Thermal strain imaging: a review

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Thermal strain imaging (TSI) or temporal strain imaging is an ultrasound application that exploits the temperature dependence of sound speed to create thermal (temporal) strain images. This article provides an overview of the field of TSI for biomedical applications that have appeared in the literature over the past several years. Basic theory in thermal strain is introduced. Two major energy sources appropriate for clinical applications are discussed. Promising biomedical applications are presented throughout the paper, including non-invasive thermometry and tissue characterization. We present some of the limitations and complications of the method. The paper concludes with a discussion of competing technologies.

Keywords: ultrasound; thermal strain imaging; tissue differentiation; non-invasive thermometry

1. INTRODUCTION

From the original A-mode system to modern scanners producing real-time two- and three-dimensional images of anatomy and blood flow, ultrasound (US) is celebrating over 50 remarkable years. It has become a standard clinical tool in the diagnosis and treatment of illness and injury. Perhaps the best-known use of US is for non-invasive imaging of internal organs and the developing foetus. It does, however, have other applications in medical diagnostics, such as in tissue characterization and measurement of tissue motion in vivo.

The purpose of this paper is to review a US application called thermal strain imaging (TSI), representing a collection of techniques that have appeared in the literature over the past several years. We hope to provide enough of the basic theory and several applications to demonstrate its clinical potential. TSI exploits changes in ultrasonic tissue properties in a localized region as that region is heated through absorption of a directed-energy source. As the temperature increases in soft tissue, the tissue expands and the ultrasonic propagation speed changes, introducing physical and apparent shifts in scatterer position, respectively [1–7]. The latter is dominant over a wide range of operating conditions near body temperature (nominally 37°C) [8,9]. The local temporal gradient of scatterer shift, often called the thermal strain, is directly related to tissue composition and temperature.

TSI has been developed primarily for two medical applications: non-invasive thermometry and identification of lipid pools and lipid-bearing tissue within otherwise water-bearing tissue [1–5,8–31]. As demonstrated in §2, TSI can be used to image the distribution of temperature change in a region during thermal therapy based on changes in sound speed with temperature. The type of directed-energy source used for heating is determined primarily by the therapeutic application and TSI can monitor the procedure, helping to optimize energy delivery for the desired clinical outcome. Many investigators have explored TSI for this application, and there are significant limitations on the technique as a general thermometry tool [1–5,8–19]. Nevertheless, there are several clinical applications where TSI can potentially monitor and optimally guide thermal therapies. One such application will be presented in subsequent sections.

In contrast, TSI for tissue characterization (i.e. identification of lipids) exploits the fact that temperature-dependent changes in the sound speed for water-bearing tissues are of the opposite sign to those in lipid-bearing tissues. Imaging of thermally dependent sound speed changes using a small temperature rise represents a potentially non-invasive tool to identify lipid pools and lipid-bearing tissue within otherwise water-bearing tissue. For this application, a directed-energy source is used to deliver a short heat pulse providing a localized, non-invasive temperature change of about only 1–2°C [20–25,27–31].
Several different directed-energy sources have been tested for TSI [15–44]. Here, we consider two appropriate for clinical applications: electromagnetic (radiofrequency (RF) and microwave) and ultrasonic. Both have been used extensively for therapeutic applications [20–48] requiring rapid heating of internal soft tissue, and both represent highly controlled sources that can be tuned for non-invasive tissue characterization applications of TSI. Electromagnetic radiation, when applied to tissue over a short period, causes a temperature rise owing to absorption depending on tissue dielectric properties. Similarly, ultrasonic heating arises from local tissue absorption of high-frequency pressure waves. Apparent US speckle displacements owing to a local temperature change associated with a directed-energy source are determined from local changes in the sound speed and can be estimated using speckle tracking (ST). Temporal (thermal) strains derived from these displacements can be used for TSI.

This paper is organized as follows. Section 2 presents the theoretical background and the operating equations describing TSI. Section 3 briefly describes the major heating sources of TSI. Section 4 gives some examples where TSI has been successfully applied. We start with tissue differentiation and identification of vulnerable arterial plaque owing to the strong contrast between water-bearing and lipid-bearing tissue. A preliminary study on regulating energy delivery during intracardiac RF ablation using TSI is then presented. In §5, we present some limitations and challenges of the method. Finally, the paper concludes with a discussion of potential clinical applications in §6.

2. BASIC THERMAL STRAIN THEORY

TSI has been proposed for both non-invasive thermometry and tissue differentiation using phase-sensitive ST to create thermal (temporal) strain images based on the temperature dependence of sound speed. We first demonstrate the theory using a general heating source and then focus on several specific directed-energy sources in §3.

