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4pBA5. Radial shear strain elastography imaging of carotid atherosclerotic plaques in a porcine model
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The objective is to show the feasibility of shear strain elastography (SSE) in vivo with intravascular ultrasound (IVUS) radio-frequency (RF) data acquired at 20 MHz in carotid arteries of atherosclerotic pigs. We previously proposed the Lagrangian speckle model estimator (LSME) to estimate the strain tensor including the shear strain that could be involved in atherosclerotic plaque hemorrhage, inflammation and rupture mechanisms. However, the LSME performance to compute SSE had never been validated. Atherosclerotic pigs with significant plaques on carotids were studied. To induce atherosclerosis, pigs were put on an atherogenic diet and partial ligations of common carotid arteries were performed. Diabetes was induced by selective intra-arterial injection of streptozotocin. IVUS acquisitions were performed before sacrifice and histology analyses were realized on fixed dissected carotids. SSE maps at end diastole were estimated with a new implementation of the LSME and matching with histology sections was realized. SSE clearly identified all plaques with cohabitation of high positive and high negative shear values, and minimum shear elsewhere within the vessel wall. This study demonstrates the performance of the LSME implementation to estimate the shear strain distribution, and the feasibility of SSE to highlight atherosclerotic plaque vulnerability characteristics.

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INTRODUCTION

Histological studies have shown that vulnerable plaques (i.e., those prone to rupture with thromboembolic complications) are typically characterized by a large extracellular necrotic core, a high inflammatory cell burden and a thin fibrous cap infiltrated by macrophages (Vengrenyuk et al., 2006; Virmani et al., 2006). The main diagnostic and prognostic criteria of atherosclerosis evolution are changes in plaque morphology and degree of stenosis, which can accurately be assessed with intravascular ultrasound (IVUS) (Carlier and Tanaka, 2006). However, the prediction of plaque rupture remains a major challenge for ultrasound imaging methods but the identification of plaque component mechanical property is seen as a promising avenue (Finet et al., 2004). Several IVUS-based technologies were developed for evaluation of vessel lesion characteristics and for therapy planning, namely endovascular elastography (EVE) (de Korte et al., 2000; 2002), palpography (Céspedes et al., 2000; Schaar et al., 2006) and virtual histology (VH) (Nair et al., 2002; 2007). Early advances on EVE relied on radial deformation estimates (de Korte et al., 1998). Later, circumferential strain (Maurice et al., 2008; Liang et al., 2008) and radial shear strain elastography (Maurice et al., 2007) were proposed for IVUS imaging. So far, radial shear EVE has not been validated; in this study we demonstrate the validity of radial shear strain elastograms with gold standard finite element (FE) simulations based on vascular phantom experiments, and then the potential of the method to localize and identify vulnerable plaque features in a swine model.

MATERIALS AND METHODS

Vascular phantoms were fabricated with polyvinyl alcohol cryogel (PVA-C) tissue mimicking material. The protocol followed the methodology described elsewhere (Maurice et al., 2005; Le Floc’h et al., 2010). Two vessel phantoms were constructed; the first one had a homogeneous wall experiencing one freeze-thaw cycle (cycle duration of 24 h, temperature of ± 20°C). The second heterogeneous phantom was made with six freeze-thaw cycles for the vessel wall, and the inclusion mimicking a soft necrotic core was filled with PVA-C before the last cycle (the inclusion thus underwent only one freeze-thaw cycle). With this method, the stiffness increases with the number of freeze-thaw cycles. Arterial phantoms were mounted in a flow circuit and pressurized with a water column. Cross-sectional radio-frequency (RF) images were acquired at different static pressure steps of 0.5 kPa with an IVUS scanner (In-Vision Gold, Volcano Therapeutics, Rancho Cordova, CA, USA) equipped with the Remora RF digitizer and a 20 MHz catheter.

Static finite element (FE) computations were performed using the COMSOL multiphysics software (Structural Mechanics Module, version 3.5, COMSOL Inc., Grenoble, France). The stiff (mimicking fibrosis) and soft (mimicking lipid) PVA-C phantom components were modeled as isotropic and quasi-incompressible (Poisson’s ratio = 0.49), with Young’s moduli $E_{\text{fibrosis}} = 145$ kPa and $E_{\text{lipid}} = 17$ kPa, as experimentally determined (Le Floc’h et al., 2010).

