis. The experimental error due to change in measured temperature caused by electromagnetic interference and imprecise knowledge of thermocouple locations was previously estimated to be 3.36 °C, comparable to the RMS error of 3.75 °C between measured and simulated temperatures at the thermocouple locations (Subramanian and Mast, 2015). Use of thermocouples could also potentially affect tissue heating and echo decorrelation imaging results. Electromagnetic interference could potentially cause the thermocouple to act as a heat source, causing local heating that would affect comparisons between echo decorrelation and tissue temperature at nearby locations. Increased vapor or bubble activity at the thermocouple surface could also result in increased echo decorrelation. However, in these experiments, no enhancement of tissue ablation or echo decorrelation was observed near the thermocouple locations. As illustrated in Figs. 3 and 4, ablation and decorrelation near the thermocouples was similar to other locations at comparable distance from the RFA probe tip. Thus, any heating or decorrelation artifacts caused by thermocouples were relatively small.

As a predictor of tissue temperature, echo decorrelation imaging performed significantly better than integrated backscatter. Temperature elevations beyond 40, 60, and 80 °C were predicted by echo decorrelation with greater AUROC as well as greater sensitivity and specificity values at the optimum prediction threshold, compared to integrated backscatter. In particular, echo decorrelation served as a much better predictor for ablative tissue temperatures > 60 °C and > 80 °C. Although sensitivity values were relatively low at the optimum threshold, specificity values were high (> 0.94 for both echo decorrelation and integrated backscatter imaging). At the decorrelation threshold, where the number of false positive predictions equals the number of false negative predictions for unbiased prediction of lesion areas, the positive and negative predictive values equal the sensitivity and specificity values respectively. The high specificity and negative predictive values obtained at this threshold are due in part to the relatively large number of spatiotemporal points with tissue temperature below 40, 60, and 80 °C respectively. Still, the high AUROC values show

the capability of echo decorrelation for accurate prediction of regions where tissue temperature exceeds 40, 60, and 80 °C, useful for treatment monitoring.

For prediction of tissue ablation, both echo decorrelation imaging and integrated backscatter imaging performed well in these experiments (AUROC 0.919 for echo decorrelation, 0.893 for integrated backscatter). These results are consistent with trends from previous studies, including *ex vivo* experiments using a clinical RFA probe in bovine liver (AUROC 0.855 for echo decorrelation, 0.593 for integrated backscatter) and *in vivo* experiments using the same clinical RFA system in porcine liver (AUROC 0.833 for echo decorrelation, 0.734 for integrated backscatter). In all three studies, AUROC for both echo decorrelation and integrated backscatter indicated prediction of tissue ablation significantly better than chance (AUROC = 0.5), but AUROC for predicting tissue ablation using echo decorrelation was significantly higher than for integrated backscatter. AUROC values for both parameters were largest in the present study, possibly due to its simpler and more controlled experimental geometry.

A future goal is to create a clinical ablation algorithm, with an end point specified by echo decorrelation exceeding a given threshold within a region of interest (ROI). Once echo decorrelation throughout the ROI exceeded this threshold, the ROI would be considered ablated and the treatment stopped. For such a procedure implemented clinically, it may be desirable to optimize for accurate negative prediction of tissue ablation, so that any unablated regions can be correctly identified, reducing the likelihood of local cancer recurrence. This requires a predictor with high specificity. In the studies reported here, echo decorrelation imaging successfully achieved high specificity for prediction of ablative tissue temperatures at the defined optimum threshold (specificity > 0.97 and > 0.98, sensitivity > 0.44 and > 0.26 for predicting tissue temperatures > 60 °C and > 80 °C, respectively). Although corresponding specificity values for integrated backscatter were comparable to echo decorrelation, sensitivity values were substantially lower (0.344 and 0.049 for temperatures > 60 °C and > 80 °C). Thus, echo decorrelation is a more suitable parameter for use in ablation control algorithms of this kind. Even higher specificity could be achieved by employing a higher echo decorrelation threshold, at the cost of further reduced sensitivity. Integrated backscatter imaging would be less effective in such a treatment algorithm.

For success of ultrasound echo decorrelation imaging as an ablation monitoring and control tool, the physical mechanisms of echo decorrelation should be better understood. This study has contributed to this goal by providing new information on the temperature dependence of echo decorrelation. Echo decorrelation has been shown through scattering theory and simulations to correspond with spatial-frequency decoherence of the tissue reflectivity (Hooi et al., 2015). Thus, elevated echo decorrelation values, shown here to be associated with ablative tissue temperatures, correspond to heat-induced changes in the scattering tissue medium, which include gas activity (Nahirnyak et al., 2010; Gudur et al., 2012) as well as structural changes directly related to temperature, such as cellular swelling, microvascular changes, denaturation of collagen and other proteins, and microstructural tissue damage from vaporization (Kruskal et al., 2001; Wright and Humphrey, 2002; Bischof and He, 2006). Any of these physical changes may modify the attenuation, sound speed, density, and other acoustic properties of tissue; changes in these properties over the short time scales

employed in echo decorrelation imaging (~ 20 ms in the present study) will cause elevated echo decorrelation. The elevated echo decorrelation observed here at ablative temperatures indicates decoherence of the tissue reflectivity, most likely caused by a combination of multiple heat-induced tissue changes. In general, the specific physical changes incurred by tissue during ablation will depend on the tissue type; however, because ablation comprises irreversible change to tissue, echo decorrelation imaging may be expected to observe the progress of these changes.

