Ultrasound in Med. & Biol., Vol. 40, No. 3, pp. 485–495, 2014

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2013.10.006

● *Original Contribution*

REAL-TIME MONITORING OF HIGH-INTENSITY FOCUSED ULTRASOUND TREATMENT USING AXIAL STRAIN AND AXIAL-SHEAR STRAIN ELASTOGRAMS

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(*Received* 21 *March* 2013; *revised* 7 *October* 2013; *in final form* 9 *October* 2013)

Abstract—Axial strain elastograms (ASEs) have been found to help visualize sonographically invisible thermal lesions. However, in most studies involving high-intensity focused ultrasound (HIFU)-induced thermal lesions, elastography imaging was performed separately later, after the lesion was formed. In this article, the feasibility of monitoring, in real time, tissue elasticity variation during HIFU treatment and immediately thereafter is explored using quasi-static elastography. Further, in addition to ASEs, we also explore the use of simultaneously acquired axial-shear strain elastograms (ASSEs) for HIFU lesion visualization. Experiments were performed on commercial porcine liver samples *in vitro*. The HIFU experiments were conducted at two applied acoustic power settings, 35 and 20 W. The experimental setup allowed us to interrupt the HIFU pulse momentarily several different times during treatment to perform elastographic compression and data acquisition. At the end of the experiments, the samples were cut along the imaging plane and photographed to compare size and location of the formed lesion with those visualized on ASEs and ASSEs. Single-lesion and multiple-lesion experiments were performed to assess the contribution of ASEs and ASSEs to lesion visualization and treatment monitoring tasks. At both power settings, ASEs and ASSEs provided accurate location information during HIFU treatment. At the low-power setting case, ASEs and ASSEs provide accurate lesion size in real-time monitoring. Lesion appearance in ASEs and ASSEs was affected by the cavitation bubbles produced at the high-power setting. The results further indicate that the cavitation bubbles influence lesion appearance more in ASEs than in ASSEs. Both ASEs and ASSEs provided accurate size information after a waiting period that allowed the cavitation bubbles to disappear. The results indicate that ASSEs not only improve lesion visualization and size measurement of a single lesion, but, under certain conditions, also help to identify untreated gaps between adjacent lesions with high contrast. (E-mail: Arun.K.Thittai@uth.tmc.edu) **© 2014 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Axial strain, Axial- shear strain, Cavitation bubbles, Elastography, High-intensity focused ultrasound, Multiple lesions, Real time, Single lesion, Strain, Stress, Treatment monitoring, Ultrasound.**

INTRODUCTION

High-intensity focused ultrasound (HIFU) is a non-invasive method for treatment of solid cancer (Chapelon et al. 1999; Fry et al. 1950; Gelet et al. 2000; Hynynen et al. 1996; Lynn and Putnam 1944; Sibille et al. 1993). With ultrasound waves focused on small regions inside a tumor, the acoustic energy can be converted into localized thermal energy that can heat tissue to temperatures >60°C and cause coagulation necrosis (Dubinsky et al. 2008). Because this procedure is non-invasive, an imaging device that could be used for image guidance and intra-operative assessment that is also non-invasive is appropriate. Currently, magnetic resonance imaging (MRI) thermometry and ultrasound B-mode (US) imaging are used. MRI-guided HIFU machines can provide accurate temperature measurements in three dimensions. The MRI temperature map can point to the location of the HIFU focus, as well as indicate the degree of tissue damage (Cline et al. 1994; de Senneville et al. 2007; Hynynen et al. 1996). The limitations of MRI are that it is expensive and labor-intensive and may not be appropriate for patients with magnetic metal implants.

Current ultrasound-guided HIFU (US-HIFU) has its own limitations. US-HIFU systems estimate the dimensions and location of the thermal lesion by monitoring tissue changes related to the formation of cavitation bubbles

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(Uchida et al. 2006; Wu et al. 2007). These cavitation bubbles induce increased scattering and attenuation (Barkman et al. 1999; Clarke and ter Haar 1997), which can partially reflect ultrasound waves and cause unpredictable HIFU energy to deposit on normal tissue outside the HIFU focus. Inside the focal zone, cavitation results in rupture and tearing of tissue (Barkman et al. 1999; Clarke and ter Haar 1997). Further, the distribution of bubbles is unstable, random and poorly correlated to the true location and size of the thermal lesion. Therefore, cavitation bubbles in HIFU ablation may not be used reliably as a monitoring tool for treatment evaluation. An appropriate monitoring system should provide the spatial temperature map of heating or have the capability to visualize the thermal lesion in real time. Thus far, ultrasound temperature imaging (Liu and Ebbini 2010; Seip and Ebbini 1995) and ultrasound elastic imaging (Bercoff et al. 2003; Bing et al. 2009; Kallel et al. 1999; Maleke and Konofagou 2008; Righetti et al. 1999; Stafford et al. 1998; Zhang et al. 2011) have been investigated and reported to have the potential to monitor HIFU treatment.

