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Acoustic radiation force impulse imaging of vulnerable plaques: a finite element method parametric analysis

Joshua R. Doherty [a,*], Douglas M. Dumont [a], Gregg E. Trahey [a,b], Mark L. Palmeri [a,c]

[a] Department of Biomedical Engineering, Duke University, Room 136 Hudson Hall, Box 90281 Durham, NC 27708, USA
[b] Department of Radiology, Duke University Medical Center, Durham, NC, USA
[c] Department of Anesthesiology, Duke University Medical Center, Durham, NC, USA

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ABSTRACT

Plaque rupture is the most common cause of complications such as stroke and coronary heart failure. Recent histopathological evidence suggests that several plaque features, including a large lipid core and a thin fibrous cap, are associated with plaques most at risk for rupture. Acoustic Radiation Force Impulse (ARFI) imaging, a recently developed ultrasound-based elasticity imaging technique, shows promise for imaging these features noninvasively. Clinically, this could be used to distinguish vulnerable plaques, for which surgical intervention may be required, from those less prone to rupture. In this study, a parametric analysis using Finite Element Method (FEM) models was performed to simulate ARFI imaging of five different carotid artery plaques across a wide range of material properties. It was demonstrated that ARFI imaging could resolve the softer lipid pool from the surrounding, stiffer media and fibrous cap and was most dependent upon the stiffness of the lipid pool component. Stress concentrations due to an ARFI excitation were located in the media and fibrous cap components. In all cases, the maximum Von Mises stress was < 1.2 kPa. In comparing these results with others investigating plaque rupture, it is concluded that while the mechanisms may be different, the Von Mises stresses imposed by ARFI imaging are orders of magnitude lower than the stresses associated with blood pressure.

1. Introduction

Cardiovascular disease is the leading cause of death and disability in the United States (Roger et al., 2011). The majority of cardiovascular clinical events are attributed to atherosclerosis, a process in which fatty deposits, inflammation, cells, and scar tissue accumulate between the endothelium lining and smooth muscle walls of arteries (Naghavi, 2010). This can result in the formation of plaques, whose rupture has been shown to be the most common cause of complications including sudden cardiac death, acute coronary syndromes, and/or stroke (Casscells et al., 2003; Davies, 2000; Falk et al., 1995; Virmani et al., 2000).

It is widely accepted that plaques with a large, soft, lipid-rich necrotic core covered by a thin fibrous cap are more vulnerable to rupture (Falk et al., 1995; Lee and Libby, 1997). Plaque rupture is believed to occur when the fatigue strength of the fibrous cap is exceeded. This has been supported by several groups who, using Finite Element Method (FEM) techniques, reported increased stresses in ruptured plaques compared to those with no evidence of rupture found in histology (Cheng et al., 1993; Huang et al., 2001; Li et al., 2006). The presence of a lipid pool is believed to be particularly dangerous because it confers greater stress within the overlying cap and hence increases the propensity of rupture (Loree et al., 1994). For this reason, and also because formation of the lipid pool precedes that of the fibrous cap and ultimately plaque rupture, the ability to reliably differentiate a soft lipid core from an otherwise stiffer, more stable region may help clinicians in treatment planning.

Recent developments in medical imaging have allowed for the morphological and structural characterization of plaques *in vivo* (Sanz and Fayad, 2008; Waxman et al., 2006). Using high resolution magnetic resonance imaging (MRI), the lipid, fibrous, calcified, hemorrhagic, and thrombotic regions in plaque tissue have been differentiated using histology as a gold standard (Hatsukami et al., 2000; Hatsukami and Yuan, 2010; Kawahara et al., 2007; Saam et al., 2007; Touze et al., 2007; Trivedi et al., 2004). Catheter-based probes using optical coherence tomography (OCT) (Tearney et al., 2006) or intravascular ultrasound (IVUS) provide information regarding plaque size and arterial wall thickness in the coronary artery. For differentiating soft lipid cores from more stable calcified regions, an alternative to the high cost associated with MRI and the invasive nature of catheter-based techniques is a

* Corresponding author. Tel.: +1 919 660 5146; fax: +1 919 684 4488.
E-mail address: joshua.doherty@duke.edu (J.R. Doherty).

