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Multi-foci beamforming for thermal strain imaging using a single ultrasound linear array transducer

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Abstract

Ultrasound-induced thermal strain imaging (TSI) has been used to successfully identify lipid and water-based tissues in atherosclerotic plaques in some research settings. However, TSI faces several challenges to be realized in clinics. These challenges include motion artifacts, displacement tracking accuracy as well as limited heating capability which contributes to low thermal strain signal-to-noise ratio and a limited field of view. The goal of this paper is to address the challenge in heating tissue in TSI. Current TSI systems use separate heating and imaging transducers, which require physically aligning the heating and imaging beams and result in a bulky setup that limits *in vivo* operation. This paper proposes and evaluates a new design for heating beams that can be implemented on a linear array imaging transducer and can provide an improved heating area and efficiency as compared to previous implementations. The designed heating beams were implemented with a clinical linear array imaging transducer connected to a research ultrasound platform. *In-vitro* experiments using tissue mimicking phantoms with no blood flow showed that the new design resulted in an effective heating area of approximately 0.85 cm² and a 0.3°C temperature rise in 2 seconds of heating, which compared well with *in-silico* finite element simulations. With the new heating beams, TSI was shown to be able to detect a lipid-mimicking rubber inclusion with a diameter of 1 cm from the water-based gelatin background, with a strain contrast of 2.3 (+0.14% strain in the rubber inclusion and −0.06% strain in the gelatin

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background). Lastly, lipid-based tissue in a 1-cm diameter human carotid endarterectomy (CEA) sample was identified with good agreement to histology.

Keywords

beamforming; apodization; thermal strain imaging; multi-foci; linear array; carotid plaque characterization

INTRODUCTION

Studies have shown thermal strain imaging (TSI) can identify lipids from surrounding water-based tissues (Shi et al. 2005; Kim et al. 2008; Seo et al. 2011; Mahmoud et al. 2013; Mahmoud et al. 2014). TSI is based on the temperature dependence of sound speed in tissue. As the temperature rises, the sound speed in lipid bearing tissue decreases whereas the sound speed in water-bearing tissue increases. This results in echo shifts that produce temporal contrast which is referred to as thermal strain. Positive strain is found in lipid-based tissue and negative strain is found in water-based tissues (Duck 1990; Bamber and Hill 1979; Seip and Ebbini 1995). As a result, TSI can be used to non-invasively diagnose and monitor diseases where lipid-based tissues are key players in disease development.

Currently, the most investigated applications for TSI are for the detection of lipids in atherosclerotic plaques (Shi 2005; Kim et al. 2008; Seo et al. 2011; Mahmoud et al. 2013). Unstable atherosclerotic plaques can rupture and release thrombogenic materials leading to major cardiovascular events such as heart attacks or strokes (Davies and Thomas 1985; Libby 1995; Falk et al. 1995). Unstable plaques typically have a lipid-rich core and thin fibrous cap. Identifying such lipid-rich plaques will allow early intervention and prevent the lethal sequelae of rupture (Falk 1992; Casscells et al. 2003; Libby et al. 1998).

As a result of the potential clinical relevance of TSI, there has been technical development in several areas related to TSI. These developments involve correction of undesirable displacements due to *in vivo* tissue motion and improved strain estimates (Kim et al. 2007; Mahmoud et al. 2014; Dutta 2013; Mahmoud et al. 2013; Ding et al. 2016). Other improvements in instrumentation involve development of an ultrasound transducer array for efficient local energy delivery (Kim et al. 2008; Huang et al. 2006; Huang et al. 2007). With these advancements, TSI has been used in animal study *in vivo* and with excised human tissues (Mahmoud et al. 2013; Mahmoud et al. 2014; Kim et al. 2008). However, one of the key factors that impedes further translational efforts with TSI is the development of an efficient and less bulky heating source that will allow for assessment of plaques in human subjects. Current advancements in the field of image guided high-intensity focused ultrasound include the development of dual-mode ultrasound transducers that can effectively perform heating for ablation and imaging at the same time (Makin et al. 2005; Bouchoux et al. 2008; Casper et al. 2013). Some of these arrays involve the complex transducer fabrication and/or coordinating therapeutic and imaging transducers. Similarly, the current TSI system requires a bulky setup utilizing separate transducers for imaging and heating. Previous attempts to utilize a commercial imaging transducer for both heating and imaging

resulted in a limited field of view due to a narrow heating beam and could not be used for relatively large human plaques (Huang et al. 2007).