Seip and Ebbini (1995) proposed that by tracking shifts in the backscatter radiofrequency (RF) signal, caused by changes in the speed of sound with change in temperature, temperature estimation for real-time monitoring is feasible. However, temperature estimation above 50°C was reported to be inaccurate because of the nonlinear temperature dependence of the speed of sound in various tissues and because of thermal expansion (Liu et al. 2009; Miller et al. 2002). Other groups have exploited this shift in backscatter RF signal to estimate the "echo strain" and found that it can be used to visualize lesion formation (Miller et al. 2004; Souchon et al. 2005) as well as fully formed lesions. However, no follow-up work on this interesting approach has yet been reported. One major challenge to the aforementioned approaches is that even slight undesirable patient motion can spoil the image registration and subsequent estimation.

Elastography imaging is another widely researched technique and was introduced by Ophir et al. (1991) to exploit differences in tissue elasticity as a contrast mechanism to produce an image. It is known that protein denaturation and coagulation cause changes in the stiffness of the HIFU lesion compared with the surrounding soft tissue (Hynynen 1997; Sapin-de Brosses et al. 2010). Therefore, the feasibility of using axial strain elastograms (ASEs) to visualize and characterize the thermal lesions formed was reported in several studies (Kallel et al. 1999; Righetti et al. 1999; Souchon et al. 2003; Varghese and Ophir 1998), in which elastography was performed after the lesion had formed. Recently, Liu et al. (2011) proposed an approach combining temperature estimation and elastography for HIFU lesion determination during therapy. They exploited the reliability of temperature estimation from RF signals to locate and monitor lesions before the necrosis threshold, using elastographic estimations thereafter. We recently introduced a technique called axial-shear strain elastography (Thittai et al. 2005, 2007). In this technique, the axial-shear strain experienced by the tissue element caused by quasi-static compression (as in elastography) is imaged and referred to as the axial-shear strain elastogram (ASSE). Axial-shear strain is estimated using the equation

$$\varepsilon_{\text{axial}-\text{shear}} = \left(\frac{\partial v}{\partial x}\right) \tag{1}$$

where v is the displacement along the direction of compression (axial), and x is the lateral direction. We found that an ASSE can be used to visualize the HIFU-induced lesion boundary and that it provides more robust measurement of the lesion size (area) than that obtained from the corresponding ASE (Thittai et al. 2011).

Bercoff et al. (2004) proposed the use of supersonic shear imaging to monitor elasticity during HIFU treatment, before and after formation of the lesion. Further, Arnal et al. (2010) proposed combining US thermometry and supersonic shear-based elasticity imaging during HIFU therapy in *ex vivo* settings. The results to date seem interesting and bode well for further investigations. There are other elastographic methods, such as vibration elastography (commonly referred to as *sonoelastography*) (Parker et al. 1990), acoustic radiation force impulse (ARFI) imaging (Bing et al. 2009; Nightingale 2011; Nightingale et al. 2002) and harmonic imaging, that are all under various stages of investigation for possible use in all-ultrasound HIFU treatment and monitoring systems (Desser and Jeffrey 2001; Konofagou and Hynynen 2003; Maleke and Konofagou 2008). A major challenge to ARFI-based approaches is their reliance on pulse sequences necessary for radiation pressure-induced motion, which may require long exposure times and prolong the duration of HIFU treatment.

All of the above-described reports focus mostly on visualization of the formation of a single HIFU lesion and its characterization. However, it must be noted that typically, several small overlapping HIFU lesions are formed to treat a large region (Clement 2004). It is important to receive feedback on this progress, preferably in real time, to avoid missing any small region within the planned treatment area, because these untreated gaps can increase the chance of cancer relapse (Wu et al. 2004). Thittai et al. (2011) suggested that ASSEs may become a useful modality in such situations to visualize thin untreated region under certain conditions. The primary condition is that the