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recently developed ultrasound-based elasticity imaging method, termed Acoustic Radiation Force Impulse (ARFI) imaging.

ARFI imaging characterizes the mechanical properties (i.e. stiffness) of soft tissue by measuring the tissue deformation from a localized acoustic radiation force excitation (Nightingale et al., 2001). Briefly, the method uses a single ultrasound transducer to (1) apply an impulse-like (short duration) excitation within the tissue and (2) track the resulting deformation spatially and temporally using ultrasonic correlation-based methods. ARFI imaging generates sufficient acoustic radiation force (on the order of dynes) capable of displacing soft tissue approximately 1–10 μm (Nightingale, 2011). The axial displacements are inversely related to tissue stiffness; meaning that soft regions will displace more than stiffer regions (Palmeri et al., 2006a; Palmeri et al., 2005). Similar to diagnostic B-mode imaging, the interrogation region can be translated across the transducer to create 2-D tomographic images that reflect the stiffness of soft tissue. For a thorough description of ARFI imaging and the various clinical settings in which the method has been applied, the reader is referred to Doherty et al. (Doherty et al., in press). To characterize plaque and arterial tissues, the method has been used in several *ex vivo* and *in vivo* scenarios (Dumont et al., 2006; Dumont et al., 2009; Trahey et al., 2004). Most recently, Dahl et al. (Dahl et al., 2009) demonstrated the use of ARFI imaging *in vivo* to differentiate suspected soft plaques from hard plaques in the carotid artery.

To investigate the effects of material properties on the ability of ARFI imaging to differentiate a soft lipid pool from an otherwise stiffer region, this study uses FEM models to simulate ARFI imaging of carotid artery plaques. A parametric analysis is performed in five different plaque geometries by varying the specified material properties. Because fracture of a fibrous cap could lead to significant consequences, the Von Mises stress contours induced by an ARFI excitation are also investigated.

2. Methods

The FEM models used herein are adapted from models previously developed by Palmeri et al. (Palmeri et al., 2005) for investigating the response of soft tissue to an ARFI excitation. These models have been experimentally validated in calibrated gelatin-based tissue-mimicking phantoms (Nightingale et al., 2006; Palmeri et al., 2005) and used to investigate the dynamic response of elastic inclusions to an ARFI excitation (Palmeri et al., 2006a).

2.1. Plaque mesh generation

Three-dimensional, rectangular, solid meshes consisting of 0.1 mm, trilinear, cubic elements were created using LS-PREPOST2 (Livermore Software Technology Corp., Livermore, CA). The mesh extended ± 5 mm in the lateral (x) dimension, 5 mm in the elevation (y) dimension, and 25 mm in the axial (z) dimension. Half-symmetry was assumed on the front face ($x-z$ plane, $y=0$ mm). The back ($x-z$ plane, $y=5$ mm), left ($y-z$ plane, $x=-5$ mm), and right ($y-z$ plane, $x=5$ mm) faces were assumed to be non-reflecting. Full-constraints were assumed for the top ($x-y$ plane, $z=0$ mm) and bottom ($x-y$ plane, $z=25$ mm) faces. No slip was allowed at material boundaries. Five carotid artery plaque geometries were constructed based on published histology and in vivo MRI images by Li et al. (Li et al., 2006). Each image was manually segmented to define the media (i.e. arterial wall), lumen, fibrous cap, and lipid pool components and positioned in a tissue component. Material properties were assigned using custom-written MATLAB™ (MathWorks, Natick, MA) scripts. The geometry of the lateral-axial plane was assumed constant in the elevation dimension to construct 3-D models from the 2-D segmented images.

