DISEASED ARTERY WALL MECHANICS: CORRELATION TO HISTOLOGY

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ABSTRACT

Increased mechanical stresses in the fibrous cap of atherosclerotic plaque can lead to rupture and consequently thrombosis, which can cause stroke and myocardial infarction. It is hypothesized that sites of inflammation correlate with regions within the tissue experiencing elevated mechanical stress/strain. By obtaining specimens of atherosclerotic plaque, and reconstructing patient specific models, we investigated possible correlations between mechanical stress patterns and histological markers of disease.

INTRODUCTION

Increased biomechanical stresses in the arterial wall can lead to rupture of the fibrous cap leading to a myocardial infarction or stroke. By investigating the correlation between plaque composition and patterns of mechanical stress, vulnerable plaque rupture may be foreseen in patients. Analysis aimed at predicting plaque rupture would depend on the parameters of the plaque that contribute to the stability of the lesion. In this study, atherosclerotic plaque specimens were obtained from four patients. These specimens were used to reconstruct the conditions in vivo, using finite element methods (FEM). The FEM model allows for detailed analysis of mechanical stress/strain and their possible correlation with wall constituents characteristic of disease progression.

METHODS

Specimens were obtained from four patients following carotid endarterectomy. During the surgery, the atherosclerotic plaque was excised and later, sectioned for staining. Five to six sections per patient were stained for lipid (LIP), collagen (COL), smooth muscle cells (SMC), and macrophages (MΦ).

Digital images of each slice were analyzed to determine plaque composition to construct a two-dimensional replica of the slice using finite element methods. The models were divided into regions of lipid, normal arterial wall, and fibrous plaque. Fibrous plaque was assumed to be any region other than lipid or normal arterial wall. Specifically, regions of fibrous plaque were identified as those containing macrophages, smooth muscle cells and collagen. Since smooth muscle cells secrete collagen, both stains may overlap in many regions. In the histology of this study the macrophage infested areas were also observed to coincide with some regions of smooth muscle cells and collagen, particularly in the region surrounding the lipid pool and in the region of the fibrous cap.

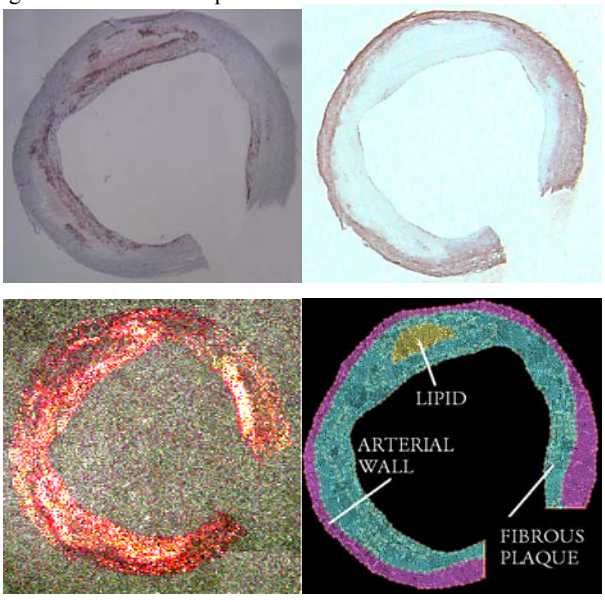

Fig. 1. Sections of a slice of atherosclerotic plaque and extracted mesh. Clockwise from the bottom left—collagen, macrophage, smooth muscle cells, and mesh extracted from histology

Each of these three regions was modeled as a rubber-like material, defined using Mooney-Rivlin parameters, which can be characterized by two constants, D_1 and D_2, the coefficients. in the strain energy density function. D_1 is proportional to the elastic

modulus at zero strain, and D_2 characterizes the elastic sensitivity of the material to increasing stress. The Mooney-Rivlin parameters used were D_1 = 2644.7 Pa and D_2=8.365 for arterial wall [1], D_1 = 50.0 Pa and D_2=5.0 for lipid [2], D_1 =5105.3 Pa and D_2= 13.0 for fibrous plaque [3], and D_1=18804.5 Pa and D_2=20 for calcification [3].

To account for residual stresses in vivo, FEM commercial software, ADINA (Watertown, MA), was used to bring together the two cut ends of the slice through application of shrinking truss elements that connected the two cut surfaces. Each model contained approximately 15,000, 9-noded elements undergoing plane strain. The model utilized a Lagrangian formulation with large displacements and strains.

After implementing a closed specimen with the residual stresses, a pressure load was applied on the interior boundary of the plaque slice. The applied pressure in the artery was ramped from 0 mmHg to the patient-specific systolic pressure, which was obtained prior to surgery.

