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Motion Artifact Reduction in Ultrasound Based Thermal Strain Imaging of Atherosclerotic Plaques Using Time Series Analysis

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Abstract

Large lipid pools in vulnerable plaques, in principle, can be detected using US based thermal strain imaging (US-TSI). One practical challenge for *in vivo* cardiovascular application of US-TSI is that the thermal strain is masked by the mechanical strain caused by cardiac pulsation. ECG gating is a widely adopted method for cardiac motion compensation, but it is often susceptible to electrical and physiological noise. In this paper, we present an alternative time series analysis approach to separate thermal strain from the mechanical strain without using ECG. The performance and feasibility of the time-series analysis technique was tested *via* numerical simulation as well as *in vitro* water tank experiments using a vessel mimicking phantom and an excised human atherosclerotic artery where the cardiac pulsation is simulated by a pulsatile pump.

I. Introduction

Plaques characterized by a large, soft lipid core and a thin fibrous cap have been identified as “vulnerable plaques”, or “rupture-prone plaques” [1]. Identifying these potentially fatal plaques before their disruption is clinically desirable and will help predict vascular risk and guide therapies. Ultrasound (US) based thermal strain imaging (US-TSI) is being investigated as a potential modality to detect lipid cores buried in normal tissue non-invasively [2]–[5]. US-TSI is based on the temperature dependence of the speed of US waves in tissue. For a small rise in temperature (<10 °C) near the normal body temperature of 37 °C, US speed increases linearly in non-fatty tissue and decreases linearly in fatty (lipid bearing) tissue [2], [6]. This change in US speed manifests as apparent strain (also called thermal strain) between two US frames captured before and after temperature rise: in lipid, it appears as positive strain or stretching; in normal tissue, it appears as negative strain or compression [2]–[8]. In US-TSI, one exploits this contrast in apparent strain to identify a

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lipid pool buried in normal tissue. In US-TSI, not only the imaging is done using US, but the slight local temperature rise (2-3 °C) required for TSI is also achieved through US induced heating. US-TSI can be performed either using IVUS [3] or using a commercial US linear array transducer that is traditionally used for imaging [5]. The latter approach is non-invasive and is suitable for applications in superficial arteries such as the carotid atherosclerotic plaques. In this study, we use a single commercial linear array transducer to perform US-TSI.

A practical difficulty for *in vivo* cardiovascular application of US-TSI is posed by another source of strain in the artery, *viz.* the mechanical strain due to pulsatile blood pressure which is higher in magnitude than the thermal strain. The total strain measured by US is a sum of the larger mechanical strain and the smaller thermal strain. If proper steps are not taken, thermal strain is completely masked by the mechanical strain. ECG gating can be a solution to the above problem. Since ECG and arterial pulsation have the same periodicity, two US frames can be captured at the same blood pressure level using ECG gating, thereby eliminating any mechanical strain between them. If ECG and blood pressure are perfectly synchronous, one can ensure that mechanical strain does not mask the thermal strain [9], [10]. However, noise in the electrical circuits often interferes with the relatively weak ECG signal since the typical ECG output level is 1 mV or less. In many cases ECG gating becomes unreliable due to electromagnetic interference through electrodes and cables, bad coupling, or false peak detection [11]. In some patients, the synchrony and regularity of ECG and cardiac pulsation may also be affected by physiological factors [12].

To avoid the above technical difficulties arising from ECG and make US-TSI technique ECG independent, we propose a time series analysis technique to separate the thermal strain and the mechanical strain from the mixed signal. We note that the mechanical strain is periodic - rising and falling periodically with blood pressure, while the thermal strain is monotonically increasing - since we keep on slowly increasing the temperature of the tissue throughout the entire imaging period. The total strain measured via US speckle tracking [13], [14] with a frame rate several times the heart rate, therefore, is a sum of a trend and a periodic component. The Holt-Winters (H-W) algorithm [15], [16] was proposed in the early 1960s to separate trends from periodic variations and has since been used extensively in business management and inventory control. In this paper, we adopt the H-W algorithm to extract the thermal strain (trend component) and the mechanical strain (cyclic component) from the total strain measured by US. H-W does not make any prior assumption about the shape of the trend or the periodic component, making it ideal for the current application where the exact temporal patterns of the thermal and mechanical strains are expected to vary from patient to patient depending on the composition and structure of the plaque and vessel wall as well as the patient's heart condition. In this paper, the applicability of US-TSI in conjunction with H-W algorithm for cardiovascular application is tested *via* numerical simulation as well as *in vitro* experiments using a vessel mimicking phantom and an excised human atherosclerotic artery connected to a pulsatile pump in a water tank.