Use \( z \) as the spatial coordinate, and let \( z_0 \) denote the depth in a soft tissue from the transducer surface as the tissue is initially at temperature \( \theta_0 \) everywhere and has a sound speed distribution \( c(\theta_0, z_0) \). The round-trip time delay of an echo from a scatterer at \( z_0 \) is [8]:

\[
\tau(z_0) = 2 \int_0^{z_0} \frac{dz'}{c(\theta_0, z')}.
\]  

(2.1)

After some temperature change, \( z_0 \) moves to \( z \) owing to thermal expansion, and the temperature distribution becomes \( \theta(z) = \theta(z_0) \). Considering one-dimensional thermal expansion of tissue,

\[
z = \int_0^{z_0} [1 + \beta(z') \cdot \delta \theta(z')] dz',
\]  

(2.2)

where \( \beta(z_0) \) is the linear coefficient of thermal expansion and \( \delta \theta(z_0) = \theta(z_0) - \theta_0 \) is the temperature change. The temperature change results in a new sound speed distribution \( \tilde{c}(\theta(z), z) = c(\theta(z_0), z_0) \) and consequently a new time delay

\[
\tilde{\tau}(z) = 2 \int_0^z \frac{dz'}{c(\theta(z'), z')}.
\]  

(2.3)

or expressed in \( z_0 \) as

\[
\tilde{\tau}(z) = \tau(z_0) - \tau(z_0) = 2 \int_0^{z_0} \frac{1 + \beta(z') \cdot \delta \theta(z')}{c(\theta(z'), z')} \frac{dz'}{c(\theta_0, z_0)}. \]  

(2.4)

Therefore, tissue heating or cooling results in a time shift

\[
\delta \tau(z_0) = \tau(z_0) - \tau(z_0) = 2 \int_0^{z_0} \frac{1 + \beta(z') \cdot \delta \theta(z')}{c(\theta(z'), z_0)} \frac{dz'}{c(\theta_0, z_0)}. \]  

(2.5)

Differentiating equation (2.5) with respect to \( z_0 \) gives the temporal echo shift per unit length owing to the temperature change around depth \( z_0 \)

\[
\frac{d}{dz_0} [\delta \tau(z_0)] = 2 \left[ \frac{1 + \beta(z_0) \cdot \delta \theta(z_0)}{c(\theta(z_0), z_0)} - \frac{1}{c(\theta_0, z_0)} \right].
\]  

(2.6)

As a first-order estimate, a linear relationship is assumed between sound speed and temperature. This approximation is valid over a large enough temperature change (approx. 10°C) near body temperature of 37°C that it can be used to describe differential speed changes owing to differential temperature changes [11]. Accordingly,

\[
c(\theta(z_0), z_0) = [1 + \lambda(z_0) \delta \theta(z_0)] c(\theta_0, z_0),
\]  

(2.7)

where

\[
\lambda(z_0) = \frac{1}{c(\theta_0, z_0)} \frac{\partial c(\theta(z_0), z_0)}{\partial \theta(z_0)} \bigg|_{\theta(z_0)=\theta_0}
\]

is a linear coefficient that determines sound speed variation versus temperature. In general, \( \lambda \) itself is a function of temperature. When \( |\lambda(z_0) \delta \theta(z_0)| \ll 1 \) and plugging equation (2.7) into equation (2.6),

\[
\frac{d}{dz_0} [\delta \tau(z_0)] \approx 2 \left[ \frac{\beta(z_0) - \lambda(z_0)}{c(\theta(z_0), z_0)} \right] \delta \theta(z_0) \]  

(2.8)

or

\[
\delta \theta(z_0) \approx \frac{1}{\beta(z_0) - \lambda(z_0)} \frac{c(\theta_0, z_0)}{\lambda} \frac{d}{dz_0} [\delta \tau(z_0)].
\]  

(2.9)

Since \( dz_0 = (c(\theta_0, z_0)/2) \, d\tau_0 \) according to equations (2.1), (2.8) leads to

\[
\frac{\partial}{\partial \tau_0} [\delta \tau(z_0)] \approx \left[ \frac{\beta(z_0) - \lambda(z_0)}{c(\theta_0, z_0)} \right] \delta \theta(z_0). \]  

(2.10)

The variable \( (\partial/\partial \tau_0)[\delta \tau(z_0)] \) has the form of a temporal strain and is called thermal strain to denote the thermal source of the apparent strain induced in US pulse-echo signals. Water-bearing tissue has \( \lambda (\circ C^{-1}) \) ranging from \( 0.7 \times 10^{-3} \) to \( 1.3 \times 10^{-3} \) and lipid-bearing tissue has \( \lambda \) ranging from \(-1.3 \times 10^{-3}\) to \(-2 \times 10^{-3}\) near normal body temperature of 37°C [49]. Given a 1°C temperature rise and neglecting thermal expansion,
the thermal strain of water-based tissue is around \(-1 \times 10^{-3}\) (i.e. \(-0.1\%\)), and the thermal strain of lipid-based tissue is around \(1.7 \times 10^{-3}\) (i.e. \(0.17\%\)). As shown later, thermal expansion can be ignored over a wide range of operating temperatures, but in water-bearing tissue at temperatures commonly used for thermal therapy, thermal expansion must be considered.

