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A negative correlation between human carotid atherosclerotic plaque progression and plaque wall stress: *In vivo* MRI-based 2D/3D FSI models

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Abstract

It is well accepted that atherosclerosis initiation and progression correlate positively with low and oscillating flow wall shear stresses (FSS). However, this mechanism cannot explain why advanced plaques continue to grow under elevated FSS conditions. *In vivo* magnetic resonance imaging (MRI)-based 2D/3D multi-component models with fluid–structure interactions (FSI, 3D only) for human carotid atherosclerotic plaques were introduced to quantify correlations between plaque progression measured by wall thickness increase (WTI) and plaque wall (structure) stress (PWS) conditions. A histologically validated multi-contrast MRI protocol was used to acquire multi-year *in vivo* MRI images. Our results using 2D models (200–700 data points/patient) indicated that 18 out of 21 patients studied showed significant negative correlation between WTI and PWS at time 2 (T2). The 95% confidence interval for the Pearson correlation coefficient is $(-0.443, -0.246)$, $p<0.0001$. Our 3D FSI model supported the 2D correlation results and further indicated that combining both plaque structure stress and flow shear stress gave better approximation results (PWS, T2: $R^2 = 0.279$; FSS, T1: $R^2 = 0.276$; combining both: $R^2 = 0.637$). These pilot studies suggest that both lower PWS and lower FSS may contribute to continued plaque progression and should be taken into consideration in future investigations of diseases related to atherosclerosis.

Keywords: Plaque progression; Blood flow; Atherosclerosis; Plaque rupture; Fluid–structure interaction

1. Introduction

Atherosclerotic plaque progression are believed to be related to multiple factors such as mechanical forces, plaque morphology and inflammation, vessel remodeling, blood conditions, chemical environment, and lumen surface condition (Friedman et al., 1987; Friedman, 1993; Giddens et al., 1993; Ku, 1997; Ku et al., 1985; Naghavi et al., 2003a, b; Ravn and Falk, 1999; Ross, 1993). The role of mechanical factors in plaque progression using sequential patient tracking data, however, has not been well documented. The governing mechanisms are not well understood. The difficulty is partially due to the fact that atherosclerosis is a slow process and patient-specific data showing plaque progression takes a long time to acquire. It has been well accepted that low and oscillating flow shear stresses (FSS) correlate positively with intimal thickening and atherosclerosis progression (Friedman et al., 1987; Friedman, 1993; Giddens et al., 1993; Ku et al., 1985; Nerem, 1992). This "low shear stress" (LSS) hypothesis has influenced the atherogenesis research field considerably in recent years. However, as plaque progression continues, stenosis becomes more severe and lumen narrowing will eventually occur which are often associated with elevated high shear stress conditions (Tang et al., 2001, 2004a, 2005).

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The LSS hypothesis cannot explain why intermediate and advanced plaques continue to grow under elevated high shear stress conditions. Several research groups reported findings controversial to the LSS hypothesis and suggested the growing importance of searching for other mechanical factors such as plaque wall (structure) stresses (PWS) and new hypotheses for mechanisms governing plaque progression process (Joshi et al., 2004; Wentzel et al., 2003, 2005). The purpose of this investigation is to quantify possible correlation between human carotid atherosclerotic plaque progression and PWS conditions by using 2D and 3D multi-component plaque models based on *in vivo* magnetic resonance images (MRI) data taken from patients at multiple time points. MRI-based atherosclerotic plaque models have been introduced by several groups (Holzapfel et al., 2002; Huang et al., 2001; Kaazempur-Mofrad et al., 2004; Long et al., 1997, 2000; Steinman et al., 2002) and our group (Tang et al., 2004b, 2005). In this paper, both 2D and 3D models were solved by a commercial finite element package ADINA (ADINA R & D Inc., Watertown, MA) to obtain plaque stress/strain conditions (Bathe, 1996, 2002). Linear regression analysis was performed to quantify correlations between plaque maximum principal stress (Stress-P_1) and plaque progression measured by wall thickness increase (WTI). Statistically significant negative correlations were found in 18 out of 21 patients studied.