II. Theory of US-TSI and H-W

A. TSI of an atherosclerotic plaque in the presence of blood flow

The apparent strain (a.k.a. thermal strain) (ε_{th}) between two US frames captured at temperatures θ_0 and θ respectively ($\theta > \theta_0$, $\theta_0 \cong 37^\circ\text{C}$, $\theta - \theta_0 < 10^\circ\text{C}$) as a function of location ($\underline{x}$) is given by [2], [3], [7]:

$$\begin{aligned}\varepsilon_{th}(\underline{x}) &= [(\beta - \alpha)(\theta - \theta_0)](\underline{x}) \\ &\cong [-\alpha(\theta - \theta_0)](\underline{x}) \quad \text{when } |\beta| \ll |\alpha|\end{aligned} \quad (1)$$

where $\beta(\underline{x})$ is the thermal expansion coefficient and $\alpha(\underline{x}) = \left[\frac{1}{c} \times \frac{\partial c}{\partial \theta} \right]_{\theta=\theta_0}(\underline{x})$ is coefficient of thermal dependence of sound speed (c) at temperature θ_0 . It has been reported in literature [2], [3] that for a small rise in temperature ($< 10^\circ\text{C}$) near 37°C , both α and β are practically constant over the range θ_0 to θ , and $|\beta| \ll |\alpha|$. In normal tissue, α is positive (i.e. US speed increases with temperature increase) while in fatty (lipid bearing) tissue α is negative (i.e. US speed decreases with temperature increase) [6]. As a result, the thermal strain ε_{th} due to a rise in temperature is negative in normal tissue and positive in fatty tissue.

In US-TSI, the heat required for the temperature rise $\theta_0 \rightarrow \theta$ is induced by US according to the equation:

$$Q_{us}(\underline{x}) = (2\zeta P_{np}^2 \gamma / \pi c)(\underline{x}) \quad (2)$$

where Q_{us} [W/cc] is the heat produced per unit time per unit volume, ζ is the acoustic absorption coefficient, P_{np} is the peak negative US pressure, γ is the US transmit duty cycle, and c is the US speed [4], [5], [17]. Typically, a longer ultrasound pulse than what is used for imaging is necessary to generate any appreciable temperature rise. The time required to ultrasonically increase the temperature of the tissue in a given region Ω from θ_0 to θ is determined by the bioheat equation:

$$\rho C \frac{\partial \theta}{\partial t} = \nabla \cdot (k \nabla \theta) - W_b C_b (\theta - \theta_0) + Q_{us} \quad \text{in } \Omega \quad (3)$$

where ρ is the density of the tissue, C is its specific heat, t is time, k is the thermal conductivity of the tissue, W_b is the blood perfusion rate and C_b is the specific heat of blood. Since our target region Ω is an atherosclerotic plaque, the luminal boundary $\delta\Omega_{lum} \subset \delta\Omega$ undergoes a steady convectional cooling due to blood flow in the artery while the remaining boundary is assumed to be at constant temperature θ_0 :

$$\begin{aligned}\frac{\partial \theta}{\partial t} + \nabla \cdot (\underline{v}_b \theta) &= 0 & \text{in } \delta\Omega_{lum} \subset \delta\Omega \\ \theta &= \theta_0 & \text{in } \delta\Omega \setminus \delta\Omega_{lum}\end{aligned} \quad (4)$$

where $\underline{v}_b$ is the blood flow velocity. Eq. (1)-(3) govern the thermal strain development in an atherosclerotic plaque. In addition to the thermal strain, there is also a mechanical strain

(ε_{me}) in the plaque caused by pulsatile blood pressure with a period τ , so that the total strain (ε) at any given time t is given by:

$$\varepsilon(t) = \varepsilon_{me}(t) + \varepsilon_{th}(t) \quad \text{in } \Omega \quad (5)$$

where the mechanical strain component satisfies the periodicity condition $\varepsilon_{me}(t) = \varepsilon_{me}(t - \tau) \forall t$. The total strain ε is what a US imaging system will measure via speckle tracking. The challenge for cardiovascular TSI is to extract the thermal strain ε_{th} from the total strain ε .

