Published in final edited form as:

Ultrasound Med Biol. 2016 May ; 42(5): 1167–1181. doi:10.1016/j.ultrasmedbio.2015.12.024.

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 impacts the performance of model-based elastography. In simulations diameters of 200,400, and 800 microns were used, where the latter diameter represented a cluster of microvessels. In phantoms, we used a microvessel with diameter of 750 microns. 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 microvessels geometry. The results demonstrate that incorporating geometrical information about plaque microvasculature obtained with contrast-enhanced ultrasound imaging improves the accuracy of estimates of the stress distribution within the fibrous cap precisely.

Keywords

model-based elastography; IVUS; 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 intravascular ultrasound elastography (IVUSE) and virtual histology (VH) 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). To predict

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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 about the biomechanical properties of vascular tissues of individual patients has 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 or strain measured with IVUS and a continuum mechanical model to measure 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 to a well-posed problem (i.e., one that produces a unique solution) by incorporating geometric information (spatial priors) in 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 are ignored during the mechanical property recovery process. These concerns are justified because advanced plaques often contain microvasculature that promotes intraplaque 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). While linear (Vavuranakis, et al. 2008) and nonlinear (Goertz, et al. 2006, Maresca, et al. 2013) approaches have been reported, nonlinear imaging approaches can enhance imaging sensitivity and specificity by up to 30 dB (Goertz, et al. 2005). Nonlinear CE-IVUS techniques based on second harmonic (Goertz, et al. 2006), subharmonic (Goertz, et al. 2007), higher harmonics (Ma, et al. 2014) and

ultraharmonic (Maresca, et al. 2013) imaging modes have been reported. Nonlinear 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. 2006, Ma, et al. 2014). In a study conducted with a prototype IVUS catheter, Maresca and colleagues demonstrated that ultraharmonic imaging can be performed with bandlimited (60% fractional bandwidth) transducers (Maresca, et al. 2013, Maresca, et al. 2014). 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 nonlinear response of UCAs when operating at high frequencies (Shekhar and Doyley 2012, Shekhar and Doyley 2013).

In this work, we hypothesize that incorporating geometric information about plaque microvasculature, obtained from CE-IVUS, in the image recovery process will enhance performance of modulus and stress elastograms. This paper describes a prototype system of CE-IVUS that we have 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.

MATERIALS AND 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 nonlinear scaling to a pre-deformed IVUS RF image to match the post-deformed image. This was performed by minimizing a functional, Π , shown below (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 post-compression image, I_2 is the pre-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 $0.57 \text{ mm} \times 0.27$ radian kernels that overlap by 80% in both the axial and lateral direction.

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

Soft priors reconstruction method

We computed Young's modulus elastograms using an iterative inversion method (Doyley, et al. 2000, Huntzicker, et al. 2014, Oberai, et al. 2009). This algorithm computes the Young's modulus by minimizing the difference between measured displacements and those computed by a mathematical model, according the functional, Ω , expressed as follows:

$$\Omega(E) = \|u_m - u_c(E)\|^2 + \alpha \|L[E]\|^2, \quad (2)$$

where u_m is the $n \times 1$ vector of measured displacements, u_c is the $n \times 1$ vector of computed displacements, α is the regularization parameter, E is the $n \times 1$ vector of Young's moduli, and L is the $n \times n$ penalty matrix designed to limit modulus variation within *a priori* geometric regions, defined as follows (Yalavarthy, et al. 2007):

$$L_{i,j} = \begin{cases} 1 & i=j \\ 0 & i \cap j \notin R, \\ -\frac{1}{m} & i \cap j \in R \end{cases} \quad (3)$$

where m is the total number of nodes in each geometric region R , and i and j are indices of L . The L matrix (i.e., Laplacian) computes the average modulus in each region explicitly as follows:

$$L_1 \cdot E = E_1 - \frac{E_2}{N} - \frac{E_3}{N} - \dots - \frac{E_N}{N} \approx E_1 - \langle E \rangle. \quad (4)$$

We implemented this reconstruction method in MATLAB (Release 2014b, Mathworks, Natick, MA, USA), which was executed on a 12-core Intel Xeon E5-2695 processors running at 3.5 GHz and 64 GB of RAM. On this system, it took 20 seconds to complete one iteration.