In this study, we used computer simulations, *in vitro* phantom experiments, and ex-vivo human tissue experiments to design and evaluate novel heating beamforming that can be implemented on a linear imaging array and provides a broad, homogeneous heat source for TSI-based heating. The acoustic pressure field was simulated using Field II and was compared with water tank experiments (Jensen and Svendsen 1992). The temperature rise, estimated with finite element simulation of tissue thermal models, was confirmed by temperature measurements with thermocouples. TSI performance was evaluated using a tissue mimicking phantoms and an excised carotid plaque from a human subject.

BACKGROUND

Thermal strain imaging (TSI)

Thermal strain imaging (TSI) utilizes the temperature dependence of sound speed in tissues. For a relatively small temperature change ($<10^{\circ}\text{C}$), the relationship between sound speed and temperature in tissue is approximately linear. The resulting thermal (or temporal) strain $\frac{\partial}{\partial t}[\delta t(z)]$ due to echo shifts for a given change in temperature $\delta T(z)$ can be expressed as

$$\frac{\partial}{\partial t}[\delta t(z)] \cong [\beta(z) - \lambda(z)] \delta T(z) \quad (1)$$

where $\lambda(z)$ [$^{\circ}\text{C}^{-1}$] is the linear coefficient for sound speed vs. temperature and $\beta(z)$ [$^{\circ}\text{C}^{-1}$] is the linear coefficient of thermal expansion (Maass-Moreno and Damianou 1996; Shi et al. 2005). For temperatures less than 50°C , β is an order of magnitude smaller than λ and can be neglected (Maass-Moreno and Damianou 1996). This is the case in operating TSI. Near 37°C , the normal body temperature, λ is positive for water-based tissue with typical values ranging from 0.7×10^{-3} to 1.3×10^{-3} and negative for lipid-based tissues with typical values ranging from -1.3×10^{-3} to -2.0×10^{-3} (Duck 1990). As the temperature increases, the sound speed in water-based tissues increases, resulting in a negative thermal strain while the sound speed in lipid-based tissues decreases thus resulting in positive thermal strain (Bamber and Hill 1979; Seip and Ebbini 1995).

To construct thermal strain images, beamformed radio-frequency (RF) data are collected before and after the tissue is heated. Speckle displacements due to sound speed changes are then estimated from the beamformed RF data using speckle tracking methods or Loupas estimator (Lubinski et al. 1999; Pinton et al. 2006; Ding et al. 2016.). Speckle tracking is used in this paper. Finally, thermal strain is then calculated as the axial derivative of displacements.

Design of heating beams

In conventional ultrasound imaging, a narrow beam is preferred for better image resolution. This can be achieved with delay-and-sum beamforming, in which ultrasound signals are aligned so that they are in-phase at the focus. On the other hand, in TSI, a wide heating ultrasound beam is desired to create a larger heated area. Using separate heating sources

with larger ultrasound beams is one way to create such a heated area. Previous studies showed compelling results for TSI in which the heating source was a 6-single-element array transducer, a two-element confocal transducer, or a 512 element two-dimensional therapeutic phased array (Seo et al. 2011; Stephens et al. 2013; Hall and Cain 2006). Although separate heating sources can provide extended regions of interest, they also involve bulky setups. An early work by Huang et al. presented the feasibility of inducing and imaging thermal strain using a single linear ultrasound array (Huang et al. 2006; Huang et al. 2007). However, because a conventional single focus beam was used to generate the heating beam, the heated region was limited to a 3-mm diameter region.

A new beamforming technique was proposed in our earlier study (Nguyen et al. 2014). This beamforming allows the use of imaging transducer as a heating source with improved heated area. This beamforming technique involves dividing the transducer into sub-apertures of 30–34 elements and applying a separate delay profile to each sub-aperture. Doing so effectively increases the number of lateral foci per transmit and broadens the sum beam as explained below. For systematic solutions for multiple-focus field patterns, readers are referred to papers by Ebbini et al., Ibbini et al. and Bostros et al. (Ebbini et al. 1988; Ebbini and Cain 1989; Ibbini and Cain 1990; Botros et al. 1996). For interest in multi-focus transducer design, readers are referred to papers on split-focus and dual-focus transducer in the field of HIFU thermal ablation (Daum et al. 1999; Jeong et al. 2010; Patel et al. 2008; Sasaki et al. 2003; Seip et al. 2001).