B. Extracting thermal strain from the total strain using H-W algorithm

There are various forms of the H-W. The one used here is described in [18] under Exhibit 4-2 (additive seasonals). The first step in the H-W algorithm is to find an estimate $\hat{\tau}$ of the period τ (heart rate in our case) either through autocorrelation or through Fourier transform of $\varepsilon(t)$. This estimate is then used to solve the implicit set of equations [18]:

$$\begin{aligned} \hat{\varepsilon}_{th}(t) &= \kappa (\varepsilon(t) - \hat{\varepsilon}_{me}(t - \hat{\tau})) + (1 - \kappa) (\hat{\varepsilon}_{th}(t - 1) + b(t - 1)) \\ b(t) &= \lambda (\hat{\varepsilon}_{th}(t) - \hat{\varepsilon}_{th}(t - 1)) + (1 - \lambda) b(t - 1) \\ \hat{\varepsilon}_{me}(t) &= \mu (\varepsilon(t) - \hat{\varepsilon}_{th}(t)) + (1 - \mu) \hat{\varepsilon}_{me}(t - \hat{\tau}) \quad \forall t=1, 2, 3, \dots \end{aligned} \quad (6)$$

where $\hat{\varepsilon}_{th}(t)$ and $\hat{\varepsilon}_{me}(t)$ are the estimates of thermal and mechanical strains respectively. $b(t)$ is a local slope term which can be interpreted as the rate of temperature rise. The parameters κ , λ and μ can take any value between 0 and 1 [19]. In this paper, we chose κ , λ and μ so that the squared sum of reconstruction errors $(\sum_t (\hat{\varepsilon}_{th}(t) + \hat{\varepsilon}_{me}(t) - \varepsilon(t))^2)$ is minimum, as recommended by Hyndman et al. in [20]. In Eq. (6), t is assumed to be discrete since US image frames are acquired at discrete intervals of time. When the expression $(t - \hat{\tau})$ is negative, it is replaced by t . Eq. (6) also needs initialization of $b(0)$, $\hat{\varepsilon}_{th}(0)$ and $\hat{\varepsilon}_{me}(i)|_{i=0:\hat{\tau}}$ which are obtained as following [20]: (i) Compute the moving average of the original series $\varepsilon(t)$ between $t=0:2\hat{\tau}$ with window size $\hat{\tau}$. (ii) Ignoring the first and last $\lceil \frac{\hat{\tau}}{2} \rceil$ points, fit a linear trend to the moving averaged series. Extrapolate the fitted line down to $t=0$. The intercept of the extrapolated line at $t=0$ is $\hat{\varepsilon}_{th}(0)$ and the slope is $b(0)$. (iii) Subtract the extrapolated fitted line between $t=0:\hat{\tau}$ from the original series to get $\hat{\varepsilon}_{me}(i)|_{i=0:\hat{\tau}}$. Once the initialization is complete, the system of equations (6) are solved for all following t with a march-forward approach until the thermal and mechanical strain estimates $\hat{\varepsilon}_{th}(t)$ and $\hat{\varepsilon}_{me}(t)$ are obtained for the entire time series.

III. Materials and Methods

A. Numerical simulation of US-TSI of atherosclerotic plaque

The TSI process governed by equations (1)-(5) was numerically solved using the finite element (FE) method (COMSOL V.3.5a, Burlington, MA) for a plaque, the geometry of which is outlined in Fig. 1 [1], [21]. In Fig. 1, the vessel with 8 mm inner diameter and 0.8 mm wall thickness contains a lipid pool that is 3 mm at its thickest portion with a 0.5 mm fibrous cap separating the lipid from the ~5 mm wide lumen (the dimensions are based on a typical plaque in human carotid artery). A 4 mm thick muscle layer surrounding the vessel provides additional stiffness against distension. Each type of tissue was assigned its typical

