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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, and blood conditions, chemical environment, and lumen surface condition (Friedman, 1987, 1993;

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Giddens et al., 1993; Ku, 1997; Ku et al., 1985; Naghavi et al., 2003a, 2003b; 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 correlate positively with intimal thickening and atherosclerosis progression (Friedman, 1987, 1993; Giddens et al., 1993; Ku et al., 1985, 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, 2005b). 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, 2002; Huang et al., 2001; Kaazempur-Mofrad et al., 2002; Long et al., 1997, 2000; Steinman et al., 2002) and our group (Tang et al., 2004b, 2005b). 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; Bathe, 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 twenty-one (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 (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, 2001b). 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, 2001b). A custom-designed computer package CASCADE (Computer-Aided System for Cardiovascular Disease Evaluation) developed by the Vascular Imaging Laboratory (VIL) at the University of Washington (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. Figure 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. All segmented 2D slices were read into ADINA input file, pixel by pixel. To get a starting geometry from the in vivo MRI data, the original in vivo geometry was reduced by 8–10% before the data was read into ADINA so that the actual in vivo shape could be recovered when initial axial pre-stretch and pressurization were applied. The reduction rate varied from patient to patient and was numerically determined for an optimal match with in vivo shape after pressurization. The 2D geometry was then divided into many "areas" so that mesh could be made to curve-fit plaque components in the vessel wall. Computational meshes were made under ADINA computing environment. Finer mesh was used at the thin cap and other places as needed. A 3D FSI model was developed using Y21 data for validation purpose and the 3D correlation results showed good agreement with 2D models (details given in 3.2).

For 2D and 3D solid models, both artery wall (normal tissue) and plaque components (calcification, lipid core, and others) were assumed to be hyperelastic, isotropic, incompressible and homogeneous. The nonlinear modified Mooney-Rivlin model was used to describe the material properties of the vessel wall and plaque components (Bathe, 2002; Huang et al., 2001; Tang et al., 2004b). The strain energy function is given by,

$$W = c_1(I_1 - 3) + c_2(I_2 - 3) + D_1[\exp(D_2(I_1 - 3)) - 1], \quad (1)$$

$$I_1 = \sum C_{ii}, I_2 = 1/2[I_1^2 - C_{ij}C_{ij}], \quad (2)$$

where I_1 and I_2 are the first and second strain invariants, $\mathbf{C} = [C_{ij}] = \mathbf{X}^T\mathbf{X}$ is the right Cauchy-Green deformation tensor, $\mathbf{X} = [X_{ij}] = [\partial x_i/\partial a_j]$, (x_i) is current position, (a_i) is original position, c_i and D_i are material parameters chosen to match experimental measurements and current literatures (Humphrey, 2002; Kobayashi et al., 2003). For the 3D FSI model, the flow was assumed to be laminar, Newtonian, viscous and incompressible. The incompressible Navier-Stokes equations with arbitrary Lagrangian-Eulerian (ALE) formulation were used as the governing equations. No-slip conditions, natural traction equilibrium boundary conditions and continuity of displacement were assumed on all interfaces between all components and the interface between solid and fluid. Inlet and outlet were fixed in longitudinal (axial) direction, but allowed to expand/contract with flow otherwise. The complete FSI model is given below:

$$\rho(\partial \mathbf{u}/\partial t + ((\mathbf{u} - \mathbf{u}_g) \cdot \nabla)\mathbf{u}) = -\nabla p + \mu \nabla^2 \mathbf{u}, \quad (3)$$

$$\nabla \cdot \mathbf{u} = 0, \quad (4)$$

$$\mathbf{u}|_{\Gamma} = \partial \mathbf{x}/\partial t, \partial \mathbf{u}/\partial n|_{\text{inlet, outlet}} = 0, \quad (5)$$

$$p|_{\text{inlet}} = p_{\text{in}}(t), p|_{\text{outlet}} = p_{\text{out}}(t), \quad (6)$$

$$\rho v_{i,tt} = \sigma_{ij,j}, i, j = 1, 2, 3; \text{ sum over } j, \quad (7)$$

$$\varepsilon_{ij} = (v_{i,j} + v_{j,i} + v_{\alpha,i}v_{\alpha,j})/2, i, j, \alpha = 1, 2, 3; \text{ sum over } \alpha, \quad (8)$$

$$\sigma_{ij} \cdot n_j|_{\text{out_wall}} = 0, \quad (9)$$

$$\sigma^r_{ij} \cdot n_j|_{\text{interface}} = \sigma^s_{ij} \cdot n_j|_{\text{interface}}, \quad (10)$$

where standard notations were used (Tang et al., 2004b). Material stress-stretch curves for fibrous tissue (vessel), lipid pool, and calcifications, prescribed inlet and outlet pressure conditions and the corresponding flow rates obtained from the FSI model are given by Fig. 3. Patient-specific maximum and minimum pressure values (by arm prior to MRI scan) were used to adjust the profile in Fig. 3 for each patient studied. The inlet pressure was prescribed in the lumen for all 2D models. Stress- P_1 and flow shear stress values corresponding to maximum pressure were used in the correlation analysis.