Stress estimation

We computed the 2D stress tensor, σ_{ij} as follows:

$$\sigma_{ij} = E \left(\frac{\nu}{1-2\nu} \delta_{ij} \epsilon + \epsilon_{ij} \right), \quad (5)$$

where ν is the Poisson's ratio, ϵ is the Cartesian strain tensor from the finite element (FE) model, and δ is the Kronecker delta. Simulations revealed that the accuracy of the estimated and measured strains were comparable; however, the estimated strains were 4 dB less noisy than the measured strains (Richards, et al. 2015). We also observed this trend in phantoms. To visualize the peak stresses within the vessel, we computed the principal stress, which represents the peak stress component at every pixel location, as follows:

$$\sigma^i = \max(\gamma_1, \gamma_2) \quad \sigma^{ii} = \min(\gamma_1, \gamma_2), \quad (6)$$

where γ_1 and γ_2 are the eigenvalues of the stress tensor, and σ_1 and σ_{ii} are the maximum and minimum principal stresses, respectively (Richards, et al. 2015).

NUMERICAL SIMULATION

The goal of this study was to corroborate the hypothesis that *a priori* knowledge of microvessel geometry improves the accuracy of stress and modulus elastograms. We simulated three vessels with wall, plaque, microvessel, and fibrous cap components to corroborate this hypothesis.

Mechanical model

The finite element method was used to compute displacements and stresses from the simulated vessel. We set the wall, plaque, and cap regions of the vessel to have Young's moduli of 1000, 25, and 1250 kPa, respectively. These values were chosen to mimic the composition of the coronary artery (Baldewsing, et al. 2004). Since Young's moduli of microvasculature are unknown, we also explored the impact of microvessel stiffness on the recovered mechanical properties. More specifically, we simulated vessels with Young's moduli of 1, 10, and 100 Pa. In all cases, we assumed the simulated microvessels were incompressible (i.e., they had a Poisson's ratio of 0.495). The simulated vessels had an outer diameter of 12 mm and an inner diameter of 3 mm (Huntzicker, et al. 2014).

Each vessel contained six microvessels, both within the wall and the simulated plaque. The diameters of the microvessels were modeled between 200 and 800 μm . These diameters were chosen to represent the width occupied by a cluster of microvessels (not individual vessels) that can be detected *in vivo* with contrast imaging (Goertz, et al. 2006, Kwon, et al. 1998). To prevent rigid body motion, we embedded the phantom in a soft, compressible medium ($E = 1 \text{ Pa}$, $\nu = 0.0001$) with dimensions three times that of the phantom itself (Hansen, et al. 2013). The boundaries of this outer region were fixed.

We created a uniform mesh of 27,150 linear triangular elements for this analysis using COMSOL (COMSOL Inc. Burlington, MA, USA). We applied 20 mmHg of pressure on the inner lumen to simulate small strains due to blood flow. This pressure was chosen to effect small strains in the vessel to minimize decorrelation effects in displacement tracking (Varghese and Ophir 1997). The maximum strain observed in all three phantoms was 4%.

Acoustic model

We used the FIELD II simulation environment (Jensen 1991) to compute the acoustic response of a 40 MHz single element IVUS transducer with a 30% fractional bandwidth. We simulated the response of the pre-deformed vessel model by randomly distributing scatterers and generating 256 radial A-lines. The scatterer density was set to achieve fully developed speckle (16 scatterers per wavelength) (Wagner, et al. 1983), and the speed of sound was assumed to be 1540 m/s. We generated post-deformed images by redistributing the point scatterers of the pre-deformed vessel according to the FE displacement field. We added five sets of Gaussian white noise to these simulated RF images to test the robustness of the reconstruction. This noise was applied to create a signal-to-noise ratio (SNR) of 12 dB to match that of our IVUS system (Richards and Doyley 2011).