thermal and mechanical properties as summarized in Table 1 [22]–[27]. Realistic heating and blood pressure data were used as inputs: (i) The US heat input was computed *via* Eq. (2) from the 3D pressure map of a commercial US linear array transducer (L 14-5/38, 6 MHz center frequency, SonixTOUCH, Ultrasonix Inc., Richmond, BC, Canada) measured in a water tank using a hydrophone (HNC, Onda, Sunnyvale, CA). (ii) The blood pressure of a subject with arrhythmia was taken from a clinical database [28]. Although the material properties used in the FE simulation are based on literature review, no significant effort was made to mimic the exact *in vivo* physiological conditions. The purpose of the simulation was to test the feasibility of US-TSI+H-W in the presence of realistic US heating and arterial pulse pressure.

The simulation produced temperature rise ($\theta - \theta_0$), thermal strain ($\epsilon_{th}(t)$) and mechanical strain ($\epsilon_{me}(t)$) as outputs. Synthetic 2D RF frame was constructed by convolving the measured point spread functions of the US linear array transducer (L14-5, 6 MHz, SonixTOUCH) with randomly distributed virtual US scatterers in the tissue geometry [29]. The mechanical and thermal strains from the FE simulation were used to relocate the virtual scatterers, and subsequent synthetic RF frames were constructed in the same way. The total strain between the synthetic RF frames was computed through phase sensitive 2D speckle tracking [13] and H-W was then applied to extract the thermal strain from the total strain.

B. US-TSI water tank experiments with arterial phantom

US-TSI+H-W was tested experimentally on a vessel-mimicking phantom connected to a pulsatile pump (model #1423, Harvard Apparatus, Holliston, MA). A hollow cylindrical phantom 120 mm long, 33 mm outer diameter and 12 mm thick, was fabricated with a three-layer shell – the inner and outer layers were made from 10% polyvinyl alcohol (PVA, Sigma-Aldrich, St. Louis, MO) while the 6 mm thick sandwiched middle layer was made from rubber (60% Hardener and 40% Plastic-Softener, M-F Manufacturing, Fort Worth, TX). In terms of sound speed change with temperature, rubber and PVA show similar behaviors as lipid and water bearing tissues respectively. To mimic the mechanical properties of plaque, PVA (which represents non-fatty tissue) was made stiffer than rubber (which represents lipid) by increasing the number of freeze-thaw cycles [30]. Both PVA and rubber were seeded with US scatterers – cellulose powder (Sigmacell, 20 μ m, Sigma-Aldrich, St. Louis, MO) for PVA and amberlite powder (150-300 μ m, Sigma-Aldrich, St. Louis, MO) for rubber. The phantom was placed in a water tank and connected to the pulsatile pump running at 60 RPM. The 6 MHz linear transducer connected to SonixTOUCH was used for both heating and imaging using an interleaved US pulse sequence described below [5]. Each pulse sequence lasted for 100 ms and consisted of a 10 ms long imaging phase, a 40 ms long heating phase, and a 50 ms resting phase. During the imaging phase, beamformed RF data were acquired using standard diagnostic 0.16 μ s long B-mode pulses. After the imaging phase, 160 heating pulses (each pulse 2.56 μ s long with a repetition interval of 250 μ s) were transmitted from the middle 64-element sub-array. In order to dampen the effects of undesired tissue motion due to acoustic radiation force (ARF) as well as allow the transducer to cool, a 50 ms waiting time was allowed after heating before acquiring a new RF data set [5]. In all, the average heating duty cycle was $(2.56 \mu\text{s}) / (250 \mu\text{s}) \times (40 \text{ ms}) / (100 \text{ ms}) = 0.4\%$ (which is substantially low compared to ARF

applications that needs about 15% duty cycle [31]). A total of 40 frames were collected (corresponding to 40 US pulse sequence described above) and the entire US-TSI data acquisition took $40 \times 100 \text{ ms} = 4 \text{ s}$ (equivalent to 4 pump cycles). After collection, the RF data was processed using phase-sensitive 2D speckle tracking (2DST) to obtain the displacement fields between adjacent RF frames. The total strain field was computed through spatial derivative of the displacement field [13] and H-W was applied to extract the thermal strain from the total strain. A second experiment was performed on the phantom with the pump off (i.e. there is no mechanical strain), all other conditions remaining the same. The thermal strain obtained with the pump off was compared with the thermal strain extracted using H-W.