5. Conclusion

A series of RFA experiments with ultrasound imaging and matched temperature simulations have provided new information on the temperature dependence of echo decorrelation, as well as the ability of echo decorrelation to predict tissue temperature. Elevations in tissue temperature were significantly but weakly correlated with both local echo decorrelation and backscatter changes. Neither echo decorrelation nor integrated backscatter were effective as linear predictors of tissue temperature, with RMS errors > 10 °C. Both echo decorrelation and integrated backscatter were successful as predictors of tissue temperature elevation above thresholds relevant to ablation, 40, 60, and 80 °C. Echo decorrelation was a better predictor than integrated backscatter for these temperature thresholds, with significantly higher AUROC values as well as higher sensitivity and specificity. These results confirm the potential utility of echo decorrelation imaging as a tool for ablation monitoring and control.

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Figure 1.

(a) Schematic diagram of the *in vitro* RFA experiments. (b) Experimental setup for RFA experiments. (c) Ultrasound B-mode image showing tips of the RFA electrode (yellow circle) and two thermocouples (red circles) 9 mm (right) and 11 mm (left) away from the RF electrode.

Figure 2.

Time-dependent echo decorrelation and temperature for a representative treatment. (a) Instantaneous echo decorrelation near the RFA probe, without temporal averaging. (b) Corresponding running-averaged, $\log_{10}$ -scaled echo decorrelation (blue line) and cumulative decorrelation (green line). (c) Simulated tissue temperature at the same location.

Figure 3. Hybrid echo decorrelation images and tissue temperature for a representative RFA treatment. (a) After 15 s treatment. (b) After 20 s treatment. (c) 60 s treatment. The red crosses indicate the location of the two thermocouples.

Figure 4.

Parametric images, simulated temperatures, and tissue histology for three representative RFA treatments. (a) Hybrid echo decorrelation images, with dashed lines (yellow, red, and black) representing boundaries predicted using optimum decorrelation thresholds for temperatures greater than 40, 60, and 80 °C. (b) Hybrid integrated backscatter images, with dashed lines (yellow, red, and black) representing boundaries predicted using optimum integrated backscatter thresholds for 40, 60, and 80 °C. (c) Temperature profiles simulated using the tissue physical parameters estimated by UKF with equal-temperature contours at 40, 60, and 80 °C represented by dashed yellow, red, and black lines respectively. (d) Scanned tissue sections, with dashed black lines representing lesion boundaries.

Figure 5.

Scatter plots of mapped image parameters plotted against simulated tissue temperature for all sampled spatiotemporal points in the 15 RFA experiments. (a) Running-average, $\log_{10}$ -scaled echo decorrelation. (b) Running-average, decibel-scaled integrated backscatter.

Figure 6.

ROC curves for prediction of RFA effects. (a) Prediction of tissue temperatures greater than 40, 60, and 80 °C using echo decorrelation. (b) Prediction of tissue temperatures greater than 40, 60, and 80 °C using integrated backscatter. (c) Prediction of lesion boundaries segmented from gross tissue histology.

Figure 7. Scatter plots comparing measured to predicted ablated areas. (a) Areas predicted using echo decorrelation. (b) Areas predicted using integrated backscatter.

Table 1

Numerical results of ROC analysis for prediction of tissue temperatures greater than 40, 60, and 80 °C for $N=15$ *in vitro* RFA exposures.

Temperature		Echo Decorrelation Imaging		
Threshold (°C)	AUROC	Optimum threshold (log ₁₀ -scaled)	Sensitivity	Specificity
40	0.871	−3.008	0.628	0.948
60	0.948	−1.988	0.442	0.972
80	0.966	−1.398	0.268	0.986

Temperature		Integrated Backscatter Imaging		
Threshold (°C)	AUROC	Optimum Threshold (dB)	Sensitivity	Specificity
40	0.865	4.071	0.606	0.946
60	0.877	8.531	0.344	0.968
80	0.832	13.00	0.049	0.982

Table 2

Numerical results of ROC analysis for prediction of tissue ablation for $N=15$ RFA exposures.

	AUROC	Optimum threshold	Sensitivity	Specificity
Echo decorrelation ($\log_{10}$ -scaled)	0.919	-1.604	0.537	0.947
Integrated backscatter	0.893	9.408 dB	0.469	0.940