We simulated contrast-enhanced ultrasound images by modeling contrast-filled microvessels as echogenic regions. More specifically, to produce CTRs that were consistent with those observed experimentally (i.e., between 10-13 dB), we set the amplitude of the point scatters within the microvessels to be 5 times that of the main vessel. This approach of simulating contrast-enhanced ultrasound images does not account for inter-vessel variation. However, since we used a conservative estimate of CTR, these effects can be ignored. Prior research in ultraharmonic contrast-enhanced IVUS imaging has achieved CTRs above 20 dB experimentally (Daeichin, et al. 2015, Lindsey, et al. 2014). We computed CTR as follows,

$$CTR=20\log_{10}\frac{I_c}{I_t}, \quad (7)$$

where I_c is the contrast intensity and I_t is the residual tissue intensity in the log-compressed ultraharmonic images (Goertz, et al. 2005, Goertz, et al. 2006, Maresca, et al. 2013). Intensities for the contrast and suppressed tissue regions were taken at the same radial distance (Maresca, et al. 2013). The regions of interest (ROIs) were segmented manually in MATLAB.

Modulus reconstruction

All modulus elastograms were reconstructed from an initial guess of 500 kPa for the wall and cap regions, and 50 kPa for the plaque region. The wide range of modulus values within the vessel necessitates the use of separate initial guesses, as using a homogeneous initial guess can cause the reconstruction algorithm to converge on local minima. We chose an initial guess of one order of magnitude less than the vessel wall as a conservative estimate of contrast between the wall and the plaque. Reconstructions were performed both with and without geometric information. When used, the geometry was included as additional *a priori* regions in the reconstruction procedure. All reconstructions were performed using a uniform FE mesh. This mesh consisted of 8,999 linear triangular elements. We applied 20 mmHg of pressure to the inner lumen, and eight consecutive nodes were fixed along the outer boundary to prevent rigid body motion (Baldewsing, et al. 2004). The regularization parameter, α , was set to 10^{-10} for all reconstructions. Image reconstruction was halted when the functional changed by less than 1%. This typically took between 8-10 iterations.

PHANTOM STUDY

Phantom fabrication

We fabricated two vessel phantoms with inner diameters of 3 mm, outer diameters of 12 mm, and lengths of 200 mm. Each phantom contained a semicircular soft simulated plaque. One phantom (i.e. phantom #1) contained a single 750 μm microvessel in the wall, while the other (phantom #2) contained a 750 μm microvessel in the simulated plaque. The phantoms were produced using a suspension of 10% polyvinyl alcohol cryogel (PVAc) (Elvanol 71-30, Dupont, Wilmington, DE, USA) with 3% cornstarch for additional scattering. We used a controlled process to fabricate all phantoms (Huntzicker, et al. 2014). Microvessels were represented by lengths of plastic monofilament (Zebco, Tulsa, OK, USA) with a diameter of 750 μm suspended in tension along the length of the phantom. After three 24 hour freeze-thaw cycles (20°C to -20°C), the semicircular rod was removed and the void

was filled with additional PVAc. This mixture contained 6% cornstarch for visible contrast. Each phantom was then subjected to two more cycles. After thermal cycling, the phantoms were removed from their molds and stored at room temperature in water.

Independent estimates of the mechanical properties (Young's modulus) of the simulated plaque and vessel wall were obtained by using a Landmark Servohydraulic Test System (MTS Testing Systems, Eden Prairie, MN, USA) to perform uniaxial compression tests. Mechanical testing was performed on five cylindrical-shaped samples (diameter: 2 cm, height: 2 cm) that were fabricated from the same solutions as the vessel phantoms. To minimize variations in stiffness over time, we performed all mechanical tests on the same day as the IVUS experiments.

Elasticity imaging

We used a commercially available IVUS ultrasound scanner (ILab™, Boston Scientific/Scimed, Natick, MA, USA) and a 40 MHz Atlantis Pro imaging catheter (Boston Scientific, Natick, MA, USA) with a 30% fractional bandwidth for all acquisitions. All RF echo frames were digitized to 10 bits at a sampling frequency of 200 MHz using a PCI bus and a data-acquisition card (Compuscope 14200-1GB; Gage Applied, Lockport, IL, USA) (Richards and Doyley 2013). Phantoms were submerged in a bath of deionized water. The percentage gas saturation was 70%, as measured by a dissolved oxygen sensor (model MW- 600, Milwaukee Instruments, Rocky Mount, NC, USA). We used a water column system to control the static pressure on the inner lumen of the phantom. This was monitored using a pressure wire (Millar Instruments Mikro-Cath, Houston, TX, USA). Column heights were set to achieve a pressure differential of 2.5 mmHg. For each phantom, 5 sequential sets of IVUS images at high and low pressure were collected at the same location to measure variance.