C. US-TSI water tank experiment with excised human atherosclerotic vessel

Under IRB approval at University of Pittsburgh, a 40 mm long human atherosclerotic femoral artery was harvested from a consented patient during above-knee-amputation (AKA) surgery. The artery was connected to a pulsatile pump and the same US-TSI+H-W protocol described above for the phantom was followed. After data collection, the artery was fixed in formalin and embedded in a mold with OCT compound and placed in a -80°C freezer. The portion of the artery near the imaged section was then cut into 8-10 μm thick slices and stained using Oil-Red-O to identify lipid rich areas. The stained image was observed under microscope (Olympus, IX81) using X10 objective lens.

IV. Results and Observations

A. Numerical simulation of US-TSI

This subsection reports the results obtained from FE simulation and synthetic US-TSI+H-W. Fig. 2 shows that the temperature rise at a point in lipid in 4 s due to US heating is about 4°C . The corresponding theoretical estimate of the thermal strain in lipid is 0.6% (using $\alpha = -0.15\%$). The US-TSI+H-W estimate of thermal strain stays close to the theoretical curve throughout the entire imaging time and neither converges to nor diverges from the theoretical value with increasing number of cycles. The error bars indicate variability of the H-W thermal strain estimate for five different synthetic speckle realizations. Fig. 3 shows the thermal strain image of the cross-section after 4 s. The lipid rich region shows positive (red) thermal strain while the water bearing part shows negative (blue) thermal strain (ref. Fig. (1)).

B. US-TSI of arterial phantom

This subsection reports the results of US-TSI+H-W from vessel mimicking phantom connected to a pulsatile pump. The pulse pressure over one pump cycle and the corresponding total, mechanical, and thermal strains are reported in Fig. 4. The slightly positive thermal strain is totally suppressed by the strongly negative mechanical strain in the total strain image (Fig. 4 (b)). However, after performing the time series analysis using H-W algorithm, the extracted thermal strain is clearly visible and shows a monotonically increasing trend (Fig. 4 (c)). Similarly, the extracted mechanical strain shows an expected cyclic pattern (Fig. 4 (d)). Note that the strain color bars differ for each row of images, and that the middle row, in particular, represent strains approximately one order of magnitude

smaller than the other images. The line plots on the right show the corresponding average strains as functions of time (1 full pump cycle) around a $2\text{ mm} \times 2\text{ mm}$ region in rubber marked by $\times$ in the images on the left, with the error bars indicating spatial variability in the said region. Although a by-product of the time series analysis process, the mechanical strain is also useful to identify soft lipid pools. Due to the stiffness contrast with its surroundings, soft lipid pools can be identified with a high magnitude of mechanical strain – a fact that is used in ultrasound elasticity imaging (UEI) [32]–[34].

The total strain over 4 cycles in a $2\text{ mm} \times 2\text{ mm}$ region in rubber with the pump on is shown in Fig. 5 (a). In Fig. 5 (b) the thermal strain extracted *via* H-W with the pump on is compared with the thermal strain obtained *via* US-TSI only when the pump was off (i.e. when there is no mechanical strain). The error bars indicate spatial variability in the $2\text{ mm} \times 2\text{ mm}$ region. Somewhat higher thermal strain was observed when the phantom was static (i.e. the pump was off) throughout the entire imaging period. Note that the pattern of the thermal strain curves obtained *via* US-TSI+H-W in Fig. 2 (simulation) and Fig. 5 (b) (phantom experiment) are similar. Since the thermal strain developed in rubber during the 4 s of US-TSI is about 0.7% (Fig. 5 (b)), assuming $\alpha = -0.15\%/^{\circ}\text{C}$ in Eq. (1), the expected temperature rise inside rubber would be 4.7°C .

C. US-TSI of excised human artery

US-TSI+H-W results from an excised atherosclerotic human femoral artery connected to a pulsatile pump are reported in this subsection. The thermal and peak mechanical strains extracted *via* US-TSI+H-W are shown in Fig. 6 (a) and (b) respectively. Oil-red-O staining of the imaged section is shown in Fig. 6 (c). A region in the vessel wall exhibits high positive thermal strain – indicating the presence of lipid which was confirmed by histology. The identified lipid area also exhibits high mechanical strain, indicating softness of lipid. The average thermal strain developed in the lipid rich region is about 0.75%. Assuming $\alpha = -0.015\%/^{\circ}\text{C}$ in Eq. (1) [3], the expected temperature rise in lipid would be 5°C . Figure 6 (d) shows the thermal strain extracted using H-W in a $1\text{ mm} \times 1\text{ mm}$ region in lipid as a function of time, with the error bars indicating spatial variability in the said region.

