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● *Original Contribution*

ECHO-COMPUTED TOMOGRAPHY STRAIN IMAGING OF HEALTHY AND DISEASED CAROTID SPECIMENS

Renate W. Boekhoven,* Marcel C. M. Rutten,* Marc R. van Sambeek,†
Frans N. van de Vosse,* and Richard G. P. Lopata*

*Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands; and †Vascular Surgery, Catharina Hospital Eindhoven, Eindhoven, The Netherlands

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Abstract—To improve our understanding of the mechanical behavior of human atherosclerotic plaque tissue, fully 3-D geometrical, morphological and dynamical information is essential. For this purpose, four-dimensional (3-D+t) strain imaging using an ultrasound tomography approach (echo-computed tomography) was performed in carotid arteries *in vitro*. The method was applied to a carotid phantom (CPh), a porcine carotid artery (PC) and human carotid atherosclerotic plaque samples (HC, n = 5). Each sample was subjected to an intraluminal pressure, after which 2-D longitudinal ultrasound images were obtained for 36 angles along the circumferential direction. Local deformations were estimated using a 2-D strain algorithm, and 3-D radial strain data were reconstructed. At systole, median luminal strains of 15% (CPh) and 18% (PC) were found, which is in agreement with the stiffness of the material and applied pressure pulse. The elastographic signal-to-noise ratio was consistent in all directions and ranged from 16 to 36 dB. Furthermore, realistic but more complex strain patterns were found for the HC, with 99th percentile systolic strain values ranging from 0.1% to 18%. (E-mail: r.w.boekhoven@tue.nl) © **2014 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Atherosclerosis, Ultrasonography, Strain imaging, Echo-computed tomography.**

INTRODUCTION

Atherosclerotic carotid plaque rupture is an important cause of ischemic stroke. Stroke was reported to account for 1 in every 18 deaths in 2007 in the United States (Roger et al. 2011). Pathological studies have demonstrated that the majority of ruptured atheromas that trigger an acute myocardial or cerebral infarction contain a prominent lipid pool and numerous inflammatory cells, particularly macrophages (Davies et al. 1993; Falk 1989; Moreno et al. 1994). The activated inflammatory cells secrete mediators that thin and weaken the fibrous cap overlying the lipid-rich core of the lesion by reducing synthesis and increasing degradation of collagen (Libby and Aikawa 2002). Furthermore, apoptosis of smooth muscle cells has been associated with calcification, thrombosis and inflammation (Littlewood and Bennett 2003). Post mortem studies have identified one type of vulnerable plaque, the thin-cap fibroatheroma, as the culprit lesion in approximately 80% of sudden cardiac deaths. This type of plaque is typically a minimally occlusive plaque characterized histologically by the following features: (i) thin fibrous cap (<65 mm), (ii) large lipid pool and (iii) activated macrophages near the fibrous cap (Chau et al. 2004; Davies et al. 1993; Virmani et al. 2006).

Plaques, either vulnerable or stable, are mostly located at bifurcation sites, for example, in the carotid artery. Plaque rupture is one of the underlying pathologies for both stroke and myocardial infarction. Currently, the selection of patients eligible for carotid endarterectomy is based on stenosis size only, which is commonly diagnosed with duplex ultrasound. Surprisingly, Rothwell and Warlow (1999) reported that about 80% of the patients treated with carotid endarterectomy actually had a stable plaque. To improve diagnosis and reduce unnecessary operations, it is essential to be able to determine plaque stability. For this purpose, the morphology of the plaque and the corresponding mechanical properties should be characterized. However, dynamic and geometric information of the plaque is necessary.

Address correspondence to: Renate W. Boekhoven, Department of Biomedical Engineering, Eindhoven University of Technology, PO Box 513, 5600 MB Eindhoven, The Netherlands. E-mail: r.w.boekhoven@tue.nl

Different methods of extracting mechanical properties of plaque components have been investigated *in vitro*. Mechanical testing has been performed on atherosclerotic samples by means of 2-D indentation (Barrett et al. 2009) and static and/or dynamic uni-axial or bi-axial testing (Holzapfel et al. 2002). From these studies, specific material properties of plaque components were determined. For a more realistic assessment of plaque mechanics, the vessel should be intact. Blondel et al. (2003) performed an inflation test on cadaveric human plaque tissue, from which the change in outer diameter was determined with an opto-electronic device, and the intraluminal pressure was recorded.