From equation (2.10), it is clear that there is a linear relationship between thermal strain and temperature change. The proportionality constant is directly related to the dependency of sound speed on temperature. The variation in sound speed with temperature for most water-bearing soft tissue follows a similar pattern to that of water. Around 37°C, \(\lambda\) has a positive value and overwhelms \(\beta\) for water-bearing tissue by at least an order of magnitude. However, at temperatures above about 50°C, there is no further increase in the sound speed and \(\lambda\) may become slightly negative. At this point, thermal expansion can contribute to physical displacements at the same level as sound speed variations to apparent displacements. Figure 1 shows the sound speed in both blood and bovine liver as a function of temperature. The peak of these curves lies somewhere between 45°C and 55°C. As discussed below, this interesting property can potentially be used to regulate energy delivery during intracardiac RF ablation.

To produce a thermal strain image, conceptually, the US speckle pattern is measured immediately before and after a heat pulse is applied to the medium. In reality, real-time ultrasonic images are acquired continuously before, during and immediately after the application of the heat pulse. Speckle formation and statistical properties are directly related to the underlying tissue microstructure and can be used to track apparent tissue motion as a spatial marker [50,51]. Two-dimensional ST can be used to quantify displacements between any image pair based on the similarity between the fine structure (speckle patterns) of these images [21,22,26,50–52].

In two-dimensional ST, a complex correlation coefficient function \(R\), representing similarities between a speckle pattern, derived from the analytical signal representation of the RF image, centred at \((b_0, m_0)\) in image \(i\) and speckle patterns centred around \((b_0, m_0)\) in image \((i+1)\), is computed as [50,51]

\[
R_{b_0, m_0}(k; j) = \frac{\sum_{b=-B}^{B} \sum_{m=-M}^{M} s_i^*(b_0 + b, m_0 + m)s_{i+1}(b_0 + b + k, m_0 + m + j)}{\sqrt{\sum_{b=-B}^{B} \sum_{m=-M}^{M} |s_i(b_0 + b, m_0 + m)|^2} \sqrt{\sum_{b=-B}^{B} \sum_{m=-M}^{M} |s_{i+1}(b_0 + b + k, m_0 + m + j)|^2}}. \tag{2.11}
\]

The kernel size \((B \times M)\) is directly related to the spatial resolution and signal to noise ratio (SNR). The trade-off is one of precision (i.e. smaller variance) versus spatial resolution. The smaller the kernel size, the higher the spatial resolution. However, as the kernel size is reduced below the autocorrelation width of the US pulse, the variance will increase. For large kernel size representing several speckle spots, strain decorrelates the US signal and both spatial resolution and precision are reduced. Thus, the correlation kernel size should be about the size of the speckle for optimal strain estimation [51]. Additional gains in SNR are possible by spatially filtering the correlation function over several speckle spots at the price of degraded spatial resolution.

The two-dimensional displacement \((d_x, d_y)\) is initially estimated by finding the peak position of the magnitude of the spatially filtered correlation coefficient function using a parabolic fit. The axial displacement \(d_x\) is then further refined by calculating the position of the phase zero-crossing around the peak correlation coefficient [50,51]. Since there is no phase information in the lateral direction, lateral displacement \(d_y\) estimates have much larger variance than axial ones. In general, two-dimensional ST produces three outputs at each image pixel: axial displacement, lateral displacement and the magnitude of the correlation coefficient at the peak position \((\rho = |R|)\) at peak, which can be used as a similarity/quality metric for the correlation process.

The thermal strain \((\partial/\partial T)\delta t(Z))\) in equation (2.10) can be estimated at each image point from the displacement outputs (i.e. apparent displacement) of the two-dimensional ST procedure as

\[
\text{thermal strain} \ (b, m) = s_x(b, m) = \frac{d_x(b, m + n) - d_x(b, m - n)}{2n \cdot \Delta d}, \tag{2.12}
\]

where \(d_x(b, m + n)\) is the displacement (in millimetre) at pixel \((b, m + n)\), \(d_x(b, m - n)\) is the displacement (in millimetre) at pixel \((b, m - n)\), and \(\Delta d\) is the spatial extent (in millimetre) of a pixel in the sampled system. The window size \(n\) used to calculate the final strain should be about the size of the correlation function filter. The final spatial resolution of the resulting TSI is determined by \(n\). The thermal strain has the same form as mechanical strain and can be confused with mechanical strain if large mechanical deformations are present. As discussed below, great care must be applied in TSI to ensure that mechanical strains do not
confound thermal measurements. Results using this algorithm are presented in §4 for several applications.

3. HEATING SOURCE

Controlled heating is a key component of any TSI system. Although US heating is preferred since it is easier to integrate into a commercial US imaging system, both US and electromagnetic sources have been investigated.

3.1. Microwave-induced heating

In early work by Shi et al. [20,21], tissue differentiation based on TSI (called microwave-induced thermal imaging then) was proposed. Microwave radiation was used to induce a temperature rise, and thermal strains resulting from local changes in sound speed were estimated using phase-sensitive, correlation-based ST 
[51,53]. In later work from the same group [22,23], TSI was tested on a tissue phantom using intravascular ultrasound (IVUS) imaging catheters. The ultimate goal was to design an appropriate directed-energy source to provide controlled heating of coronary arteries during an IVUS procedure to help differentiate plaque characteristics in the coronaries using TSI.

