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● *Original Contribution*

IMPROVED ESTIMATION OF ULTRASOUND THERMAL STRAIN USING PULSE INVERSION HARMONIC IMAGING

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Abstract—Thermal (temporal) strain imaging (TSI) is being developed to detect the lipid-rich core of atherosclerotic plaques and presence of fatty liver disease. However, the effects of ultrasonic clutter on TSI have not been considered. In this study, we evaluated whether pulse inversion harmonic imaging (PIHI) could be used to improve estimates of thermal (temporal) strain. Using mixed castor oil–gelatin phantoms of different concentrations and artificially introduced clutter, we found that PIHI improved the signal-to-noise ratio of TSI by an average of 213% or 52.1% relative to 3.3- and 6.6-MHz imaging, respectively. In a phantom constructed using human liposuction fat in the presence of clutter, the contrast-to-noise ratio was degraded by 35.1% for PIHI compared with 62.4% and 43.7% for 3.3- and 6.6-MHz imaging, respectively. These findings were further validated using an *ex vivo* carotid endarterectomy sample. PIHI can be used to improve estimates of thermal (temporal) strain in the presence of clutter. (E-mail: kangkim@upmc.edu) **© 2016 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Thermal strain imaging, Temporal strain imaging, Non-invasive ultrasound thermometry, Oil–gelatin phantom, Ultrasound clutter, Pulse inversion harmonic imaging.**

INTRODUCTION

Ultrasound thermal strain imaging (TSI), previously referred to as temporal strain imaging, is a non-invasive imaging technology that relies on the temperature dependence of the speed of sound as a means of differentiating fatty tissue from water-based tissue. In water-based tissues, the speed of sound increases with increasing temperature, and in lipid-based tissues, the speed of sound decreases with increasing temperature. This relationship is quantified with the material constant λ (in units of %/°C) and is a measure of the percentage change in sound speed per unit change in temperature (Seo et al. 2011a). For water-based tissues like normal liver and muscle, λ has been found to be between 0.06%/°C and 0.13%/°C. For lipid-based tissues like abdominal fat, λ is typically between −0.13%/°C and −0.20%/°C (Duck 2013). Clinically, TSI development is focused on non-invasive detection of fatty liver disease and identification of lipids in atherosclerotic plaques (Mahmoud et al. 2013, 2014).

In TSI, a reference ultrasound image is acquired. Next, custom beamforming and pulse sequences are used to generate a high-intensity ultrasound beam that will homogeneously increase the temperature in the target region by <2°C. The temperature increase is the result of absorption of the propagating ultrasound wave. After the heating sequence is completed, a post-heating ultrasound image is acquired. As a result of the change in the sound speed, there is an apparent displacement (time shift), u, between received echoes in the reference and post-heating images. The derivative of this displacement in the ultrasound wave propagation (axial) direction is the "thermal (temporal) strain," du/dz, and is

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proportional to the change in sound speed. In water-based tissue, this strain is negative and the tissue appears to undergo relative compression. In lipid-based tissue, the strain is positive and the tissue appears to undergo relative expansion. For the small temperature changes used in TSI, the temperature-induced mechanical strain resulting from volumetric tissue expansion is approximately an order of magnitude smaller than the apparent strain resulting from the change in sound speed and can typically be ignored (Seo et al. 2011a). Thus, the governing equation for TSI is

$$\frac{du}{dz} = -\lambda\Delta T, \tag{1}$$

where ΔT is the temperature change. In TSI, u is tracked by comparing the reference and post-heating images, and du/dz is calculated from the measured displacement.

Ultrasound non-invasive thermometry (NIT) is based on the same underlying physics as TSI, but incorporates three major differences. First, NIT is typically used to assess temperature changes during high-intensity focused ultrasound (HIFU) or radiofrequency (RF) ablation procedures, which result in temperature changes in the range 2°C to >20°C (Liu and Ebbini 2010; Seo et al. 2011b). In this temperature range, it is no longer acceptable to ignore thermally induced mechanical strains. As a result, the governing equation is modified to

$$\frac{du}{dz} = (\alpha-\lambda)\Delta T, \tag{2}$$

where α is the coefficient of thermal expansion. Finally, in NIT, the material constants are assumed to be known parameters. The temperature change is found by dividing the measured strain by the material constants.

Both TSI and NIT have been tested using *in vivo* animal models and *ex vivo* tissue preparations (Ding et al. 2015; Kim et al. 2008; Lai et al. 2010; Liu et al. 2008; Mahmoud et al. 2014; Miller et al. 2004). For TSI, these studies have been aimed at identifying the lipid-rich core of atherosclerotic plaques or quantifying hepatic steatosis. The clinical applications of NIT are focused on monitoring of thermal ablation as well as theranostic approaches using temperature-sensitive drug delivery vehicles. However, a number of challenges are present in human patients that are absent or less flagrant in small animal models. One major challenge is clutter-based degradation of image quality (Lediju et al. 2008). *Clutter* is a general term for noise that serves to decrease image contrast. One prominent source of clutter in patients is near-field reverberation. Near-field reverberation occurs because the propagating ultrasonic wave is reflected multiple times within superficial tissue layers (*e.g.,* skin, subcutaneous fat). These multiple reflections corrupt echoes arriving from deeper tissue structures and appear as a haze in the ultrasound image (Dahl and Sheth 2014). One method commonly used in clinics to reduce clutter is harmonic imaging. Harmonic imaging exploits the non-linear propagation of the fundamental wave and images the resulting second harmonic signal. The second harmonic signal is typically weak in the near field and reaches its peak intensity in the focal zone, which helps to mitigate near-field clutter artifacts (Christopher 1997).

Recently, groups have found that harmonic imaging can be used not only to improve traditional B-mode images, but also to improve ultrasound-based displacement tracking which serves as the basis for acoustic radiation force and shear wave imaging (Doherty et al. 2013; Song et al. 2013). Doherty et al. found that PIHI provides the greatest improvement to ultrasonically tracked displacements. In the pulse inversion technique, two 180° phase-shifted (inverted) fundamental pulses are transmitted sequentially. Summation of the received signals from these pulses results in cancellation of the fundamental signal and amplification of the harmonic. Because TSI measures strain calculated from ultrasonically tracked apparent displacements, we hypothesized that PIHI could also be applied to improve estimation of apparent strains produced as result of temperature-induced changes in the speed of sound. In this article, we describe how PIHI can be used to improve the quality of thermal (temporal) strain images using a variety of relevant imaging phantoms and *ex vivo* human tissue samples. Conventionally, NIT uses the same ultrasound tracking scheme as TSI. As such, we point out potential applications and parallels of this work to NIT when they are relevant.

METHODS

Ultrasound TSI pulse sequence

The pulse sequence and timing for the TSI sequence are diagrammed in Figure 1a. PIHI was incorporated into the imaging portions of the TSI pulse sequence using a research ultrasound platform with an external HIFU power supply (Vantage, Verasonics, Kirkland, WA, USA) using an ATL L7-4 transducer (Philips Healthcare, Amsterdam, Netherlands) (Christopher 1997). The −6-dB bandwidth of this transducer was measured to be 3.3–6.6 MHz. The overall sequence consists of imaging, followed by a heating phase, and ends with a post-heating imaging phase. There is a 35-ms pause between the first imaging phase and the beginning of the heating phase and a 500-μs pause between the end of the heating and the beginning of the final imaging phase. These pauses are inserted to allow time for data transfer and power supply switching.