Ultrasound in Med. & Biol., Vol. ■, No. ■, pp. 1–15, 2015

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2015.11.015

● *Original Contribution*

THE IMAGING MODULOGRAPHY TECHNIQUE REVISITED FOR HIGH-DEFINITION INTRAVASCULAR ULTRASOUND: THEORETICAL FRAMEWORK

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(*Received* 24 *April* 2015; *revised* 10 *October* 2015; *in final form* 13 *November* 2015)

Abstract—Mechanical characterization of atherosclerotic lesions remains an essential step for the detection of vulnerable plaques (VPs). Recently, an intravascular ultrasound (IVUS) elasticity reconstruction method (iMOD) has been tested *in vivo* by our group. The major limitation of iMOD is the need to estimate the strain field in the entire VP despite attenuated depth penetration signals when using high-definition (HD) IVUS systems. Therefore, an extended iMOD approach (E-iMOD) was designed and applied to coronary lesions of patients imaged *in vivo* with IVUS. The E-iMOD method (i) quantified necrotic core areas with a mean absolute relative error of 3.5 ± 3.5% and (ii) identified Young's moduli of the necrotic cores and fibrous regions with mean values of 5.7 ± 0.8 kPa and 794.5 ± 22.0 kPa instead of 5 kPa and 800 kPa, respectively. This study demonstrates the potential of the improved HD-IVUS modulography technique E-iMOD to characterize coronary VPs. (E-mail: jacques.ohayon@imag.fr) © **2015 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Elastography, Modulography, Linear elasticity, Inverse problem, Vulnerable plaques, Coronary disease.**

INTRODUCTION

Atherosclerotic coronary plaque rupture and subsequent thrombosis is the leading cause of acute coronary syndrome and responsible for the majority of cardiovascular deaths (Fleg et al. 2012; Go et al. 2013; Lloyd-Jones et al. 2010). Vulnerable plaques (VPs; plaques likely to rupture) possess specific geometrical (Virmani et al. 2006), mechanical (Cheng et al. 1993; Loree et al. 1992; Ohayon et al. 2001; Riou et al. 2014) and biological (Broisat et al. 2011) features. An early and accurate determination of these properties remains an essential step to implementing preventive therapeutic strategies (Libby 2001).

Studies have shown that fibrous cap thickness index (<65 μm) alone is not a sufficient predictor of plaque rupture (Cardoso et al. 2014; Ohayon et al. 2008; Virmani et al. 2000). Biomechanical studies have identified peak cap stress (PCS) amplitude as an additional key predictor of plaque disruption (Finet et al. 2004; Ohayon et al. 2014). *In vivo* imaging modalities are needed to characterize and identify specific biomechanical factors responsible for plaque instability and rupture (Fleg et al. 2012; Magnoni et al. 2015). Following the spirit of Ophir and colleagues (Cespedes et al. 1993; Ophir et al. 1991), several intravascular ultrasound (IVUS) strain-elastography (de Korte et al. 2002; Maurice et al. 2004; Richards and Doyley 2013) and strain-palpography (Céspedes et al. 2000; Deleaval et al. 2013; Schaar et al. 2005) reconstruction techniques were developed to characterize atherosclerotic coronary lesions and to predict their vulnerability to rupture. IVUS

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strain-elastography approaches were developed to highlight the spatial strain distribution (*i.e.*, strain-elastogram) over the entire vessel wall (Keshavarz-Motamed et al. 2014; Majdouline et al. 2014; Maurice et al. 2007; Richards and Doyley 2013) or over a restricted thick endoluminal region (de Korte et al. 2002; Doyley et al. 2001). Such IVUS imaging techniques based on the optical flow (Keshavarz-Motamed et al. 2014; Majdouline et al. 2014; Maurice et al. 2004), time-delay correlation estimation (de Korte et al. 2002) or a non-rigid image-registration method (Richards and Doyley 2013) allowed the calculations of intraplaque strain images during the cardiac cycle. However, these methods did not overcome the main limitation related to the complex morphologies of atherosclerotic lesions, which alter the intraplaque strain fields and inhibit direct translation into intra-parietal stress and plaque mechanical properties.

