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Original contributions

MRI-based biomechanical imaging: initial study on early plaque progression and vessel remodeling

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Abstract

The goal of the study is to develop a noninvasive magnetic resonance imaging (MRI)-based biomechanical imaging technique to address biomechanical pathways of atherosclerotic progression and regression in vivo using a 3D fluid-structure interaction (FSI) model. Initial in vivo study was carried out in an early plaque model in pigs that underwent balloon-overstretch injury to the left carotid arteries. Consecutive MRI scans were performed while the pigs were maintained on high cholesterol (progression) or normal chow (regression), with an injection of a plaque-targeted contrast agent, Gadofluorine M. At the end of study, the specimens of carotid arterial segments were dissected and underwent dedicated mechanical testing to determine their material properties. 3D FSI computational model was applied to calculate structure stress and strain distribution. The plaque structure resembles early plaque with thickened intima. Lower maximal flow shear stress correlates with the growth of plaque volume during progression, but not during regression. In contrast, maximal principle structure stress/stain (stress-P1 and strain-P1) were shown to correlate strongly with the change in the plaque dimension during regression, but moderately during progression. This MRI-based biomechanical imaging method may allow for noninvasive dynamic assessment of local hemodynamic forces on the development of atherosclerotic plaques in vivo.

Keywords: MR; Atherosclerosis; Biomechanics; Stress; Stain; Contrast agent

1. Introduction

Atherosclerosis is first formed by thickened intima that responses to chronic arterial injury. The subsequent plaque progression depends upon the plaque growth and/or vascular remodeling. The focal and eccentric nature of atherosclerotic plaques are well recognized [1–3] as the plaques often form at regions near bifurcations, bends and branch ostia. These complicated events involve a cascade of molecular and cellular processes that characterize the activation of vascular endothelial cells and platelets, recruitment of leukocytes through expression of cellular adhesion molecules (e.g., $\alpha_v\beta_3$ integrins, selectins, proteoglycans, etc.), increased vascular permeability to lipoproteins, smooth muscle cell (SMC) proliferation, increased endothelial cell apoptosis and altered hemostatic and fibrinolytic balances for thrombogenesis. Although many systemic factors such as hypertension, smoking, hyperlipidemia and diabetes mellitus have profound impacts on endothelial cell function and plaque progression [4], local biomechanical factors such as flow-generated shear stress (SS) have been identified to influence remarkably the formation, remodeling, and progression of vascular plaque through the activities of local mechano-transduction mechanisms [5].

The commonly held concept is that low or oscillatory flow SS promotes the development of early fibroatheromas while higher physiologic SS activates various atheroprotective genes on endothelial cells, leading to the stability of the plaque [6]. Cheng et al. [7] designed a unique taped polymeric cast to induce low and high shear stress around

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one carotid artery of ApoE$^{-/-}$ mice. Significantly larger plaque was observed in the region of low SS with intraplaque hemorrhage. In a progression study with a coronary plaque porcine model [8], lower SS was associated with high-risk plaques, characterized by lipid accumulation, inflammation, thin fibrous cap, severe internal elastic lamina degradation and excessive expansive remodeling. Serial in vivo study in patients with coronary artery disease (CAD), by using the intravascular ultrasound imaging technique (IVUS), has also demonstrated strong correlation between regions of low SS, and the sites exhibited coronary plaque progression and expansive remodeling [9]. Using the same imaging technique, however, Fukumoto et al [10] show localized high SS is related to plaque rupture in vivo, but the flow SS appears to have no effect on plaque regression from lipid lowering therapy [11]. Recently, study in carotid artery with relatively severe stenosis by Tang et al. [12] pinpointed that structure tensile stress within the plaque, in addition to flow SS, may also play an important role in the regulation of plaque progression and vulnerability. No study has been reported so far to exam the impact of both structure stress and SS on the progression and regression of early plaques.