Assuming linear propagation, the –6 dB lateral beamwidth can be estimated as (Christensen 1988; Shung 2005)

$$\text{Lateral beam width} \cong F/\# * \lambda = \frac{\text{focal depth}}{\text{aperture size}} * \lambda \quad (2)$$

Therefore, for a given depth and frequency, dividing the transducer into sub-apertures increases the f-number. This results in broadening the lateral beam width. Secondly, by implementing multiple lateral foci, the heated area also increases. In addition, interleaving transmit beams with short time intervals and relatively small spacing will effectively broaden the heated area with desired uniformity (Fig. 1). The sub-aperture size for each focus is designed so that the resulting intensities at each focus are within 3dB of the mean focal intensity. Fig. 1 illustrates the delay profiles for a 128-element linear array transducer that is electronically focused at different lateral points. The overall heating beam is created by temporally interleaving 3-foci and 4-foci beams. The lateral foci are evenly spaced across the focal depth. Furthermore, the foci for the 3-foci beam are positioned between the foci for the 4-foci beam (Fig. 1). As a result, the effective width of the overall heating beam is equivalent to a 7-foci beam.

METHODS

Pressure fields

Field II simulation—The heating beams were first simulated with Field II (Jensen and Svendsen 1992). The beamforming described in Background section was applied to a model of a 128-element L7-4 linear array. The excitation center frequency was 5 MHz. The intended heating area was from 20 mm to 30 mm in depth and −4 to 4 mm in the lateral direction. The axial focal depth was set to 25 mm and the lateral distance between each focus was 1.5 mm. A sound speed of 1540 m/s was used to calculate the delay profiles. 3D transient pressures (4x1x5 cm³) were calculated with the computation time of about 20 min. The simulation was performed on a Hewlett-Packard Pavilion system with an Intel Core 2 Duo E7500 processor with a clock speed of 2.93 GHz and 8 GB of memory. The parameters used in the Field II simulation are presented in Table 1.

Hydrophone measurements—The designed heating beams were implemented on a research ultrasound platform (Verasonics Data Acquisition System (VDAS) V-1 Model, Verasonics, Redmond, WA). The axial-lateral pressure field from the commercial linear array transducer (L7-4, ATL) was then measured in a water tank using a hydrophone (HGL0200, Onda, Sunnyvale, CA, USA) with a computer controlled translational stage.

Temperature rise

Finite element simulation—Three dimensional intensity fields were computed using Field II. The input acoustic intensity was averaged from the intensities of two pressure profiles that were normalized with positive and negative peak pressures measured in the hydrophone experiment. Acoustic intensity was computed based on a pulse length of 15 cycles and a pulse repetition frequency of 5 kHz. The heat source q_v is calculated using (Nyborg 1988):

$$q_v = 2\alpha I \quad (3)$$

where α [Np/cm] is the absorption coefficient for soft tissue and I [W/cm²] is the time-averaged acoustic beam intensity. A finite-element (FE) based 3-D heating simulation (Comsol Multiphysics v3.2, Comsol Inc. Burlington, MA) was conducted based on the bio-heat transfer equation and the simulated pressure (Weinbaum and Jiji 1985; Palmeri and Nightingale 2004):

$$\dot{T} = \kappa \nabla^2 T - \frac{T}{\tau} + \frac{q_v}{c_v} \quad (4)$$

where T [°C] is the temperature, κ [cm²/s] is the thermal diffusivity for soft tissue, τ [s] is the perfusion time constant, q_v [J/cm³] is the rate of heat production, and c_v [mW·s/cm³/°C] is the heat capacity per unit volume for soft tissue. Table 2 presents the parameters used in the FE simulation. Comsol simulation (5 x 1 x 6 cm³) with 270992 tetrahedral elements and

a total of 48783 mesh points was completed in about 2 hours with the aforementioned computer.