Correlations were sought by segmenting each slice into 16 pieces of 22.5 degrees each. In order to assure accuracy and consistency, the right most end of the cut specimen was labeled as 0 degrees and the left most end of the cut specimen was labeled as 360 degrees. Each histological variable (LIP, COL, SMC, and MΦ) was examined over the intimal layer of the slice and recorded as an absolute value within each 22.5 degree sector of the slice. Correlations were sought between the histological variables, and mechanical factors namely, average cyclic strain ($\overline{\varepsilon}_{cy}$), average circumferential stress ($\overline{\sigma}_{\theta}$), and average effective stress ($\overline{\sigma}$) over each of the 16 sectors. Since the variables being correlated are not normally distributed, the Spearman rank order correlation coefficient and its corresponding significance test were used in this study [4].

RESULTS

FEM Models

Bandplots of $\overline{\varepsilon}_{cy}$, $\overline{\sigma}_{\theta}$, and $\overline{\sigma}$ were created for each of the six different slices are presented in Fig. 2 for a a model containing calcification, lipid pools, fibrous plaque and normal arterial wall.

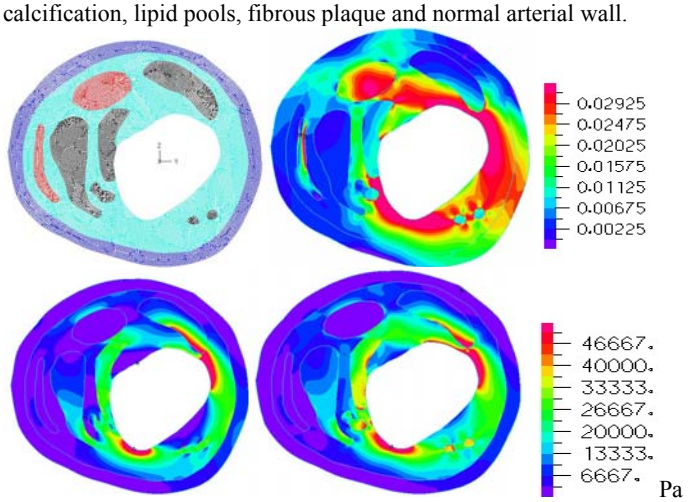

Fig. 2: Stress/strain distributions in a slice of atherosclerotic plaque. Clockwise from top left hand corner, Composition of plaque (red= lipid, black= calcification, green =fibrous plaque and blue =arterial wall), $\overline{\varepsilon}_{cy}$, $\overline{\sigma}$, and $\overline{\sigma}_{\theta}$.

Maximum $\overline{\varepsilon}_{cy}$ was in the lipid pool, as expected due to the viscous like material properties of lipid. Note that one would expect the region surround the lipid pools to be high in stress due to the lipid's inability to support stress. However, this is not the case in this particular model due to support of the load by the calcified region, which experiences maximum stresses as it are closest to the lumen boundary and is the stiffest material in the plaque.

Correlations

Using the Spearman rank order correlation coefficient, significant ($P<0.05$) negative correlations were found between collagen and macrophage content, and the three physiological variables ($\overline{\varepsilon}_{cy}$, $\overline{\sigma}_{\theta}$, and $\overline{\sigma}$) (see Fig.3 for a typical correlation pattern). No significant correlation was found with smooth muscle cell and lipid. Both intracellular and extracellular lipids were quantified in the histology analysis, however in the FEM model, only lipid pools were modeled. Hence, a rigorous correlation analysis was not possible between lipid and the mechanical variables. The correlations found between smooth muscle cells and the stress/strain variables were few and weak. As evident in Fig. 3, a stronger correlation coefficient is found between histological parameters and cyclic strain than stresses, notwithstanding the lipid correlations. This trend is consistent with the notion that it is the fluctuation, rather than mean stress alone that elicits the remodeling response of the plaque.

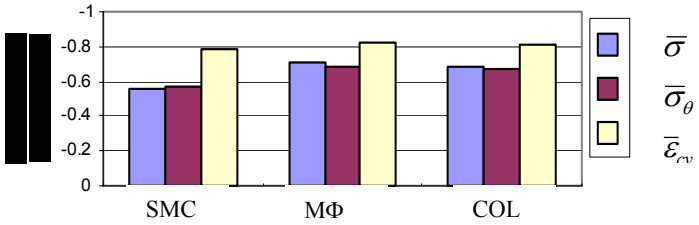

Fig. 3: Correlations seen in Model 5

CONCLUSIONS

From these preliminary results, it appears that macrophage and collagen content are reasonable indicators of high stress or cyclic strain. We can also confirm previous studies showing that lipid pools increase the stress felt in the plaque, whereas calcification decreases it. Further, this investigation also supports the theory that the thickness of the fibrous cap plays an important role in the effective and circumferential stress in the plaque. Areas of high effective stress, circumferential stress, and cyclic strain, are important diagnostic tools in determining the vulnerability of the plaque. By examining different relationships between the histology of the plaque and the stress in the artery, we hope to be able to non-invasively detect plaque vulnerability.

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