Atherosclerotic pigs with significant plaques on a few carotids were studied. To induce atherosclerosis, pigs were put on an atherogenic diet for 20 weeks, as previously described (Soulez et al., 2012). In brief, a partial ligation of common carotid arteries was performed with an absorbable suture on one side and a permanent suture on the other side to create a 70% stenosis. Diabetes was induced by selective intra-arterial injection of streptozotocin. Atherosclerotic plaques developed upstream and downstream of the partial ligation, and at the site of the suture for the absorbable silk. A greater variability in plaque sizes was observed with the absorbable suture. Routine IVUS acquisitions were performed before sacrifice. IVUS scans were conducted using an automatic pull back system (Avanar F/X, Volcano Therapeutics) and a 20 MHz array probe. Knowing the pullback speed (0.5 mm/s) and the frame rate permitted to calculate the distance between the carotid bifurcation and the plane of view. Repositioning of the IVUS catheter was done to collect RF data on a few cardiac cycles with the catheter in static longitudinal position at the site of the detected plaque.

RESULTS

In Vitro Performance and FE Validation

As depicted in Fig. 1, the measured elastogram (right) for the homogeneous PVA-C phantom #1 had shear strain values close to zero, as predicted by the simulation (left). The simulated (left) and measured (right) SSE for the soft inclusion condition (phantom #2) had similar profiles with high shear strain positive and negative values located at
the level of the mimicked thin fibrous cap. These results suggest that SSE may allow an evaluation of the shear pattern close to the thin cap fibroatheroma, which may be a good biomechanical predictor of plaque rupture.

**FIGURE 1.** Performance of the radial shear strain IVUS elastography method to map vulnerability features of mimicked atherosclerotic plaque. **Column 1:** Simulated radial shear strain elastograms obtained by finite element modeling considering a normal vessel (top) and an artery with a soft plaque (i.e., segmented area, bottom). **Column 2:** Measured radial shear strain elastograms obtained by the LSME-EVE method. Color maps show the magnitude of shear strains (multiply by 100 to get strain in percent).

**In Vivo Performance with the Pig Model**

SSE was determined on frames acquired at end-diastole to reduce motion artifact. Six-mm thick sections every 5 mm and added serial sections when a plaque was detected were prepared for histology. Plaques were stained with hematoxylin phloxine saffron, movat and/or von Kossa. Picrus-sirius red stain was also used for collagen analysis and for grading intimal thickening in AHA (American Heart Association) stage I-III lesions (Stary, 2000). Figure 2 (top) shows a type I atherosclerotic plaque (initial lesion with foam cells). As observed earlier for the *in vitro* study, the elastogram depicted cohabitation of high positive and negative shear values within the plaque. The small plaque at 9 o’clock was manually segmented and the mean absolute value of SSE was determined. It was $1.5 \pm 0.14\%$ for the plaque versus $0.2 \pm 0.03\%$ for the remaining normal portion of the carotid artery wall. Figure 2 (bottom) presents an example of a type IV AHA plaque (atheroma with a confluent extracellular lipid core). The plaque at 10 o’clock revealed a mean absolute SSE of $7.4 \pm 2.0\%$ versus $1.5 \pm 0.13\%$ for the presumably “normal wall” section. Those examples correspond to a specific cardiac cycle of a given acquisition. These preliminary results tend to corroborate the hypothesis that soft materials, surrounded by more rigid vessel components, promote SSE inhomogeneities. Although preliminary to conclude, higher mean shear strains were noticed for the more advanced plaque. The mean shear strains also appeared higher within the plaque when compared with the remaining portion of the artery wall.
FIGURE 2. Examples of results for AHA type 1 (top) and type IV (bottom) atherosclerotic plaques in a pig model. Column 1: B-mode IVUS images reconstructed from RF data. Column 2: measured shear strain elastograms obtained by the LSME method in end diastole. Column 3: histology section. Color maps of the elastograms show the magnitude of shear strains (multiply by 100 to get strain in percent). Note that the top left B-mode image shows the presence of the carotid bifurcation; the segmentation of the normal wall thus included two vessels for this example.

DISCUSSION

The quantification of the mechanical properties of atherosclerotic plaque components at any given time of the remodeling process remains a major issue, as it could lead to the development of therapies for the prevention of plaque rupture events. This study highlighted the performance of the LSME to estimate the shear strain distribution, and the potential of SSE to highlight atherosclerotic plaque vulnerability characteristics (i.e., high shear strains close to the boundaries of the fibrous cap). The LSME performance to compute the shear strain elastogram had never been tested nor validated with real IVUS measurements. When proven of interest on a larger database and eventually in human, this technique may be of strong interest to determine vulnerable plaques at risk of inducing a sudden coronary syndrome. Indeed, the LSME can identify plaque areas subjected to high shear stresses. This can provide important insights for endovascular therapy planning and preoperative lesion assessment, in complement with existing elastography, palpography and virtual histology IVUS methods.

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