As an example, a microstrip loop radiator was designed to optimize efficiency and deliver continuous microwave radiation at a frequency of 915 MHz to tissue equivalent phantoms [20,21]. It created an approximately uniform radiation pattern for planes parallel to the antenna surface. Nevertheless, the electromagnetic field strength decreased as a function of distance from the radiator. The power was estimated to be 70 W. During microwave heating, beamformed RF data were collected using a Volcano Therapeutics In-Vision IVUS system sampled at 50 MHz.

Although the concept of microwave heating for TSI was successfully demonstrated, a few practical limitations were observed. The primary one was overheating on the surface, as the antenna used in this study cannot be focused. A more complicated antenna array must be designed to focus the energy only to the target area before this technique can be used clinically.

3.2. Ultrasound-induced thermal strain imaging with a therapeutic and an imaging transducer

A simple and controlled energy delivery system for US heating in TSI was successfully designed and tested using a two-element confocal transducer [25]. As an extension of this work, a 513 element two-dimensional therapeutic phased array (Besançon, FR, USA) was combined with a conventional US scanner (iU22, Philips, WA, USA) [28]. The array was used as the US heat source [29]. It is a 150 mm diameter spherical section with a 150 mm geometric radius. The operating frequency was 1 MHz. By applying appropriate phase shifts to elemental drive signals, pulse sequences [29] were designed to uniformly heat an extended region of interest (ROI) over a few seconds. With the designed US heating beam pattern and pulse sequence, the targeted ROI was uniformly heated with reasonably low peak intensity over a few seconds. Note the mechanical index (MI) used in this study is relatively high (approx. 6), but an MI below Federal Drug Administration (FDA) guidelines producing the same temperature rise can be achieved at higher frequencies using a diagnostic US transducer. The temperature rise in an ROI of the rubber phantom was estimated by TSI (0.56%) to be 3.2°C within 2 s, very close to predictions.

3.3. Ultrasound-induced thermal strain imaging with a single transducer

Recent experiments have explored the feasibility of inducing and imaging thermal strain using one US array [30,31]. A US scanner (Sonix RP, Ultrasound, Canada) drove a linear array probe (L14-5/38) to heat and image a gelatin phantom with a cylindrical 3 mm diameter rubber inclusion. Based on TSI, the inclusion was identified as a lipid-bearing material with a 1.1 s heating time. According to the A value for lipid-bearing tissue, the rate of temperature rise within the inclusion was of the order of 1°C s⁻¹.

When the US scanner (Sonix RP) operates in clinical mode in which a short pulse is transmitted for imaging, it maintains an MI not greater than 0.96 for all image points. In Huang et al. [31], it was demonstrated that it is possible to induce a temperature rise high enough (approx. 1°C) for tissue composition characterization in peripheral vessels such as the carotid artery within 1 s with a reasonable duty cycle (of the order of 2%) using the same imaging system.

3.4. Radiofrequency ablation for intracardiac applications

Catheter-based intervention has become the treatment of choice for many cardiac arrhythmias. Currently, the energy source used most often in these procedures is unipolar RF energy, typically 300–1000 kHz, which allows precise destruction of targeted tissue. The goal is to successfully ablate critical tissue within the tachycardia circuit or focus but avoid local complications and collateral damage to adjacent anatomic structures. As will be shown in §4, an intracardiac catheter monitoring a cardiac ablation can use TSI to help guide the procedure. Alternative energy sources for ablation and the biophysics of RF lesion formation could be found in other papers and will not be covered here [32–48,54–58].

3.5. Discussion

For thermometry applications, the heating source is determined primarily by the therapeutic procedure. For tissue characterization studies, however, the heating source should be optimized for non-invasive impact and easy integration with a traditional US imaging system. US heating using an array transducer focused only to the ROI delivers more controlled heating than other potential directed-energy sources. Also, an US heating/ imaging scheme using a single US probe connected to a commercial US scanner will provide significant system practicality, and it does not require a specially designed electromagnetically shielded room. In summary, both
electromagnetic [20–23,32–48] and US heating [24–31] have been used to demonstrate the feasibility of TSI. Future clinical applications will primarily use US heating for TSI unless electromagnetic heating is already integrated into the system for therapeutic purposes.

4. BIOMEDICAL APPLICATIONS OF THERMAL STRAIN IMAGING

4.1. Plaque characterization and remote detection of lipid-bearing tissue

Coronary heart disease affects 13 million Americans and causes about 0.5 million deaths in every year in the USA [59]. The underlying mechanism of most acute coronary events is the disruption of atherosclerotic coronary plaques to release thrombogenic material leading to intraluminal thrombus [60–62]. Rupture-prone plaques in the coronary arteries, or “vulnerable plaques”, typically consist of a large lipid-rich core in the central portion of the eccentrically thickened intima and a thin fibrous cap. Identification of these potentially fatal plaques before their disruption is clinically desirable and will help predict cardiovascular risk and guide therapeutic treatment.

TSI features strong contrast between lipid-bearing and water-bearing tissues since they have the opposite sign for the $\lambda$ parameter near 37°C. Therefore, it has the potential to identify a lipid laden pool within a vulnerable plaque. We have explored TSI for this application using two types of high-resolution US imaging system: catheter-based IVUS and ultrasonic microscopy.