As an alternative, ultrasound (US) strain imaging or elastography, first introduced by Ophir et al. (1991), can be used to assess material behavior and material properties (de Korte et al. 1998). Strain imaging estimates the deformation of the artery wall, whereas elastography extracts the material properties from the measured deformation field and the applied force, in this case the intraluminal pressure. Various methods have been proposed for the assessment of radial strain in the vessel wall, with either intravascular ultrasound (IVUS) or linear array imaging techniques, and using different methods for estimating the deformation of the vessel wall (Chen et al. 2004; Langeland et al. 2005; Ophir et al. 1991; Yagi and Nakayama 1988). One-dimensional radiofrequency (RF)-based strain imaging was performed *ex vivo* (de Korte et al. 2000a, 200b) by means of IVUS, at multiple locations in the femoral or coronary vessel wall, to assess local plaque characteristics. High radial strains were measured at the shoulder regions of the plaques. Palpography, a simplification of IVUS elastography, assesses the radial strains only on the luminal vessel wall surface and, thus, the surface of the plaque where rupture occurs (Schaar et al. 2003). Modulography produces a plaque's modulogram (i.e., a Young's modulus image) by solving the inverse elasticity problem from the strain obtained from IVUS elastography (Baldewsing et al. 2004).

The aforementioned IVUS techniques are invasive, use 1-D signal processing and suffer from motion perpendicular to the ultrasound beam. Two-dimensional methods, like speckle tracking (McCormick et al. 2012; Ryan and Foster 1997; Shapo et al. 1996), optical flow methods (Maurice et al. 2008; Wan et al. 2001) and non-rigid image registration (Liang et al. 2008), have been proposed to improve the 1-D methods mentioned above using the B-mode data as input. However, to improve the accuracy and resolution of displacement and strain estimates, RF-based algorithms are more favorable. Two-dimensional RF-based strain imaging, using linear or phased array probes, allows the accurate assessment of small displacements, especially in the axial beam direction, non-invasively. By cross-correlation of 1-D or 2-D pre-compression RF windows with 2-D post-compression RF windows, displacements in the two directions can be estimated (Konofagou and Ophir 1998; Lopata et al. 2009a, 2009b). The feasibility of estimating lateral displacements, that is, displacements perpendicular to the ultrasound beam, and the subsequent improvement in axial displacements and strains (parallel to the ultrasound beam) were first reported in Konofagou and Ophir (1998). Such an RF-based cross-correlation technique was applied to vascular phantoms and *in vivo* data by Ribbers et al. (2007), resulting in non-invasive, 2-D strain images of the vessel wall. Lopata et al. (2009a) quantified the improvement over 1-D strain imaging when using 2-D data segments, the improvement of accuracy and precision for different window sizes and the differences between single- and multi-step data processing. It was concluded that a multi-step algorithm with decreasing (axial) window sizes improves precision, but also enables the assessment of larger strains. A two-step (or "hybrid") approach previously reported by Chen et al. (2007) had revealed good improvement in strain image quality for carotid strain imaging. The 2-D RF-based method was adapted for vascular strain imaging and combined with beam steering by Hansen et al. (2009) for transverse cross-section imaging. Because of the lack of phase information in the lateral direction, estimation of displacements in the lateral direction is less accurate. This also prevents 2-D matrix arrays from being used for 3-D carotid strain imaging. Beam steering overcomes this issue by using only axial displacement estimates acquired at different angles, but requires hardware modifications of the US system.

Biological soft tissue is anisotropic and non-linearly elastic; therefore, it tends to deform non-uniformly in all three dimensions. Hence, an assessment of the complete 3-D deformation for the entire geometry is necessary to estimate the material properties of the plaque and to obtain a complete understanding of the mechanics playing a role in rupture. Schaar et al. (2005) proposed a 3-D RF-based IVUS palpography method using a catheter pullback. The method was applied in coronary arteries, again only estimating the deformation on the luminal border of the vessel wall (the innermost 600 mm), both in phantoms and *in vivo* in rabbits and humans. They reported a high level of reproducibility. Three-dimensional strain tensor estimation *in vitro* was reported by Liang et al. (2010), where non-rigid image registration was used on IVUS data by means of a catheter pullback. Most IVUS manual pullback techniques are less suited for calcified plaques, and the manual pullback of the catheter causes the image reconstruction to be erroneous.

Previously it was reported that plaque geometry could be assessed *in vitro* by means of an ultrasound