Young's modulus reconstruction of atherosclerotic plaque (*i.e.*, modulogram), based on the strain field measurements, remains a challenge that has been pursued by a variety of methods (Baldewsing et al. 2008; Doyley 2012; Le Floc'h et al. 2009). Following the spirit of Baldewsing et al. (2005) and Doyley's works (Doyley 2012; Richards and Doyley 2011), our group (Bouvier et al. 2013; Le Floc'h et al. 2009, 2010, 2012) demonstrated that by pre-conditioning the algorithm based on the best estimation of plaque component boundaries, we could improve the elasticity reconstruction. An original pre-conditioning step to extract the plaque morphology and an iterative approach combining a dynamic watershed segmentation method with an optimization procedure were proposed to highlight modulograms of human coronary atherosclerotic lesions (this approach was named iMOD for imaging modulography; Le Floc'h et al. 2012). However, one major limitation of such a method is the need to estimate accurately the strain field in the entire lesion. This may be difficult as the amplitude of the original signal becomes attenuated as the depth of penetration increases and shadow artifacts produced by calcified nodules impair imaging of deep plaque structures. Strain-elastograms are also difficult to reconstruct when using intravascular imaging techniques with limited depth penetration signals, such as optical coherence tomography (OCT) or the new generation of high-definition intravascular ultrasound (HD-IVUS) imaging systems equipped with high-frequency catheters $\geq$60 MHz (Kobayashi et al. 2014; Waters et al. 2011).

Therefore, the present biomechanical study was designed to extend the theoretical framework of the iMOD technique when considering HD-IVUS catheters with limited depth penetration. This extended iMOD technique (E-iMOD), based on the continuum mechanics theory prescribing the strain field in the limited endoluminal region, was successfully applied to 10 VP morphologies: three modeled plaque geometries and seven coronary lesions of patients imaged *in vivo* with IVUS. The robustness and performance of the new elasticity reconstruction technique E-iMOD was investigated with regard to noise, which may affect prediction of plaque vulnerability.

MATERIALS AND METHODS

To test the numerical performance of the proposed E-iMOD algorithm, the finite element (FE) method was used to generate our input set of the intraplaque displacement and strain fields. As realistic human VP geometries were needed to perform the FE simulations, we used VP geometries of patients imaged *in vivo* with an IVUS system operating at 40 MHz. To simulate the acquisitions that we would obtain with limited depth penetration HD-IVUS catheters, the resulting FE displacement and strain fields computed in the endoluminal plaque regions and the luminal contours were the only inputs of our inverse model. Let us notice that the plaque component's contours were not given to solve the inverse problem.

IVUS study and plaque geometries

To study the performance of the proposed E-iMOD method, we used a patient population including five plaque geometries considered in a previous work conducted by our group on the elasticity-palpography technique (Deleaval et al. 2013). This will allow us also to discuss the complementarities of these two approaches when applied to the same VP morphologies.

Patient population. Arteries were explored in seven patients with stable angina and referred for percutaneous coronary intervention (PCI) at the Hospital of Cardiology and Pneumology of Lyon. Investigations were approved by institutional board of the hospital's cardiology department, and consent was obtained from the patients.

Intravascular ultrasound imaging. The dataset of non-ruptured VP geometries was obtained from systematic IVUS scans of the left main, left anterior descending and left circumflex coronary arteries following the protocol described by Rioufol et al. (2002). The recorded cross-sectional IVUS images corresponded to the sites exhibiting the thinner fibroatheroma cap. An iLab IVUS system (Boston Scientific, Watertown, MA, USA) equipped with 40-MHz catheters (Atlantis SR Pro 3.6F, Boston Scientific) was used for these clinical investigations.

IVUS image analysis. The IVUS echogenecity aspects were used to characterize atherosclerotic VP components. Anechogenic, homogeneous reflective and bright zones indicate presence of lipid or cellular deposition, organized or disorganized fibrosis and calcified regions, respectively (Di Mario et al. 1998). A manual