As a relatively new approach to arterial vascular wall imaging, catheter-based IVUS using high-frequency (>20 MHz) probes provides cross-sectional, tomographic perspectives of the vessel and permits real-time measurements of lumen area and plaque size at a spatial resolution beyond that of conventional US imaging [63–65]. It serves as a valuable tool for atherosclerotic disease diagnosis and image-guided interventional procedures, such as angioplasty and atherectomy. However, standard IVUS shows low sensitivity in detecting subendothelial plaque components like lipid-rich lesions, critical to assessing plaque stability [66].

Investigations of vessel wall mechanical properties with strain and elasticity imaging indicate a possible relationship between plaque elastic properties and composition [67–69]. IVUS RF data analysis also shows promise for in vivo plaque classification [70]. All these techniques increase the potential utility of IVUS to detect high-risk plaque in coronary arteries. Shi et al. [22] presented TSI as an add-on technique, potentially enhancing IVUS for vulnerable plaque characterization.

In initial experiments by Shi et al. on TSI for vulnerable plaque characterization, the temperature was not uniform over the entire experiment because of thermal diffusion and relative distances from the antenna. Three B-scan frames taken at the beginning, middle and end of heating are represented in figure 2 on the left. In the right panel, the corresponding thermal strain images are superimposed on the B-scan and displayed over a range of $-0.16$–$0.16\%$ for better image contrast. The heating process of both rubber and gelatin can be visualized from the strain images. As expected, rubber has positive thermal strain and gelatin has negative strain. In figure 2, the contour of the gelatin is highlighted with two dashed circles based on strain contrast. The diameters of the inner and outer circles are 6.4 and 10.4 mm, respectively. They match the real dimensions (6.8 and 11.2 mm) very well. The microwave antenna is also visible in the figure and poor correlations were found near it, suggesting overheating in areas next to the antenna.

Kim et al. [28], evaluated plaque discrimination for a small temperature change (1°C) for high-resolution TSI studies using a US microscope. A custom US microscope using a 50 MHz single element focused ultrasonic transducer produced high-resolution TSI images of an excised porcine coronary artery. Samples were placed in a temperature-controlled water chamber and scanned transversely and longitudinally.

As soon as warm water was poured into the outer Petri dish, a slow and monotonic temperature rise was observed in the tissue. Temporal (thermal) strain was estimated in the region where temperature increased monotonically. The accumulated thermal strain image is overlaid onto the referenced B-scan image in figure 3. Blue (bottom white arrow) represents negative temporal strain owing to increased sound speed and red (top black arrow) represents positive temporal strain owing to decreased sound speed. Both transverse and longitudinal TSI images compare well with B-scans of arterial wall structures, including intima, media, adventitia and covered fatty tissue.

The average thermal strain over an extended region is estimated to be $0.47 \pm 0.04\%$ in fatty tissue including adventitia and $-0.24 \pm 0.05\%$ in intima and media, representing temperature rises of $2.8 \pm 0.2$°C and $2.4 \pm 0.5$°C, respectively. Note that average values of $\lambda$ were used; (0.1°C)$^{-1}$ for water-based tissue and (–0.17°C)$^{-1}$ for fatty tissue. The temperature change inside the tissue monitored by a thermocouple was 1.6°C. This result demonstrates the feasibility of high-resolution TSI using two-dimensional phase-sensitive correlation-based ST. TSI clearly differentiates lipid-bearing tissue from water-bearing tissue, and temperature estimates from TSI agree reasonably well with measured temperature changes.

Most clinical applications will require both remote heating and imaging of the tissue ROI. As an initial test of the ability of TSI to remotely detect lipid-bearing tissue at depth using conventional US equipment for both heating and imaging, a set of experiments was performed on the right kidney of a normal 3 kg New Zealand white rabbit [28].

Figure 4a represents the B-scan of the kidney. The box displays the cross section of the heating volume along the beam direction, where the red arrow (left to the right) shows the propagation direction for US heating and the blue arrow (top to the bottom) identifies the propagation direction for thermal imaging. The hypoechoic pattern reflects the collecting system and the small hyperechoic part inside represents fat. Figure 4b depicts the correlation coefficient of US ST between two image frames before and after heating. They correlate well overall except a small spot right
above the fat, which might be a blood vessel. Finally, fatty tissue surrounding the collecting system was clearly differentiated and thermal strain maps match well with anatomy, as illustrated in figure 4c–e.

Finally, to test the potential of US-induced TSI for vulnerable plaque characterization remotely (i.e. non-invasively), a canine aorta was prepared with fatty tissue inside the lumen [28]. Figure 5b,e depicts TSI maps overlaid on the B-scan. Figure 5c,f represents the correlation coefficients of US ST between two image frames before and after heating. TSI scans match well with anatomy both in transverse and longitudinal views, although there is an artefact (red instead of blue identified by white arrow) at the right upper side of the artery, especially near the outside boundary with the gel in the transverse scan (figure 5b). Relatively lower correlation with lower echogenecity was observed in this region.