Thermocouple measurements—The heating beam sequence was implemented on a commercial linear array transducer (L7-4) and driven by the VDAS. A schematic of the experiment is depicted in Fig. 2 in which a gelatin phantom was used. Fifteen cycle pulses were repeated 9000 times with a pulse repetition frequency of 5,988 Hz. These 5-MHz 15-cycle pulses utilized the temporally interleaved 4-foci and 3-foci heating beams previously described. The elapsed time between the 4-foci and 3-foci beams was 47 μ sec. The average duty cycle during heating period was 3.6. The temperature rise measurements were repeated 5 times at the center of the heating beam at 25 mm depth using a thermocouple connected to a data logger (QuadTemp, Thermoworks Inc. Lindon, UT) during heating and cooling periods.

Thermal strain imaging (TSI)

The system was then used to both induce and image thermal strain using the aforementioned multi-foci beamforming. Beamformed RF data were acquired 20 msec before and 20 msec after the heating sequence. A cylindrical rubber inclusion, with a 10-mm diameter, which is a typical size of a human carotid lumen, was embedded in a gelatin background. While plaques are typically smaller than lumen, the heating beam should cover the whole lumen to detect the plaques that might be positioned anywhere throughout the lumen. The sound speed in rubber was previously shown to have similar negative trend with the sound speed in lipid-based tissue as temperature rises (Miller et al. 2002). Rubber was fabricated using two parts plastics (M-F Manufacturing, Fort Worth, TX: Plastic Hardener - 3328H, Plastic Softener - 4228S), seeded with 0.4% polystyrene spheres (Sigma Aldrich, Amberlite model I6641) by weight. Another 2-layer phantom, consisting of gelatin (top layer) and porcine lard (Morrell Snow Cap) (bottom layer) was also imaged with both multi-foci and single focus heating beams in order to compare the effective heating areas. While lard tissue has inherent scatterers, cellulose (1% in weight) was used as scatterers in gelatin. The focal depth for heating beams is fixed at 25 mm in both phantoms. Additionally, the same heating time, i.e. same number of transmit events for a given PRF, transmit voltage, and frequency were applied for the two heating beam scenarios of proposed multi-foci and conventional single focus. When all active elements are focused to a single lateral focus, the peak pressure is higher than when the active elements are focused at separate lateral foci. Furthermore, because no interleaving is done with a single lateral focus, the number of beams is effectively twice as large. These differences lead to higher strain magnitudes for the single focus heating beams as seen later in the experimental results. The rationale for having the top gelatin layer instead of continuum lard phantom is that the high attenuation of the lard prevents ultrasound waves from penetrating to the designed focus depth for effective evaluation of the heated area. Finally, under University of Pittsburgh IRB approval and with informed consent (satisfying the requirements from World Medical Association Declaration of Helsinki Ethical – Principles for Medical Research Involving Human Subjects), a human carotid endarterectomy (CEA) sample embedded in a gelatin block was imaged with the designed multi-foci heating beams. The TSI image was then compared with O red oil histology in which lipid stains red.

Due to the temperature rise, echo shifts associated with changes in sound speed are expected when the pre- and post- heating frames are compared, which result in appeared strain called thermal (or temporal) strain. 2D phase-sensitive speckle tracking was used to estimate these frame-to-frame axial displacements (Lubinski et al. 1999). The kernel size for tracking was approximately 525 μm (axial) $\times$ 525 μm (lateral). To reduce estimation variance and potential peak-hopping probability, a correlation filter about 1.5 times the kernel size was applied to the correlation coefficient functions during the tracking process. This correlation filter was defined as Gaussian shaped filter that was convolved with the correlation coefficients. The kernel size was set at 2 mm. Thermal (or temporal) strains were then estimated as the spatial derivative of the axial displacements using a 2-mm 2nd order Savitzky-Golay filter.

RESULTS

Pressure Fields

Fig. 3 depicts the pressure field simulated with Field II normalized to the peak pressure for each beam of 4- foci (a), 3-foci (c), and combined 7-foci I. The normalized pressure field of combined beam measured using the hydrophone in the water tank is shown in Fig. 3g. Lateral beam profiles of each beam at 25 mm depth are also plotted (Fig. 3. b, d, f, h). The -6 dB beamwidth for each focus ranges from 0.97 to 1.18 mm and compares well with theoretical values of 0.75–0.86 mm obtained using Eq. 2. The pressure variability between the lateral foci is within 3 dB for simulated results and within 5 dB for experimental results. This higher variability of pressures in hydrophone measurements may be a result of differing element sensitivities or angular responses. Alternatively, imperfect alignment between the transmitting plane of the array and the scanning plane of the hydrophone can also be a contributing factor to the discrepancy between the simulated beam and the measured beam. Overall, the measured pressure field compares well with the pressure field simulated using Field II.