V. Discussion

The data presented herein demonstrate that H-W successfully separates thermal strain from mechanical strain in the presence of pulsatile motion, which suggests the feasibility of US-TSI in conjunction with H-W algorithm to noninvasively detect large lipid pools in atherosclerotic plaques in the presence of cardiac pulsation. In Fig. 2, the US-TSI+H-W estimate of thermal strain deviates slightly from the theoretical curve (about 4% in average over 4 s) obtained from FE simulation with realistic US heat and blood pressure inputs but otherwise ideal conditions. The deviation is due to errors induced by aperiodicity in the typical clinical blood pressure data and also by inaccuracies in speckle tracking. (In the hypothetical case where the blood pressure is precisely periodic with a constant period, the average error over 4 s was found to be as small as about 1.5 %.) These deviations can be smoothed if wished by using appropriate physics-based filters based on the bioheat equation [35] (a simple linear fit would have been inadequate to represent the thermal strain trend in

the presence of heat dissipation as suggested by the bioheat equation). The advantages of using the H-W algorithm are: (i) It can extract the thermal strain within three to four cardiac cycles (i.e. about 4 s) which is reasonable for clinical applications. Since the H-W theory does not suggest that the extracted thermal strain will either diverge or converge to the true value with increasing number of cycles, there is no justification for using more than three to four cardiac cycles or as long as it takes to increase the tissue temperature sufficiently. (ii) The algorithm does not make any prior assumption about the shapes of the thermal and mechanical strain curves, both of which are expected to vary from patient to patient depending on the composition and structure of the plaque and the artery as well as the patient's heart condition. (iii) The H-W algorithm can work with relatively low frame rate (a frame rate of ten times the pump rate was used in our simulation and experiments – it would translate to ~10Hz for clinical application considering human heart rate of ~1Hz). US-TSI using a single transducer is limited to low frame rates since roughly 50 ms wait time must be allowed after each US heating cycle in order for the transducer to cool and also to dampen the effects of ARF if any. Therefore, an algorithm such as H-W that can work with low frame rates is very advantageous for US-TSI.

A few studies have reported observing a linear trend in the noninvasive US displacement measurement of the arterial wall *in vivo* even in the absence of heating (see for e.g. [36]). In [36], this trend was attributed to the sliding of the transducer on the skin of the patient due to hand movement of the operator. Since the metric of interest in our study is strain (which is the spatial derivative of the displacement), it is expected that any translational artifact due to transducer movement would be annihilated through the spatial derivative. As a general note, a trend in displacement does not automatically translate to a trend in strain. We did not observe any such trend in the strain signal in our *in vitro* experiments when the US heating source was absent. Therefore, within the scope of the current study, we assume that the trend in strain is caused mainly by the US speed change due to temperature rise (thermal strain). The current paper does not prescribe any compensation method for breathing induced strain artifacts. Such artifacts can be avoided in the clinic by asking the patient to hold his/her breath during US-TSI data collection for about 4 s with current design.

Experimental data from Fig. 5 (b) shows that the thermal strain generated at a point in rubber with the pump off was somewhat higher than that with the pump running (about 25% deviation in average over 4 s). A possible explanation is that with the pump on, the point under consideration moved in and out of the US heating zone due to pulsation. Therefore, the average heating experienced by the point in the moving phantom might be lower compared to when the pump was off. Closer examination of the transducer pressure profile measured by hydrophone and 2DST displacement of the phantom could explain only about 10% difference in the total heat deposit. A major reason behind the deviation in Fig. 5 (b), therefore, remains unexplained. For *in vivo* applications, one must take this effect into consideration while designing the US heating beam.