Overall, initial results in phantoms and ex vivo tissue samples demonstrate the potential for TSI to highlight regions of high lipid concentration in otherwise primarily water-bearing tissue. Except for the study with a US microscopy where warm water delivered heat, the results shown in this subsection were all obtained with experimental systems in which the directed energy source and imaging system were synchronized but physically decoupled. For most clinical applications, however, the same device used for imaging will most likely be used for the directed energy source providing controlled heating of the ROI, such as the system

Figure 2. B-scan and combined (B-scan and thermal strain) images during microwave heating from phantom experiment. (a,c,e) B-scan images at different times \((t = 0.13 \, \text{s}, 1.1 \, \text{s} \text{ and } 3.2 \, \text{s})\). (b,d,f) Corresponding combined images. The dimensions of all images are \(20 \times 20 \, \text{mm}\). Note in (f), red and blue represent rubber and gelatin, respectively. The two circles mark inner and outer gel boundaries. In addition, the bright echoes at the lower right corner were from the microwave antenna.
4.2. Regulation of energy delivery during intracardiac radiofrequency ablation

Radiofrequency ablation (RFA) is used in electrophysiology procedures to permanently alter the myocardium in locations which support aberrant electrical conduction pathways contributing to irregular heart rhythm. Regulating power to maximize the safety and efficacy of energy application is critical for successful outcomes.

Currently, the effects of RF delivery can be monitored indirectly by real-time analysis of impedance [71], electrogram amplitude [72], the electrophysiologic behaviour of the tissue being ablated [73] and temperature at the tip of the electrode [37,74]. Among these, tissue temperature is critically related to the success or failure of catheter ablation procedures [35,36]. To ensure irreversible injury, a tissue temperature of approximately 50°C must be achieved [35,36]. The minimum temperature needed to create a complete heart block has been observed to be 48°C [37,38]. Raising tissue temperature significantly beyond this point can be unnecessary and cause complications.

Because of the importance of temperature monitoring, a standalone thermocouple or a thermistor embedded in the electrode is used during catheter RFA procedures [36,37]. During energy delivery, a portion of the electrode should be typically in contact with the tissue and the remainder in contact with surrounding blood. The electrode temperature recorded by the thermocouple reflects a complex interaction between the production of heat in nearby tissue by the RF field and convective heat loss to surrounding blood and tissue [36,41–43]. Because of convective heat losses, the temperature recorded by the thermocouple should be consistently less than that at the hottest point in the tissue, misleading the operator to increase the energy delivered.

An optical fluorometric temperature probe [37,44], for example, could be used for more sensitive measurement at increased cost and lower speed. In general, temperature sensors are additional devices to be handled and installed in an already crowded catheter tip volume.

Temperature imaging using US techniques is more attractive because of the potential to provide two-dimensional real-time temperature information at low cost. US-based temperature measurement over large temperature ranges, however, is limited because the sensitivity to sound speed changes beyond 50°C is low [6]. If a very high temperature is considered (tissue temperature of 80°C or higher), as in the case of high-intensity focused ultrasound, the effect is twofold: sound speed variations with temperature are not as sensitive and the tissue undergoes state changes that could fundamentally change the US backscatter signal character. Also, limited data are available for the relationship between temperature and the sound speed in tissues in vivo, especially, at temperatures above 50°C.

Sound speed variations with temperature introduce apparent shifts in scatterer position and thermal changes in the velocity of sound.
expansion of the medium introduces a physical shift in scatterer position. Beyond 50°C, thermal expansion is no longer negligible and contributes to the total echo shift or delay in strain calculations. Thus, TSI may not be practical for ablation monitoring based on precise temperature measurements since it is more sensitive and unambiguous for small temperature changes in the temperature range below 50°C. For ablation treatment of arrhythmia, however, a robust, reproducible indicator of tissue necrosis rather than absolute temperature monitoring is required. In particular, it is more important to know when tissue temperature has reached or exceeded 50°C so ablation can be terminated [1–19].

Considering thermally induced strain as a function of time during the ablation procedure, we hypothesized that there is a point when the slope of the thermally induced strain approaches zero. That is, by continuously tracking from a reference frame just prior to the start of ablation, the thermal strain will eventually plateau because the sound speed has reached its maximum value as a function of temperature.

The signal-processing methods proposed in this subsection were developed to investigate the feasibility of monitoring ablative therapy by identifying a point at which the magnitude of the slope of the thermal strain curve reduces significantly, caused primarily by smaller sound speed variations with temperature. The feasibility of this method for ablation monitoring was tested in vivo using an animal model.

Juvenile Yorkshire pigs were used for these studies. Electrocardiography (ECG) electrodes were connected to the body of the pig for standard three-point recording. The output of the ECG served as the trigger for a modified Irvine Biomedical Inc. generator (St Jude Medical, Inc, St. Paul, MN, USA).

A specially designed US compatible RFA system was integrated into a prototype 9F forward-looking micro-linear (ML) intracardiac echocardiography catheter array to simultaneously image and ablate the right atrial wall [75]. Additionally, a thermocouple normally residing inside the electrode was pulled out to touch the tissue for thermal strain validation. Figure 6 shows the approximate geometry for this configuration. The transmit frequency was 11 MHz with a transmit focus at 2 mm. Ablation was performed while the
integrated imaging and ablation catheter was localized and guided by fluoroscopy.