Thermal induction

Fig. 4a shows the simulated temperature profile after 2 seconds of heating. The initial temperature is set to 37°C. The intended heated area, marked in a blue dotted box, 20 mm to 30 mm in depth and -4 to 4 mm in lateral direction, has an average temperature rise of 0.34°C and a standard deviation of 0.04 °C. The temperature rise measured by the thermocouple in the gelatin experiment peaked at 0.26°C at the center of heating beam at the depth of 25 mm. As a demonstration of the temperature changes during heating period, Fig. 4b shows the plot of normalized temperature vs. time at a depth of 25 mm for both simulation (blue line) and thermocouple measurement (red line) during the heating and cooling periods at the center of the heating beam. The error bars for the thermocouple measurements correspond to the standard deviations across 5 repeated measurements. The temperature at the beginning of the heating cycle appears to increase at a faster rate in experiment results than in the simulation results. Similarly, the cooling rate is also faster in the experiment than in the simulation. These deviations can be due to 1) heat conduction along the thermocouple needle and 2) differences in thermal properties of gelatin (experiment) and tissue (simulation) including spatial variations of gelatin composition,

regardless of the author's best efforts to match the thermal properties in the simulation to the experiment gelatin.

Thermal Strain Imaging

Rubber inclusion in gelatin phantom—The reconstructed thermal strain map of the phantom is overlaid on the B-mode image in Fig. 5. The average strains in the gelatin background and rubber inclusion are -0.06% and 0.14% , with the standard deviation of 0.03% and 0.07% respectively. The strains calculated inside the rubber shows greater uniformity compared to the simulated temperature rise. This can be explained by blurring effect of the strain calculation using Savitzky-Golay filter.

Two layer lard-gelatin phantom—Fig. 6 shows the strain image overlaid on the B-mode image of a lard-gelatin phantom when multi-foci heating beams are used (Fig. 6a) and a traditional single-focus heating beam is used (Fig. 6b). The total areas of lard identified with the positive strain values are 85 mm^2 with an average strain of $+0.04\% \pm 0.01\%$ for multi-foci heating beam 18 mm^2 with an average strain of $+0.06\% \pm 0.03\%$ for single-focus heating beam. For a temperature increase of 0.3°C , the ranges of expected strains are -0.02% to -0.04% for water-based tissue and 0.04% to 0.06% for lipid-based tissue, calculated from Eq. 1. The average strains found in lard are smaller than what are found in the rubber inclusion, which can be explained by the lower sound speed coefficient (λ in Eq. 1) of lard that contains some water contents compared to pure synthetic rubber. With higher absorption coefficient and lower thermal conductivity in rubber compared to tissue, the temperature rise in rubber can be higher than lard with the same heat deposition (Stephen et al. 2013). Furthermore, high attenuation in real tissue, as in lard, can be a potential issue for heat deposition (due to lower pressure) *in vivo* applications. Possible compensation includes an increase in the power within safety guidelines as well as a decrease in the frequency of the heating beam. The desired power can be achieved by adjusting the heating duty cycle and pressure magnitude, which is regulated by MI and TI limit. Longer heating duration can be used to achieve the desired temperature rise. The heated areas in the gelatin-lard experiment compare well with the shape of the simulated heating beams shown in Figs. 3 and 4. Although multi-foci heating beams cover a noticeably larger area, it should be noted that multi-foci heating beams generated smaller average strains, i.e. lower temperature rise, in the heated area compared with the single-focus heating beam. This is because the multi-foci beam uses the same number of active elements and spreads the total energy over a larger area with two interleaved beams.

Human carotid endarterectomy (CEA)—Figs 7a shows the photo of the CEA sample before it was embedded into the gelatin phantom. Figs. 7b and c show the ultrasound B-mode images and overlaid strain images for different cross sections of the CEA sample. The thermal strain image is in good agreement with the O-red-oil histology (Fig. 7d). Lipid-based tissues across the 1-cm diameter CEA sample are shown as red in both the strain image and the histology. The percentage area of fat as calculated by ImageJ ranged from 18–36%.