Ultraharmonic imaging

Figure 1a shows a schematic diagram of the experimental setup that was used to generate contrast-enhanced ultrasound images (ultraharmonic). Custom chirp-coded pulses created using Benchlink Pro™ (Agilent, Santa Clara, CA, USA) were transmitted via a breakout box (prototype, Boston Scientific, Natick, MA, USA). Each chirp-coded pulse had a center frequency of 30 MHz, with a 10% fractional bandwidth, and 667 nanosecond pulse length. Pulse sequences were downloaded to arbitrary function generators (models 33210A and 81150A, Agilent) via a GPIB interface. A linear pulse amplifier (MR 5000 DA, ENI, Rochester, NY, USA) increased the signal by 43 dB. The excitation pulse sequence was relayed to the IVUS transducer through a diplexer (RDX-6, Ritec Inc., Warwick, RI, USA). We used a pulse repetition frequency of 10.8 kHz to produce standard IVUS frame rates (30 frames/second). We used a calibrated broadband hydrophone (HL-0085, Onda Corporation, Sunnyvale, CA, USA) to characterize the IVUS transducer used in this study. The impulse response, bandwidth, and the on-axis peak output pressures were measured (**Figure 1b-c**). The peak pressures on-axis at 2.25 mm and 3.5 mm from the catheter were 1.4 and 0.52 MPa, and the center frequency is 37 MHz with a 49% fractional bandwidth. Both the 30 MHz fundamental and the 45 MHz ultraharmonic signals were within this band. We fired two inverted pulses separated by 20 μ s, and used a 70% Tukey window for gating to reduce

distortion and sidelobes in the excitation 11 pulse (Maresca, et al. 2012). We used a 12th order Butterworth filter with 3 dB cutoff points of 41 and 49 MHz to isolate the 45 MHz ultraharmonic. We used Targestar-P-HF microbubbles (Targeson Inc. San Diego, CA, USA) as the ultrasound contrast agent. Targestar-P-HF contains decafluorobutane gas and its shell is primarily composed of phospholipid and polyethylene glycol fatty acid (Shekhar, et al. 2014). Targestar-P-HF is especially designed for high frequency nonlinear imaging – its size distribution is smaller than conventional Targetsar-P. We measured the size distribution and concentration of Targestar-P-HF with a Coulter counter (Multisizer IV, Beckman Coulter Inc., Fullerton, CA, USA) that used a 50 μm aperture, with 300 bins between 1-15 μm (**Fig. 1d**). We used a syringe to inject the contrast agent into the microvessels. Targestar-P-HF comes in a solution diluted to 1.9×10^9 microbubbles/ml. This solution was further diluted in deionized water to a ratio of 1:200.

After acquisition, the ultraharmonic RF images were registered with the elastography RF images. This was achieved by rotating and shifting the ultraharmonic images to align the centers of the main lumen and the microvessel features with the elastography acquisitions.

Elastography reconstruction

We used the Delaunay triangulation method to create finite element representations of the vessels (COMSOL Inc., Burlington, MA, USA). A single mesh was used for both phantoms consisting of 8,466 uniformly distributed linear triangular elements for a mesh density of 80 nodes/ mm^3 . We also tested a mesh with a density of 160 nodes/ mm^3 to investigate the effects of mesh density, and the results varied by under 5%. We interpolated the measured displacements to the nodal coordinates of the finite element mesh using a cubic interpolation function. Boundary conditions were selected to apply a pressure of 2.5 mmHg to the inner lumen, and measured displacements were assigned to eight consecutive nodes along the outer boundary to prevent rigid body motion (Baldewsing, et al. 2004). The *a priori* geometric information for the simulated plaque and microvessels were manually traced from the standard and ultraharmonic IVUS images, respectively. The regularization parameter α was set to 10^{-20} for all reconstructions to match the simulation study. Image reconstruction was halted when the functional changed by less than 1%. This typically took between 8-10 iterations.