Gadofluorine M. (Bayer Schering Pharma, Berlin, Germany) enhanced magnetic resonance imaging (MRI) plaque images have been reported in animal atherosclerosis models such as rabbits and swine [13–15]. Recent research using fluorescence imaging techniques has revealed that Gadofluorine M. strongly attaches to several extracellular matrix (ECM) components: collagen, elastin, proteoglycans and tenascins but has much lower affinity for normal media, lipids and macrophages [16]. Because early plaque is characterized by adaptive intimal thickening and the intimal xanthoma consists of SMCs and ECM, Gadofluorine M. maybe one of ideal contrast agents to aid in the visualization of early plaques by MRI. In this project, a single- or double-injury atherosclerotic plaque model in pigs was used to simulate the early plaque phenotype. The purpose of this investigation is to seek how stress and strain affect the progression and regression of early plaque, as well as concomitant vascular remodeling.

2. Materials and methods

2.1. Animal preparation and artery injury

Three Yucatan mini-pigs (weight=33±4 kg) were used in this initial in vivo study. A baseline blood sample was first obtained for measurement of serum lipid profile. The pigs were first fed an high cholesterol (HC) diet (modified porcine 4% cholesterol w/apple flavor diet, Purina Mills Test Diet, Richmond, IN, USA) for approximately 2 weeks. Once their total cholesterol levels increased to over 200 mg/dl, the pigs underwent the first carotid artery injury via balloon over inflation. Two of the three pigs also received a second balloon overstretch injury at the same arterial segment as the first injury. All of injuries were performed in the left carotid artery, between the second and fourth cervical vertebra (Fig. 1). The right carotid arteries served as the control cases. All animal techniques were approved by the animal study committee of our institute.

For the surgical injury of the vessels, an ear vein was first cannulated and normal saline was administered. The trachea was intubated, and inhaled isofluorine (1–3%) was used to maintain anesthesia. An 8F catheter sheath was inserted into the exposed right femoral artery. Baseline carotid artery angiography was first performed and a balloon catheter (Proflex 5, 8×2 mm, Mallinckrodt, St. Louis, MO, USA) was advanced into the left carotid artery to the level of the second or third cervical vertebrae. The balloon was inflated five times to a distending pressure of 8 atm for 30 s with 60 s between inflations. Our previous experience [17] has shown consistent disruption of the internal elastic lamina by this method. The second injury repeated the same procedure on the first injury site, as confirmed by fluoroscopic images.

2.2. Experimental protocol

Pig 1 was injured only once and was scanned twice by MRI: at 10 and 14 weeks after the injury for progression study. Pigs 2 and 3 underwent two carotid artery injuries aiming to create more aggressive atherosclerotic plaques. Four MRI scans at time points 1–4 (T1–T4) were performed

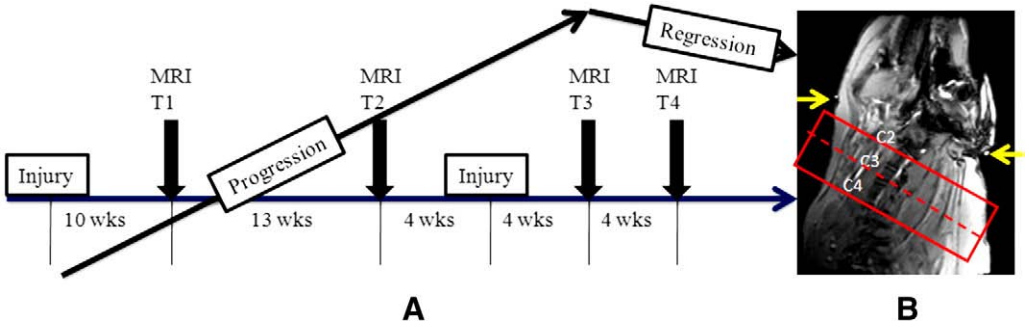

Fig. 1. (A) Time course of the experimental study for the pigs. (B) Location of imaging volume over the neck region between second and fourth cervical vertebra. T1–T4 indicates four time points for the MRI to monitor the plaque progression. Pig 1 was evaluated only at T1 and T2, but Pig 2 and 3 underwent evaluation at all time points. The yellow arrows point to the external fiducial markers (contrast ring) attaching the neck of the pig.