DISCUSSION

Apodization for beam-width enlargement

Another option for improving the main beam width is to apply magnitude apodization on the transmit beam. Apodization functions have been used in ultrasound imaging to suppress side-lobe levels relative to the main lobe for image contrast improvement (He and Lu 2000; Seo and Yen 2008; Szabo 2013; Nguyen and Yen 2013; Cobbold 2007). The side-lobe reduction from using these apodization is accompanied by the enlarged main lobe, which is desired in designing the heating beamforming for TSI. The enlargement factor is often less than two. Compared to apodized single focus beams, multi-foci beams can further enlarge the effective heating area with the use of multiple focus points. To explicate, an apodized single focus F/3 beam can achieve a theoretical main beam width of 1.8 mm. For the same maximum voltage, apodization will naturally result in less energy being delivered to the elements and a less pressure therefore being generated. We found that due to voltage drop resulting from power supply limits of our current system, it was not possible to generate sufficient heating using an apodized beam. Further improvements can be achieved by incorporating magnitude apodization into sub-apertures of the multi-foci beam.

Toward clinical realization

There are several technical challenges that TSI faces prior to clinical use. These challenges include motion artifacts, displacement tracking accuracy as well as limited heating capability. The focus of this paper is on developing a heating beam that can be using a standard imaging transducer.

In this study, a lipid-mimicking rubber inclusion was successfully differentiated from a water-based gelatin phantom using the aforementioned multi-foci heating beam. However, in-vivo tissue motion can result in low displacement SNR and inaccurate strain measurements. Tissue motion correction will be needed. In the case of imaging vessels, ECG signals can be used as references for acquiring images during the diastolic phase with minimum tissue motion for subsequent displacement tracking. Furthermore, displacement SNR can be improved by using high duty cycles with improved heating energy deposit. Increasing acoustic pressures can be considered, under the constraint of FDA approved MI limit of 1.9, to compensate for high attenuation in the skin and subcutaneous fatty tissue.

The peak acoustic intensity and the mechanical index were estimated to be $I_{\text{peak}} = (P_{\text{peak}})^2 / (\rho c) \approx 1040 \text{ W/cm}^2$ and $MI = \frac{NPP}{\sqrt{\text{center frequency}}} = \frac{4 \text{ Mpa}}{\sqrt{5 \text{ MHz}}} \sim 1.8$, respectively (NPP: negative peak pressure). Note that nonlinearity with high peak pressure is not captured in our Field II simulation. For clinical translation, it is necessary to have the mechanical index to below 1.9 to meet the FDA approved limit (Haar 2011). The decrease in peak pressure can be compensated for by increasing the duty cycle. The duty cycle was limited to 3.0% in this study because of technical limitations of our current ultrasound system, which uses the imaging power supply with an average output of 10W. An extended power supply will allow pulse lengths of up to 992 cycles which will open the possibility of higher duty cycles, a lower mechanical index and improved heating efficiency. Furthermore, similar to radiation force elasticity imaging, another challenge for TSI to be used clinically is the regulation of

thermal exposure (i.e. heating up tissue), which is currently revisited the context of short exposure time compared to long exposure as in B-mode diagnostic imaging. As mentioned in multiple publications, TI may not truly reflect bio-effects for short duration ultrasound pulses as in radiation force imaging and thermal strain imaging. A change in guidelines on TI may need to relax for these short-pulse, high-intensity ultrasound modalities (Palmeri 2004; Palmeri 2011; Deng 2015). In fact, the thermal index was calculated to be about 150 for the TSI sequence in this paper ($TI = I_{spta_0.3} * f / 210$ (mW/cm²/MHz) where $I_{spta_0.3}$ is calculated to be 6283.2 mW/cm²) (Abbott 1999).