RESULTS

Numerical simulation study

Figure 2a shows the geometry used for the simulation study. **Figures 2b-c** show the ground truth and measured radial strain for the simulated phantom with microvessel moduli of 10 Pa, respectively. **Figures 2d-e** show the ground truth and measured circumferential strains, respectively. The largest strains occurred around the largest microvessel as a result of its compression.

Figures 3a-b show the simulated microvessels (dB). The CTR between the microvessel and background regions ranged from 6.7 dB to 16.5 dB. In this simulation, all microvessels were visible, although brightness decreased with the distance from the main lumen. **Figure 3b**

shows the segmentation overlaid in white on the B-mode frame. **Figures 3c-e** show the ground truth and reconstructed Young's modulus elastograms (Pa). **Figures 3c-d** had visibly similar stiffnesses for the wall and plaque. **Figure 3e** shows a visibly softer plaque when microvessel geometry is not used. Additionally, the largest microvessel was visible, although it appeared larger and stiffer than the ground truth. **Figures 3f-h** show the maximum principal stress elastograms (Pa). The stresses within the cap were over an order of magnitude larger than those in the rest of the phantom. **Figures 3i-k** show close-ups of the maximum principal stress in the plaque cap (Pa). Each image depicts the vessel with a microvessel Young's modulus of 10 Pa.

Figures 4(a,c,e) show radial strain, circumferential strain, and principal stress profiles through the left path depicted in **Figure 3g**, while **Figures 4(b,d,f)** show radial strain, circumferential strain and principal stress profiles through the right path passing through the simulated plaque. The measured strain profiles in **Figures 4(a,c)** followed the same radial decay as the computed and ground truth strains. The microvessel had only a minor effect on the magnitude. From the measured strain profiles in **Figure 4(b,d)**, it was not possible to detect the large compressive strains within the microvessel. However, these trends were detected in the computed strains when the microvessel geometry was included. In **Figure 4(e,f)**, the computed principal stresses showed the same trend as the ground truth. However, the peak stress in **Figure 4f** was larger than the ground truth when the microvessel geometry was not included. All plots are for the simulated phantom with 10 Pa microvessels.

Figures 5 (a,b,c) show the mean Young's modulus in the vessel wall, plaque, and cap regions, respectively, plotted as function of microvessel stiffness. In all elastograms, the standard deviation was less 1%, and thus was not discernible. Both sets of elastograms (i.e., those estimated with and without knowledge of the microvessel geometry) underestimated the modulus in the vessel wall and overestimated those within the fibrous cap cap. **Figure 5d** shows the mean maximum principal stresses within the cap plotted as a function of microvessel stiffness. The true stress was similar to those reconstructed when the geometry was known. In these stress images, there was less than 5% variation between all three microvessel stiffnesses. The peak stress error was less than 2% for all phantoms when the microvessel geometry was known, while it was greater than 15% when it was not. The error in both elastograms in **Figure 4b** within the vessel wall were under 10%, whereas only the reconstructed elastogram with geometric information of the microvessels was under 10% in the cap. Both elastograms had above 10% error within the plaque region.

Phantom study

Figures 6(a,c) show the fundamental and ultraharmonic images obtained from phantom 1, respectively. The last 1mm of the sonograms are not shown because beyond 10 mm SNR was very low. The CTR of the microvessel in the ultraharmonic image was 8.6 ± 1.81 dB. **Figures 6(b,d)** show the fundamental and ultraharmonic obtained from phantom 2, respectively. The CTR of the microvessel in the ultraharmonic image was 9.2 ± 2.61 dB.

Figures 7(a,b) show the measured radial and circumferential strains for phantom 1, which decayed radially. **Figures 7(c,d)** show the modulus elastograms, reconstructed with and

without *a priori* microvessel information in kPa. **Figures 7(e,f)** show the maximum principal stress images both with and without *a priori* microvessel geometry in kPa, respectively. The microvessel was not visible in the elastogram without geometric information (**Figure 7d**) while it appeared as a soft region in **Figure 7c**.