2.2. Material properties

Literature on the material properties of human arteries and is not extensive and varies considerably (Hoskins, 2007). Choosing values consistent with the literature (Baldewsing et al., 2004; Baldewsing et al., 2005; Cheng et al., 1993; de Korte et al., 2000; Lee et al., 1996; Loree et al., 1992) a model with $E_{media}=1000$ kPa, $E_{cap}=1000$ kPa, and $E_{lipid}=25$ kPa was defined as a baseline case; where E represents the static Young's Modulus. A parametric analysis was conducted by varying the Young's modulus of each component according to the modified values listed in Table 1. The background tissue was modeled with $E_{tissue}=4$ kPa in all simulations. The material was modeled as a linear, isotropic, and elastic solid with a Poisson's ratio of 0.495.

Arterial tissues are known to exhibit nonlinear behavior throughout the cardiac cycle (Kamenskiy et al., 2012). However, the quasi-linear assumptions herein are appropriate for the infinitesimally small strains ($<1\%$) that are typically encountered with ARFI imaging as validated by the models in this study. Also, while appreciable changes in blood pressure occur over the entire cardiac cycle, it is reasonable to expect that changes occurring over the short duration (<50 msec.) used to acquire ARFI imaging data would be quite small, such that linear assumptions would be valid. Additionally, changes in arterial stiffness that may be attributed to nonlinear behavior are within the wide range of stiffnesses considered in the parametric analysis performed herein.

2.3. Acoustic radiation force excitation

Using Field II (Jensen, 1996; Jensen and Svendsen, 1992), a linear acoustic field simulation package, the pressure fields were simulated for a linear cardiovascular transducer array according to the parameters listed in Table 2, where the transmit $F/\sharp$ describes the focal geometry of the transmitted beam These imaging parameters have been demonstrated to be effective for ARFI imaging of carotid plaques, while maintaining FDA mechanical index and thermal index safety guidelines (Doherty et al., 2011).

Simulated pressure fields were converted to intensities and scaled according to empirically determined intensity values obtained from hydrophone measurements recorded using a transducer with the same parameters listed in Table 2. The acoustic radiation force field ($\vec{F}$) was determined according to Eq. (1) (Doherty et al., in press; Palmeri et al., 2005) where ($\vec{I}$) is the pulse average intensity field, α is the tissue absorption coefficient, and c is the speed of sound.

$$\vec{F}=\frac{2\alpha\vec{I}}{c} \tag{1}$$

In soft tissues, the absorption coefficient is approximated by the tissue attenuation coefficient (Christensen, 1988). Attenuation, which is unknown and varies *in vivo*, modulates both the magnitude and also the geometry of the applied force (Doherty et al., in press). To investigate these effects, the simulated acoustic radiation force was modeled with varying degrees of attenuation for values of $\alpha=0.3$ and $\alpha=0.7$, with a baseline value of $\alpha=0.5$ dB/cm/MHz.

2.4. Computational modeling and data analysis

The FEM simulations were performed using an explicit time-domain finite element algorithm available in LS-DYNA (Livermore Software Technology Corp., Livermore, CA). Effects of varied Poisson ratio and mesh dependencies (i.e. element size) were investigated. The values used herein were chosen because they minimized simulation runtime and provided results nearly identical to the convergent solution. For each simulation, datasets describing the axial displacements and associated Von Mises stresses were obtained. The Von Mises stress was chosen to represent an equivalent stress induced by the ARFI excitation. The results depicted herein represent the response that is co-planar with that of the maximum applied force.

Fig. 1 depicts the simulated axial displacements in a homogeneous, isotropic, and elastic solid material with a Young's modulus of 4 kPa induced by an ARFI excitation. The dynamic response portrayed in Fig. 1a describes the material deformation occurring at a single lateral location as a function of axial depth and time following excitation. The white dashed line depicts the time at which the maximum axial displacement occurs. Fig. 1b shows the maximum axial

Table 1
Assigned static Young's modulus values.

	Baseline	Modified
E_{media} (kPa)	1000	200, 600, 1500, 2000
E_{cap} (kPa)	1000	2000, 3000, 4000, 5000
E_{lipid} (kPa)	25	0.5, 1, 5, 50

Table 2
Simulated ultrasound transducer parameters.

Frequency (MHz)	4.0
Pulse Duration ($\sharp$ cycles)	600
Transmit $F/\sharp$	3.0
Focal Depth (mm)	20