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● *Original Contribution*

CONTRAST-ENHANCED QUANTITATIVE INTRAVASCULAR ELASTOGRAPHY: THE IMPACT OF MICROVASCULATURE ON MODEL-BASED ELASTOGRAPHY

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Abstract—Model-based intravascular ultrasound elastography visualizes the stress distribution within vascular tissue—information that clinicians could use to predict the propensity of atherosclerotic plaque rupture. However, there are concerns that clusters of microvessels may reduce the accuracy of the estimated stress distribution. Consequently, we have developed a contrast-enhanced intravascular ultrasound system to investigate how plaque microvasculature affects the performance of model-based elastography. In simulations, diameters of 200, 400 and 800 μm were used, where the latter diameter represented a cluster of microvessels. In phantoms, we used a microvessel with a diameter of 750 μm. Peak stress errors of 3% and 38% were incurred in the fibrous cap when stress recovery was performed with and without *a priori* information about microvessel geometry. The results indicate that incorporating geometric information about plaque microvasculature obtained with contrast-enhanced ultrasound imaging improves the accuracy of estimates of the stress distribution within the fibrous cap precisely. (E-mail: m.doyley@rochester.edu) © **2016 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Model-based elastography, Intravascular ultrasound, Atherosclerosis, Stress imaging, Microvasculature.**

INTRODUCTION

Clinicians could use knowledge of the stress distribution within the fibrous cap to detect life-threatening plaques and predict their propensity to rupture. Angiography and intravascular ultrasound (IVUS) can assess plaque burden in symptomatic patients (Giroud et al. 1992; Little et al. 1988), but they cannot measure plaque composition, a major determinant of life-threatening plaques. Emerging imaging techniques such as IVUS elastography and virtual histology can characterize plaque composition, information that has increased the sensitivity and specificity of detecting rupture-prone plaques (Granada et al. 2004; Schaar et al. 2001; Suh et al. 2011).

Prediction of the propensity of a plaque rupture requires additional information about the stress distribution within the fibrous cap. Mechanical testing results revealed that the fibrous cap of human coronary arteries ruptures when the peak principal stress exceeds 300 kPa (Cheng et al. 1993; Holzapfel et al. 2005). In addition, computational stress analysis reveals that distinguishing features of life-threatening plaques influence principal stresses. These include plaque morphology (Cilla et al. 2012), plaque stiffness (Cilla et al. 2012; Finet et al. 2004) and macrophage infiltration (Davies 2001; Kwon et al. 1998). Unfortunately, no diagnostic imaging methods can visualize vascular stress *in vivo*. Consequently, computational methods are currently used to estimate stresses within the fibrous cap. Although information derived using computational stress analysis has increased our understanding about the primary mechanisms that govern plaque rupture, insufficient information on the biomechanical properties of vascular tissues of individual patients decreases its diagnostic efficacy. More specifically, the mechanical properties of vessels may vary noticeably between patients; therefore, computational stress analysis performed using mechanical properties measured from cadavers may prove inadequate.

Computational stress analysis in combination with model-based intravascular ultrasound elastography (de Korte et al. 2002) can visualize the stress distribution within the fibrous cap (Lee et al. 1996; Richards et al. 2015) and predict the propensity of a plaque to rupture. Model-based intravascular elastography (Doyley et al. 2001; Richards and Doyley 2011) uses displacements

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or strain measured with IVUS and a continuum mechanical model to compute the mechanical properties within vessels (*i.e.*, to solve the inverse vascular elasticity problem). Although the inverse vascular elasticity problem is ill-posed (Barbone and Bamber 2002), we have demonstrated that it can be transformed into a well-posed problem (*i.e.*, one that produces a unique solution) by incorporating geometric information (spatial priors) into the image reconstruction process (Doyley et al. 2006; Huntzicker et al. 2014). In addition to the uniqueness, measurement errors and boundary conditions (Richards et al. 2015), there are concerns that plaque microvasculature could degrade performance, especially when microvasculature is ignored during the mechanical property recovery process. These concerns are justified because advanced plaques often contain microvasculature that promotes intra-plaque hemorrhage, which may destabilize atherosclerotic plaques (Hellings et al. 2010). These microvessels increase stresses locally (Teng et al. 2012), which if ignored could cause inverse reconstruction techniques to produce inaccurate estimates of the stress distribution within the fibrous cap.