Although the temperature rise in the *in vitro* experiments were not monitored directly using a temperature sensor, indirect temperature estimates from the thermal strain [7] from Figs. 5 (b) and 6 (a) indicated that the temperature rise due to US is around 4.6 °C in rubber and 5 °C in lipid. (The temperature rise in a different rubber phantom monitored using a

thermocouple under the same transducer setup confirmed about 4-5 °C rise in 4 s). According to the American Institute of Ultrasound Medicine, no significant, adverse biological effects are expected for temperature increase of 5 °C if the exposure time is less than 2 minutes (for 4 °C rise, the corresponding allowable exposure time is 16 minutes) (<http://www.aium.org/resources/statements.aspx>, “Statement of Heat”). Since US-TSI of current design takes only about 4 s (plus a few tens of seconds for the tissue to cool down to normal body temperature) the technique is deemed temperature-safe. Also, the measured mechanical index (MI) for US-TSI was found to be 0.96, which is well below the FDA maximum allowance of 1.9.

A noteworthy point about Fig. 6 is that it is hard to exactly match the US imaging plane with the histology section even though surgical sutures were used for landmarking. Moreover, the imaging plane and the histology plane may be slightly skewed precluding an exact match. Multiple histology sections with 1 mm step that were stained around the imaging plane consistently show the presence of fat similar to what is seen in Fig. 6 (c); however, an exact match is not claimed.

Although noninvasive UEI can also detect large soft lipid pools in plaques [32]–[34], the results are sometimes difficult to interpret due to complex mechanical boundary conditions. US-TSI can provide complementary information to UEI, and the thermal strain image and elasticity image co-registered with US B-mode image can provide comprehensive information to assess the vulnerability of a plaque.

VI. Conclusion

We demonstrated through *in vitro* experiments with phantom and excised tissue as well as computer simulation that H-W successfully separates thermal strain from mechanical strain, which suggests the feasibility of ECG-independent US-TSI to noninvasively detect large lipid pools in atherosclerotic plaques in the presence of pulsatile blood flow. The ECG-independent US-TSI can be implemented in a standalone commercial US transducer requiring only additional software installations: (i) to control US beamforming for inducing temperature rise, and (ii) to perform the signal processing for strain estimation and time series analysis as prescribed in the paper. Animal study using high fat high cholesterol diet rabbit model are ongoing in our lab to further investigate the *in vivo* applicability of the US-TSI+H-W technique presented in this paper.

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Fig. 1.
Cross-sectional geometry of the FE simulation model.

Fig. 2.

Temperature, theoretical thermal strain, and the US-TSI+H-W estimate of thermal strain in lipid obtained *via* FE simulation.

Fig. 3.

Thermal strain image obtained *via* FE simulation and synthetic US-TSI+H-W. Dashed lines indicate the US heating beam (full width at half max.).

Fig. 4.

(a) Pulse pressure over 1 pump cycle (b) Total strain (c) Decomposed thermal strain and (d) Decomposed mechanical strain. The images are reported at different phases of the cardiac cycle marked by circles in (a). Line plots show the corresponding strains in a region in rubber marked by x.

Fig. 5.

(a) Total strain measured by US 2DST in a 2 mm $\times$ 2 mm region in rubber when the pump was on. (b) Comparison of the thermal strain extracted through H-W algorithm when the pump is on with the thermal strain obtained when the pump is off (when there is no mechanical strain).

Fig. 6.

Thermal strain (a), peak mechanical strain (b) and Oil-Red-O staining (c) of excised human atherosclerotic vessel. (d) Thermal strain in a fatty region as a function of time. Dashed lines in (a) indicate the US heating beam (full width at half max.).

Table 1

Thermal and mechanical properties of tissue used in the FE simulation.

Tissue	Thermal properties		Mechanical properties	
	Specific heat (C [J/kg.K])	Coeff. of sound speed change (α)	Mass density (ρ [kg/m ³])	Stiffness [kPa]
Lipid	2490	-0.15%	910	Viscoelastic $G' = 5$, $G'' = 4$
Fibrous cap	3590	0.1%	1050	Neo-Hookean $G=10$
Vessel wall	3590	0.1%	1050	Mooney-Rivlin $C_1 = 47$, $C_2 = 357$
Muscle	3590	0.1%	1050	Linear elastic $E = 100$
Blood	3600	-	1060	Viscous $\eta = 0.003$ Pa.s