The resolution of TSI using multi-foci heating beams is determined by the heating profile, the strain imaging algorithm, as well as ultrasound imaging parameters (F-number, center frequency, SNR, transducer bandwidth). The choice of displacement estimation technique (for example, Loupas vs. normalized cross-correlation vs. higher order techniques), the tracking kernel for estimation, and kernel for derivative estimation can also affect the final spatial resolution. Papers have been written about each of these individual aspects and the authors refer the readers to the literature in these cases (Pinton 2006; Byram 2013; Dumont 2016). The Savitzky-Golay filter used in this paper is based on least squares polynomial regression with the derivative being calculated based on the polynomial fit. Least squares regression will tend to suppress high frequency content whereas the derivative operator will tend to increase high frequency content. Regarding heating profile, there is a trade-off between the uniformity and size of the heating area. In our experiments, the lateral heating foci were 1.5 mm apart which was larger than the -6 dB beamwidth for each focus. Some variability in the resulting heating profile, even after accounting for heat conduction, is expected because of this spacing. However, this variability can be removed because the strain calculation has blurring effects due to the speckle tracking kernel size (normally greater than the wavelengths and speckle size). Furthermore, the kernel length can also underestimate the peak positive strains that could be used to quantify the lipid concentration in tissue. Given these factors, the resolution of thermal strain imaging with the multi-foci heating beam is limited for detecting the underlying lipid content with sub-millimeter size. Solution that might improve TSI resolution includes higher resolution imaging with higher frequency transducers or harmonic imaging (Ding et al. 2016). Lastly, besides the variability of heating profile with the proposed multi-foci beamforming, another limitation imposed on TSI is the heterogeneous heat absorption of tissues. This heterogeneity can contribute to the non-uniformity of the heated area, which can be compensated by the smoothing effect due to heat conduction.

Heating loss from convection due to blood flow in-vivo may be a challenge for TSI. For example, no significant heating occurs within the blood as a result of convective cooling. Convective cooling of the luminal layer of the plaque could interfere with signal generation within the plaque. We previously performed simulation studies and in-vivo rabbit vessels studies which suggest that this cooling effect is localized to a very thin layer of luminal portion of the plaque. Although convective cooling is very fast, it is limited by the rate of diffusion of heat from the plaque into the blood which is a relatively slow process, especially compared to TSI heating and imaging process of 2 seconds (Mahmoud et al. 2013; Dutta et al. 2013).

The results show that the area of positive thermal strains shown in red in TSI images compare well with the lipid area indicated by the red stain in histology. However, the magnitude of thermal strains are not only dependent on the tissue components, i.e. lipid and water, but are also dependent on the local temperature rise, which depends on the uniformity of the heating beams as well as tissue thermal properties (conductivity and heat capacity). In this paper, we use the TSI technique to generate contrast between lipid- and water-based tissues and not to quantify the lipid content in tissue. On the other hand, elastography, and also ARFI (Acoustic Radiation Force Impulse), detects the lipid core of plaque based on the tissue mechanical properties between fat and water-based tissue. The lipid rich core tends to be softer relative to vessel wall. However, the mechanical contrast might be attenuated when there is diffuse lipid deposition or calcified lesions are interspersed throughout the plaque. There are currently research studies to utilize elastography and ARFI in characterizing plaques quantitatively in terms of elasticity modulus or shearwave speed (radially along the vessel cross section circumference as well as longitudinally along vessel length) or qualitatively based on the characteristic of plaques such as stiff/soft/stiff layers corresponding to vessel wall/lipid/calcified lesion respectively (Ramnarine 2014, Russell 2009). Recent in-vivo studies have shown compelling results of ARFI in characterizing fibrous cap thickness and mechanical properties of different layers in human carotid plaques (Czernuszcwicz 2015, Czernuszcwicz 2016). With diffused disease like fatty liver, there is a possibility for elastography to identify fatty liver using shearwave dispersion which can be quantified in terms of viscosity parameter. This is still a relatively new research area in the field of elastography. Preliminary TSI study has been shown to be capable of distinguishing fatty liver vs. normal liver based on their temperature-dependent sound speeds (Mahmoud 2014). In brief, TSI and elastography utilize different properties of tissue to distinguish fatty tissue vs. water based tissue and can complement each other.

The multi-foci heating beam can provide the flexibility in selecting the location of the heating area. In previous TSI systems, adjusting the region of interest was limited and even impossible in cases where the relative positions of the heating and imaging transducers are fixed (Huang et al. 2007; Stephens et al. 2013; Mahmoud et al. 2013; Kim et al. 2008). Using a single array transducer makes the system less bulky, allowing easier access for scanning. Furthermore, the region of interest induced by multi-foci heating beams can be adjusted by modifying the transmit delay profiles where the lateral foci location as well as the aperture size are adjusted accordingly. This will facilitate a real-time, free-hand TSI scanning in future.