Figure 7 shows B-mode and B-mode overlaid with thermal strain image when the thermal strain has reached its maximum magnitude. Figure 8 plots the thermal strain versus time. Several representative pixels in the focal region were averaged to plot this curve. A significant slope change is observed in the neighborhood of 50°C, suggesting that the tissue at this point is irreversibly damaged. In particular, this method appears promising for the case where heating is sufficiently fast to minimize the effects of thermal diffusion.

The potential of monitoring the progression of RF ablation in the myocardium using a slope change in the thermal strain curve has been demonstrated using in vivo measurements in a porcine model. The sound speed for most water-bearing tissue increases with temperature. However, at temperatures above about 50°C, there is no further increase in the sound speed and \( \lambda \) may become slightly negative. For ablation therapy, irreversible injury to tissue and a complete heart block occur at around 48–50°C. Using these two properties, a potential tool has been proposed to detect the moment when clinically significant tissue damage occurs using the reduced slope in the thermal strain as a function of heating time.

5. POTENTIAL LIMITATIONS

5.1. Tissue motion

A major obstacle for in vivo application of TSI is tissue motion, including respiratory and cardiac motion. Thermal strains are equivalent to their motion-induced mechanical counterparts and are typically much smaller. A 1°C temperature rise produces about −0.1 per cent thermal strain for water-based tissue and 0.17 per cent for lipids, whereas peak mechanical strains are normally of the order of a few per cent in a typical artery and 20–30% in the heart wall. Consequently, effective reduction of motion artefacts is critical for clinical use of TSI. Using ECG signals to trigger array firing, cardiac periodicity can be fully used to minimize motion artefacts, allowing thermal strains to accumulate over multiple cardiac cycles if needed with little distortion. For systems not directly synchronized with the ECG, motion compensation methods using spatial interpolation and linear least-squares fitting have been demonstrated to minimize the effects of residual tissue motion of up to 70 \( \mu \)m both for vessel studies [23] and during intracardiac imaging of the heart [76].

With some limitations, preliminary results demonstrated the practicality of ECG gated TSI using a commercially available US scanner [26]. Motion artefacts from vessel pulsations were greatly reduced when measurements were made one cardiac cycle apart, at the same phase of the cardiac cycle. Although the overall results are encouraging, some technical issues must be improved. For example, unexpected random tissue motion was observed, especially in frame-to-frame tracking. If this is mainly owing to breathing motion, it should not be a major issue in the clinic as TSI can be performed within 2–3 s while the subject holds his/her breath.

5.2. Thermal diffusion

Thermal diffusion is not a significant issue for most applications of TSI in which the heat pulse is delivered...
over a 1–5 s interval. However, for cardiac ablation monitoring in which large temperature changes (typically 15–30°C) can occur over a period of 10–60 s, thermal diffusion may be an issue. In particular, since the change in slope with time is used to monitor therapeutic effectiveness, the change in temperature with time should be constant in the ROI. This can only be assured if thermal diffusion is minimized.

To help study whether diffusion would compromise the RF cardiac ablation protocol described above, a finite element (FE) model of thermal diffusion was developed for this application [76]. Temperature rise from RF ablation as a function of time was estimated using an FE representation of the bioheat equation [77,78]:

$$\rho C \frac{\partial T}{\partial t} = k \nabla^2 T - W_b C_b (T - T_b) + Q,$$

where $k$ is the thermal conductivity of the tissue (0.533 W m$^{-1}$ K$^{-1}$), $T$ is the tissue temperature (K), $W_b$ is the blood perfusion rate (13 kg m$^{-3}$ s$^{-1}$), $C_b$ is the specific heat of the blood (4180 J kg$^{-1}$ K$^{-1}$), $C$ is the specific heat of the tissue (3720 J kg$^{-1}$ K$^{-1}$), $T_b$ is the blood temperature (310 K), $Q$ is the local power density deposition, $\rho$ is the density of the tissue (1060 kg m$^{-3}$) and $t$ is time (s) [40]. Calculation of power and temperature using the bioheat transfer equation has been proven to give realistic information [79].

The model assumes that the cardiac boundary and blood pool temperature remain at 37°C during the entire procedure. The initial temperature throughout the tissue was 37°C. A portion of the gold electrode delivering RF energy was in contact with the blood pool, limiting the extent of the heat delivered to tissue. The RF pulse sequence and exposure duration followed the experimental set-up described above. A two-dimensional, axially symmetric model was used to reduce computation time. The model consisted of 827 mesh points and 1584 triangular elements.

The temperature distribution during RF ablation is affected by two processes: resistive heating from the tip of the electrode and spatial redistribution of heat owing to thermal diffusion. We have compared the temperature rise from one of the in vivo datasets described above with this FE model. Figure 9 shows that the experimental heating protocol operates in a region where thermal diffusion has not taken over. In particular, the pulse duration for the heating scheme presented is sufficiently short that we can assume instantaneous heating of the medium with minimal thermal diffusion. In a clinical environment, rapid heating is required to reduce the effects of thermal diffusion and motion.