Figures 8(a,b) show the measured radial and circumferential strains, respectively for phantom 2, which decayed radially. **Figures 8(c,d)** show the reconstructed Young's modulus elastograms both with and without *a priori* microvessel geometry in kPa. **Figures 8(e,f)** show the maximum principal stress images both with and without *a priori* microvessel geometry in kPa. The largest principal stress occurred between the plaque and the main lumen for both elastograms. However, the reconstruction with microvessel geometric information produced larger values. The path between the arrows in **Figure 8c** defines the profiles shown in **Figure 9**.

Figures 9(a,c,e) show radial strain, circumferential strain and principal stress profiles through the path depicted in **Figure 7c**, while **Figures 9(b,d,f)** show radial strain, circumferential strain and principal stress profiles through the path depicted in **Figure 8c**. There were stress peaks on either side of the microvessel in **Figure 9e** due to its contraction. These features are not observed in the trace without microvessel geometry, which has a peak stress value that is 38% smaller. **Figure 9f** shows a similar trend, although the peak stresses are larger than in **Figure 9e**. This is due to the larger strains within the plaque. In this image, the peak stress when microvessel geometry is included is 56% larger than when it is omitted.

Figure 10 shows the quantitative Young's modulus and peak maximum principal stress values in the phantom study. The peak stresses were measured as the average stress in a 10×10 pixel region around the maximum stress. Ground truth stresses were computed for the 15 mechanical testing results using a FE simulation. We performed a pair-wise Welch's t-test ($p > 0.05$) on this data, which showed that for all regions, the Young's modulus results were statistically the same as the measured values using mechanical testing. However, there was a statistically significant difference between the peak stress elastogram without microvessel geometry and the measured values. The peak stress without microvessel geometry showed 38% error, while the stress with microvessel geometry showed 3% error.

DISCUSSION

In this study, we examined how microvessels affect our ability to reconstruct vascular moduli and stresses. The primary findings of this study were as follows: (a) Failing to account for microvessels within soft plaques produced peak stress error of over 30% in reconstructed stresses; (b) Failing to account for microvessels within soft plaques with stiff caps cause modulus errors of 20% within the cap, and 20% error in the peak stress; (c) The peak stress and cap modulus errors were reduced to under 10% when geometric information was included; (d) 40 MHz ultraharmonic contrast-enhanced imaging correctly located the microvessels within both phantoms.

Previous works have shown that peak stresses within vessels will occur between soft plaques and the main lumen (Cheng, et al. 1993, Richards, et al. 2015). Large microvessels in this

area may increase these stresses by causing larger local strains (Teng, et al. 2012). We expected that this would have a negative impact on the accuracy of our reconstruction for two reasons. First, vessel regions that are not segmented *a priori* may be averaged into the background region. This can cause them to appear larger than they are with reduced contrast, or not appear at all (Hansen, et al. 2013, Yalavarthy, et al. 2007). This effect reduces the reconstructed modulus contrast (McGarry, et al. 2013) – the extent of which depends on the relative size and quantity of the microvessels. Second, the failure to reconstruct accurate modulus values within the microvessels will also reduce the magnitude of the computed strains. Both the modulus and strain errors can propagate through the entire phantom to compensate for the missing features.

There has been little investigation as to the effect of intimal microvessels on arterial stresses. This is partially because the pressure within the microvessels cannot be measured (Simon, et al. 1973, Teng, et al. 2012). Current FE studies have modeled these structures as hollow tubes with internal pressures of 10 mmHg, while applying systolic pressure on the main lumen (Lu, et al. 2015, Simon, et al. 1973, Teng, et al. 2012). Under these conditions, the microvessels have been shown to contract. Teng et al. have also shown that there is no appreciable difference in the mechanical behavior of microvessels pressurized at 10 mmHg vs. 5 mmHg (2012). Modeling the microvessels as soft regions with a Poisson's ration of 0.1, we also observe compression (**Figure 2**). By modeling the microvessels as solids rather than voids, we are also able to use the same FE mesh for reconstructed elastograms with and without microvessel geometry. This eliminates any reconstruction differences due to mesh density. Local strains adjacent to the microvessels increased by up to a factor of two compared with the strains of equal radial distance further away from the microvessels in the ground truth simulations. The magnitude of this increase was consistent with Teng et al. (2012). We found that the local stresses on both sides of the plaque microvessels were 40% larger than those in the rest of the cap (**Figure 3**).