CONCLUSION

This study proposes and evaluates a beamforming algorithm for multi-foci heating beams implemented on a single linear array transducer. This new design provides relatively uniform heating over an extended area for TSI applications. The effective heating beam, consisting of two interleaved multi-foci beams, increased the temperature by about 0.3°C in 2 seconds over an 85 mm² area, which is about the size of average human carotid artery, in a tissue mimicking phantom with no blood flow. Lipid-based tissue in a 1-cm diameter human CEA sample was successfully detected with good agreement to histology. In-vitro and ex-vivo experiments demonstrate the feasibility of this multi-foci beam large enough to cover an

average human carotid to be used in TSI for detecting lipids in human carotid atherosclerotic plaques.

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Figure 1. Example of delay profiles at a focus depth of 25 mm for a) 4-foci and b) 3-foci transmit beamforming for a 128-element transducer. The sub-apertures are 34-30-30-34 for 4-foci beam 34-30-34 for 3-foci beam. The lateral beamwidth of each focus is designed to be 0.7–0.8mm and the spacing between lateral foci is 1.5 mm in the combined heating beam. Solid red dots indicate active heating foci when each beam is being operated. The heating sequence is further explained in Fig. 2.

Figure 2.
Experimental setup (left) and pulse sequence (right) for heating and imaging (pulse length and pulse timing are not plotted to scale)

Figure 3. Pressure fields and lateral beams at 25mm depth (indicated by the dotted white line) for the simulated 4-foci beam (a–b), the simulated 3-foci heating beam (c–d), simulated combined 7-foci heating beam (e–f), and hydrophone-measured 7-foci heating beam (g–h).

Figure 4. Simulation and experiment thermal induction result: a) Orthogonal plane of simulated temperature profiles (in °C) after 2 seconds of heating, b) Temperature vs. time at the center of the heating beam at 25 mm depth.

Figure 5.

B-scan and overlaid strain images for the gelatin phantom with a 10 mm diameter lipid-mimicking rubber inclusion, which is about the size of average human carotid artery. The rubber inclusion has positive strain of 0.14% and can be detected from the water-based gelatin background. The dotted black lines indicate an approximate heating area.

Figure 6. B-scan and overlaid strain images for lard-gelatin phantom using a) Multi-foci heating beam and b) Single-focus heating beam. The dotted black lines indicate an approximate heating area.

Figure 7.

Human carotid endarterectomy(CEA) sample: a) Picture of the carotid sample before embedded in gelatin-phantom. White dotted line indicate the approximate location of the first slice shown in b, c, and d. Subsequent slices from left to right in b, c, and d were separated by 1 mm, with the direction indicated by the arrow. For each cross section of the carotid embedded in gelatin: b) B-mode image and c) overlaid TSI image. Red indicates positive strain corresponding to fat and d) the matching Oil red O histology which stains red for fat.

Table 1

Parameters for Simulation and Experimental Setup

Parameters	Value
Number of elements	128
Center frequency	5 MHz
Sampling frequency	20 MHz (200 MHz for Field II)
Azimuthal element pitch	0.280 mm
Elevation element height	5 mm
Sound speed	1540 m/s (gelatin phantom)
Focus depth (electronic & elevation)	25 mm
Spacing of lateral foci	1.5 mm
Sub-aperture size	34-30-34 (3-foci beam) 34-30-30-34 (4-foci beam)
Attenuation	0.5 dB/cm/MHz
Imaging transmit aperture	128 elements (plane wave)
Imaging receive aperture	64 elements (dynamic receive)
Sampling rate	20 MHz, 12 bit ADC

Table 2

Parameters for FE simulation

Parameters	Value
Center frequency	5 MHz
Tissue Density	1010 kg/m ³
Sound speed	1540 m/s (body)
Thermal Diffusivity	0.00143 cm ² /s
Thermal Conductivity	1 W/(m.K) (isotropic)
Heat Capacity	3500 mJ/cm ³ /°C
Mesh size	60 x 40 x 60 cm ³ (X x Y x Z)