### 5.3. Thermal-acoustic lens

Thermally related changes in acoustic properties, especially sound speed, can distort the incoming acoustic wavefront, and potentially cause the acoustic focus to move and distort in an otherwise homogeneous media. In effect, a temperature distribution creates an acoustically inhomogeneous medium (i.e. thermal-acoustic lens effect). It has been shown that strong ripple artefacts owing to the thermal-acoustic lens effect can severely corrupt temperature estimates behind the heated region [7,80].

The overall effect from short insonifications at high power (60–70 W) from sharply focused sources is found to be small [81]. The main factors in producing thermal-acoustic lensing are the amount of prefocal heating along the propagation path and the response of the medium along this path to heating. Higher f-number systems and long, inhomogeneous (i.e. mixed fat- and water-bearing tissues) propagation result in more pronounced artefacts [82].

For the major clinical applications of carotid plaque characterization and intracardiac ablation monitoring anticipated for TSI, thermal-acoustic lensing should not be a significant issue. For peripheral artery applications, low f-number systems and short propagation paths will be used for highly localized heating of plaques. For intracardiac ablation monitoring, very short propagation paths in homogeneous, water-bearing tissue will be used. For other potential applications, however, in which high f-number insonification schemes operating over long, inhomogeneous paths are envisioned, thermal-acoustic lens effects must be considered.

### 6. CONCLUDING REMARKS

A new ultrasonic imaging technique, TSI, was reviewed in this paper. Phantom, ex vivo, and in vivo results illustrated two potential clinical applications. In the first, TSI can resolve water-based and lipid-based tissue at contrast and spatial resolution appropriate for arterial studies. In particular, it has the potential to distinguish a lipid-laden pool from the arterial vascular wall within a carotid plaque.

A major obstacle for any in vivo application such as plaque characterization in the carotid is motion, including respiratory and cardiac motion. Respiratory motion can be eliminated or minimized since TSI can be achieved within 2–3 s while the subject holds his/her breath. Using ECG signals to trigger image acquisition, cardiac periodicity can be fully used to minimize motion artefacts, allowing thermal strains to accumulate over multiple cardiac cycles with little distortion. For systems not directly synchronized with the ECG, motion compensation methods using spatial interpolation and linear least-squares fitting can help minimize the effects of residual tissue motion.

Although motion filtering algorithms have been demonstrated, finite background motion in real clinical imaging from physiological sources such as cardiac motion and respiration is unavoidable. Other imaging modalities, such as acoustic radiation force impulse imaging, have a similar problem of tracking small induced displacements during physiologic motion. Robust signal processing methods have been developed to track induced motion by synchronizing the data acquisition sequence with physiologic motion [83]. Similar methods can be developed for clinical applications of TSI [84].

A number of invasive and non-invasive imaging techniques are presently available to assess atherosclerotic...
vessels. The most common invasive method is X-ray angiography, which outlines the entire coronary vasculature and provides a measure of luminal narrowing or irregular luminal surface with excellent resolution. However, it cannot image the vessel wall directly, often causing misdiagnosis of asymmetric lesions. Angioscopy complements angiography by providing direct visualization of the plaque surface. The most significant limitation of current angioscopic systems is that direct visualization of the plaque surface is lacking calcium and therefore are not visible in CT images. Although OFDI is an important advance over OCT, there is no further increase in the sound speed. Using these two properties, a potential tool to optimize therapy and detect the moment when clinically significant tissue damage occurs is possible using the reduced slope in the thermal strain as a function of heating time.

Beside tissue motion, this application can be affected by thermal diffusion and thermal-acoustic lens effects. Thermal-acoustic lensing should not be a significant issue since very short propagation paths in homogeneous, water-bearing tissue will be used. Thermal diffusion can be minimized using a short electromagnetic pulse with sufficient power so that instantaneous heating of the medium with minimal thermal diffusion can be assumed. In a clinical environment, rapid heating is required to reduce the effects of thermal diffusion and motion.

Currently the tissue effects of RF delivery can be monitored indirectly by real-time analysis of impedance, electrogram amplitude, the electrophysiologic behaviour of the tissue being ablated and temperature at the tip of the electrode [37, 71 – 74]. Though several US investigators have looked at ways to measure temperature non-invasively and monitor lesion formation, as at the time of this writing, there is no other method to regulate energy delivery for this specific intracardiac RF ablation procedure.

The authors are aware of other interesting and independent work based on similar ideas, although for different applications [2, 10, 11, 119 – 124]. For example, the stiffness change in ablated tissues compared with normal ones, the temperature dependence of the shear modulus, and thermally induced changes in backscattered energy resulting from tissue inhomogeneities, are being investigated as tools to monitor ablation. Elastic modulus imaging for visualizing thermal ablation zones and electrode displacement strain imaging for monitoring abdominal RF A procedures are some of the new methods currently being investigated. They use the same RF data but process it differently. TSI has the clear potential to become part of RF ablation therapy of the heart, helping guide and optimize the procedure by identifying the moment of irreversible tissue damage. In the future, we will explore the possibility of integrating these measures for robust monitoring and real-time optimization of RF ablation in the heart.

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