Figure 4 highlights why these large stresses could not be recovered without prior knowledge of the microvessel locations. **Figures 4(b,d)** show that the large strains due the central microvessel in the simulated plaque could be measured in the radial direction, but not in the circumferential direction. Because these strains are highly localized, the accuracy of the radial strain benefited from the higher imaging resolution in that direction.

The effects of varying the microvessel stiffness in **Figure 5** supported the claim that similar stress and modulus results would be obtained over a range of microvessel properties. The ground truth stress in the plaque cap varied by less than a percent over the range of microvessels tested, and the variance in stress elastograms was under 5%. **Figure 5** also shows that when microvessel geometry was not included in the reconstruction, the plaque region appeared softer and the cap region appeared harder than the ground truth, in line with the averaging effects previous studies have suggested. The relative error between the cap modulus (**Figure 5c**) and cap stress (**Figure 5d**) were within 5% when the microvessel information was not included. However, there is a larger difference when the microvessel geometry was included. This is because the area of the largest microvessel was underestimated by 16% in the manual segmentation. As **Figure 2** shows, microvessel size correlates with strain, and strain is directly proportional to stress.

The experimental study was performed with Targestar-P-HF, which has a smaller mean size than clinical contrast agents. Nonlinear CE-IVUS imaging with clinical UCAs becomes progressively challenging as the frequency is increased, because they are designed to resonate at low frequencies (<10 MHz). However, previous CE-IVUS imaging studies have demonstrated that ultraharmonic imaging is feasible with Definity® (Bristol-Myers Squibb Inc., New York, NY, USA) at high frequencies, especially when its size distribution is modified (Maresca, et al. 2014). Therefore we expect that the results of this study could be reproduced with Definity® and other clinically available phospholipid-encapsulated UCAs.

The stiff plaque cap could not be modeled experimentally, due to fabrication constraints. Thus, the simulation study better mimicked the composition of the coronary artery, while this phantom study highlighted the ability to combine 40 MHz contrast-enhanced imaging with model-based elastography. The absence of the hard cap allowed for more pronounced stress concentrations between the plaque and the lumen due to the increased local strain (**Figures 7 and 8**). The softer vessel wall, as compared with simulation, also increased the mechanical impact of the microvessels. This same trend was observed in **Figures 7 and 8**. We previously reported that, when using the same reconstruction regularization, phantom modulus elastograms displays more modulus variation than simulation, which could be observed in these results as well. This was due to the increased noise in the system (Huntzicker, et al. 2014). Scaling the regularization parameter with displacement could correct for this issue, however this parameter variation would obfuscate comparisons between the simulation and phantom studies. Unlike the simulation results, there was no statistical difference in the plaque modulus of phantom 2 between elastograms (**Figure 10**). However, the cap stress is statistically different. **Figure 9** suggests that this occurred because the large strains around the microvessel could not be recovered accurately when no microvessel information was available in the reconstruction– but these local effects were not large enough to influence the modulus value of the entire region. This is also shown in **Figure 10**. Thus, the simulation and phantom studies show that the peak stresses may not be recoverable when the microvessel geometry is not known. This is due to a combination of errors in the Young's modulus because of the inability to track local displacement variation, and errors in the peak-reconstructed strains due to incorrect geometry in the finite element model. The peak stresses may be overestimated or underestimated, depending on the specific geometry and material properties of the vessel.

In this paper, we exploited ultraharmonic imaging to detect microvasculature with a commercial catheter with limited bandwidth. However, researchers are developing custom transducers and instrumentation to image plaque microvasculature (Ma, et al. 2014). Continued advances in this direction will enable the detection of microvessels with enhanced spatial and contrast resolution, which should further improve our ability to accurately determine spatial priors for stress reconstruction. In the current study, two ultrasound acquisitions were needed to measure the ultraharmonic and standard vessel RF images. We plan to optimize this setup by using a pulsatile pump to simulate blood flow, and a syringe pump to inject contrast into the vessel. With such a setup, elastography and contrast imaging could be measured simultaneously. We were also unable to examine the effects of micro-calcifications or other features that cannot be resolved using IVUS. We are

currently conducting studies to further investigate these issues. We also plan to develop better finite element models to describe the fluid-tissue interaction in microvessels, especially when elastography is performed with large applied strains ($> 2\%$).