Contrast-enhanced intravascular ultrasound (CE-IVUS) can detect plaque microvasculature, information that should enhance the modulus and stress image recovery process. Several research groups, including our own, are actively developing contrast-enhanced intravascular ultrasound imaging to visualize the adventitial vasa vasorum. CE-IVUS imaging uses the acoustic signature of ultrasound contrast agents (UCAs) to visualize plaque microvasculature (Granada and Feinstein 2008). Although linear (Vavuranakis et al. 2008) and non-linear (Goertz et al. 2006a; Maresca et al. 2013) approaches have been reported, non-linear imaging approaches can enhance imaging sensitivity and specificity by up to 30 dB (Goertz et al. 2005). Non-linear CE-IVUS techniques based on second harmonic (Goertz et al. 2006b), subharmonic (Goertz et al. 2007), higher harmonics (Ma et al. 2014) and ultraharmonic (Maresca et al. 2013) imaging modes have been reported. Non-linear imaging techniques typically require wide-bandwidth transducers that are not commercially available (>70% fractional bandwidth) (Maresca et al. 2013). Therefore, prototype dual-frequency/wideband transducers were used to overcome bandwidth in previous CE-IVUS imaging studies (Goertz et al. 2006a; Ma et al. 2014). In a study conducted with a prototype IVUS catheter, Maresca et al. (2013; 2014) demonstrated that ultraharmonic imaging can be performed with band-limited (60% fractional bandwidth) transducers. We have previously reported subharmonic imaging with a commercial IVUS transducer (Eisenbrey et al. 2012; Sridharan et al. 2013). However, the contrast-to-tissue ratio (CTR) produced in these studies was limited by the transducer bandwidth and the absence of contrast-specific pulsing. Consequently, we have developed chirp-coded excitation to enhance the non-linear response of UCAs when operating at high frequencies (Shekhar and Doyley 2012; 2013).

In this work, we hypothesize that incorporating geometric information on plaque microvasculature, obtained from CE-IVUS, into the image recovery process will enhance performance of modulus and stress elastograms. Here we describe a prototype system of CE-IVUS that we developed to visualize plaque microvasculature at 40 MHz. We also report the results of simulation and phantom studies that were performed to assess the accuracy of modulus and principal stress elastograms computed when geometric information concerning plaque microvasculature is included and excluded in the reconstruction process.

METHODS

In this study we used a non-rigid image registration process to compute displacements (Richards and Doyley 2013) and the soft priors reconstruction method to compute the Young's modulus elastograms. We computed principal stress elastograms by combining the computed modulus elastograms with the strain elastograms.

Displacement and strain estimation

We used a non-rigid image registration method to compute displacements by applying non-linear scaling to a pre-deformed IVUS radiofrequency (RF) image to match the post-deformed image. This was performed by minimizing a functional, Π (Richards and Doyley 2013):

$$\Pi[u(x)] = 0.5\int_{\Pi}(I_1(x)-I_2(x+u(x)))^2 d\Pi + 0.5\alpha\int_{\Pi}(G(x)(\nabla u(x)^{sym} : \nabla u(x)^{sym}))^2 d\Pi \quad (1)$$

where I_1 is the pre-compression image, I_2 is the post-compression image, $u(x)$ are the displacements and α and $G(x)$ are weighting factors that penalize large strains, $\nabla(x)$. We increased $G(x)$ radially to account for the expected inverse square strain decay (Richards and Doyley 2013), and set α to 10^{-10} for both simulation and phantom studies. We used axial displacements measured using cross-correlation displacement tracking as a trial solution for the registration (Huntzicker et al. 2014; Korukonda and Doyley 2011; Richards and Doyley 2013). Cross-correlation analyses were performed with 0.57 mm × 0.27 radian kernels that overlap by 80% in both the axial and lateral directions.

Radial and circumferential strains were computed by taking the gradient of the radial and circumferential displacements.