2. Methods

2.1. In vivo serial MRI data acquisition and segmentation

To quantify possible correlations between plaque progression and selected mechanical factors, the first step was to scan patients with atherosclerotic plaques multiple times (serial MRI) to obtain plaque progression data. Serial MRI data of carotid atherosclerotic plaques from 21 (numbered as Y1–Y21; age: 54–84, mean: 70.6; 19 males, 2 females) were acquired by the University of Washington (UW) group using protocols approved by the University of Washington Institutional Review Board with informed consent obtained. Scan time intervals were 18 months for Y1–Y20 and 10 months for Y21. MRI scans were conducted on a GE SIGNA 1.5-T whole body scanner using an established protocol outlined in the paper by Yuan and Kerwin (2004). A custom-designed carotid phased-array surface coil was used for all scans. Multi-contrast images in T1, T2, proton density (PD), time-of-flight (TOF), and contrast-enhanced (CE) T1 weighted images of atherosclerotic plaques were generated to characterize plaque tissue composition and luminal and vessel wall morphology (Cai et al., 2002; Yuan and Kerwin, 2004; Yuan et al., 2001a, b). The multi-contrast MRI techniques for human carotid imaging have been used and validated by histological data by Yuan and his group with several publications (Cai et al., 2002; Kerwin et al., 2003; Liu et al., 2006; Yuan and Kerwin, 2004; Yuan et al., 2001a, b). A custom-designed computer package CASCADE (Computer-Aided System for cardiovascular Disease Evaluation) developed by the Vascular Imaging Laboratory (VIL) at the UW was used to perform image analysis and segmentation (Kerwin et al., 2003). Upon completion of a review, an extensive report was generated and segmented contour lines for different plaque components for each slice were stored for 2D/3D computational model reconstructions. Fig. 1 shows 10 (selected from 24) MRI slices (T1W) obtained from a human carotid plaque sample, the segmented contour plots, and the re-constructed 3D geometry. Fig. 2 gives a sample plaque re-constructed from serial MRI data showing plaque progression.

2.2. In vivo MRI-based multi-component plaque models

2D multi-component models were used in this paper because they were less labor-intensive and the stress results provided reasonable accuracy for our correlation analysis.

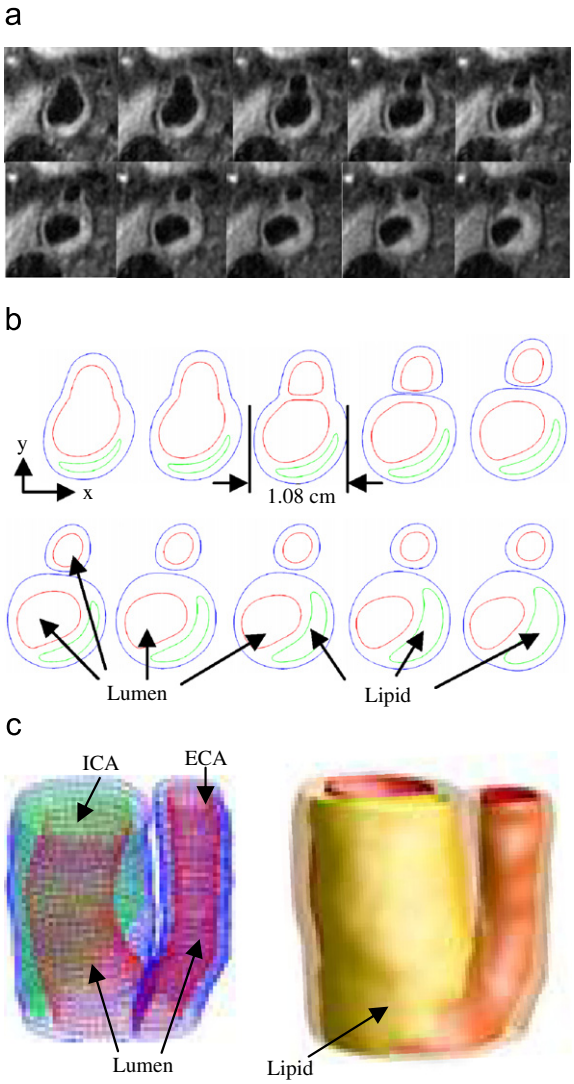

Fig. 1. *In vivo* 3D MRI images of a human carotid plaque and 3D reconstruction: (a) 10 (out of 24) MRI (T1) slices; (b) segmented contour plots; (c) re-constructed 3D plaque geometry; (d) 3D surface view.