CONCLUSIONS

Internal tissue structures such as plaque microvasculature that are not resolvable by standard IVUS will degrade accuracy of the measured stresses if they are not accounted for in the image recovery process. In this work, we demonstrated that advanced IVUS imaging techniques (such as contrast-enhanced ultrasound imaging) could provide *a priori* information regarding the spatial extent of microvasculature that improves the performance of model-based IVUS.

ACKNOWLEDGEMENTS

The National Heart and Lung Research Grant R01 HL088523 funded this work.

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Figure 2. (a) The geometry of the simulated vessel phantom; (b) The ground truth radial strain elastogram; (c) The measured radial strain elastogram from FIELD II simulations; (d) The ground truth circumferential strain elastogram; (e) The measured circumferential strain elastogram from FIELD II simulations. All strains are given as percentages

Figure 3.

(a,b) The contrast images of the simulated phantom using FIELD II. Microvessel CTRs range from 6.7-16.5dB. The manual segmentation is overlaid in white; (c-e) Young's modulus elastograms for the simulated phantom with 10 Pa microvessels (Pa) for the ground truth, reconstructed elastogram with microvessel geometry (mv) and reconstructed elastogram without microvessel geometry (no mv); (f-h) The maximum principal stress elastograms for simulated phantom with 10 Pa microvessels (Pa); (i-k) Close up images of

maximum principal stresses in the plaque cap (Pa) corresponding to the box in Fig. 3 f. The paths between the two sets of arrows in Fig 3 g define the profiles in Fig. 4.

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Figure 4.

(a,c,e) The radial strain, circumferential strain and principal stress profiles through the left path depicted in Fig. 3g; The radial strain, circumferential strain and principal stress profiles through the right path passing through the simulated plaque. Plots a-d show the actual strain, measured strain, and those computed strain with and without knowledge of the microvessel geometry. Plots e-f show the actual stress, and the stress computed with and without knowledge of the microvessel geometry.

Figure 5.

The modulus and stress recovered from the simulated vessel when the Young's modulus of the microvessel was varied displayed in units of kPa. (a-c) Mean recovered Young's modulus in the vessel wall, plaque, and cap regions when reconstructions were performed with and without knowledge of the microvessel geometry; (d) Mean maximum principal strain in the plaque cap for the two cases (i.e., when reconstruction were computed with and without knowledge of the microvessel geometry).

Figure 6.

(a-c) Fundamental and (b-d) ultraharmonic responses obtained from two phantoms with microvessels located at 0.5 mm from the lumen. The arrows in the sonograms denote the location of the microvessels. Because the SNR is very low beyond 10 mm, the last ring of 1 mm is not shown.

Figure 7.

The measured radial and circumferential strains for phantom 1 (a,b); The reconstructed Young's modulus elastograms with and without microvessel geometry for phantom 1 (kPa) (c,d); The reconstructed maximum principal stress elastograms with and without microvessel geometry for phantom 1 (kPa) (e,f). The arrows in c define the profile shown in Fig. 9.

Figure 8.

The measured radial and circumferential strains for phantom 2 (a,b); The reconstructed Young's modulus elastograms with and without microvessel geometry for phantom 2 (kPa) (c,d); The reconstructed maximum principal stress elastograms with and without microvessel geometry for phantom 2 (kPa) (e,f). The arrows in Fig. 8 c define the profile shown in Fig. 9.

Figure 9.

(a,c,e) The radial strain, circumferential strain and principal stress profiles through the path depicted in Fig. 7; (b,d,f) The radial strain, circumferential strain and principal stress profiles through the path depicted in Fig. 8. Plots a-d show the computed strain with microvessel geometry, computed strain without microvessel geometry, and the measured strain. Plots e-f show the computed stress with microvessel geometry, and the computed stress without microvessel geometry.

Figure 10. The quantitative results for the elastographic data in phantoms 1 and 2, respectively. Error bars represent the standard deviation between experiments. Units are in kPa.