2.3 Solution Methods

The 2D (solid only) and 3D FSI models were solved by ADINA. ADINA uses unstructured finite element methods for both fluid and solid models. Nonlinear incremental iterative procedures are used to handle fluid-structure interactions. The governing finite element equations for both solid and fluid models were solved by Newton-Raphson iteration method. More details of the computational models and solution methods can be found from Tang et al. (2004b), Yang et al. (2007) and Bathe (2002).

3. Results

3.1 WTI Correlates Negatively with Stress- P_1 at Time 2 Using 2D Models

For Y1–Y20, each MRI scan gave 12–14 slices with 2 mm slice thickness. For each patient, all matching internal carotid artery (ICA) slices from Time 1 (T1) and Time 2 (T2) were selected using carotid bifurcation as point of registration. We focused on ICA in this study. 100 equally spaced nodal points on the inner (lumen) boundary of each slice were selected for data collection and correlation analysis. For Y21, 40 equally spaced nodal points on the lumen boundary of each slice were selected for analysis. Fewer nodes were selected for Y21 because this sample was used to build the 3D model which had less nodal points on each slice. Vessel wall thickness increase (WTI) was defined as

$$\text{WTI} = \text{Wall Thickness at T2} - \text{Wall Thickness at T1}, \quad (11)$$

and was selected to measure plaque progression in this paper. The daily WTI (dWTI, also called plaque daily growth rate function) was obtained by dividing WTI by the number of days of the scan interval. The term “vessel wall” or simply “wall” is used with the understanding that it includes normal artery tissue and all other plaque components. Wall thickness (WT) at a nodal point x on the lumen boundary was defined as the shortest distance between x and the vessel out-boundary curve. Numerically, the distances between x and the neighboring nodal points on the vessel out-boundary curve were calculated and the minimum was chosen to be the wall thickness at the nodal point x . A shrink-expand process was applied to all slices so that lumen circumferences were preserved under specified lumen pressure. A data set consisting of 300–700 data points (100/slice, all at inner boundary) was generated for each patient (other than Y21 which had 5 matching slices with 40 points/slice selected for analysis) which included wall thickness, values of maximum principal stress (Stress- P_1) and all other stress/strain components at T1 and T2. Stress- P_1 was selected as the representative quantity for plaque wall (structure) stress (PWS). PWS refers to Stress- P_1 throughout this paper, unless indicated otherwise. The statistical analysis package SAS was used to determine possible correlations between WTI and the selected mechanical variables (Stress- P_1 and other stress/strain components). Results from all 21 patients are summarized in Table 1. Statistically significant

negative correlation was found in 18 out of the 21 cases considered. The 95% confidence interval (CI) for Pearson correlation (PC) coefficient values is $(-0.443, -0.246)$, $p < 0.0001$.

Fig. 4 gives a plot of WTI vs. Stress- P_1 from Y3 using 600 data points from 6 slices. The PC value is -0.637 ($p < 0.0001$) which is the best among the twenty-one cases considered (see Table 1). The PC values for the 6 slices analyzed individually were -0.438 , -0.461 , -0.628 , -0.754 , -0.653 and -0.502 respectively, all with $p < 0.0001$. The linear approximation obtained using the least squares method is:

$$\text{WTI (cm)} = 0.0631 - 0.000943 \sigma \text{ (KPa)}, \quad (12)$$

where σ stands for Stress- P_1 . The daily WTI (dWTI, also called plaque daily growth rate function) is obtained by dividing (12) by the days of the scan interval (525 days):

$$\text{dWTI (cm/day)} = 1.201 \times 10^{-4} - 1.797 \times 10^{-6} \sigma \text{ (KPa)}. \quad (13)$$

3.2. Correlations between WTI and Wall Thickness at T1 & T2) and Stress- P_1 at T1

Correlation analysis results are reported in Table 2. Baseline average wall thickness values were also given. While a weak positive correlation between WTI and Stress- P_1 at T_1 was observed, only 11 cases out of 21 have PC values > 0.2 (corresponding $R^2 = 0.04$). 2 cases showed negative correlation. WTI showed statistically significant negative correlation with WT at Time 1 (14 out of 21) and positive correlation with WT at Time 2 (18 out of 21).

3.3. Validation of 2D Results Using 3D FSI Model

A 3D FSI model was constructed for Y21 (the plaque sample given by Fig. 1-(c)) to validate our 2D findings. Our 3D models have been validated by in vitro experimental data (Tang et al., 2003; Tang et al, 2004a). Errors of predicted radial deformation were less than 2% (with and without lipid pool) and errors for flow rate were less than 2% and 5% for no-pool and pool cases, respectively. Figure 5 presents some baseline results showing typical stress distributions and flow behaviors obtained from the 3D FSI plaque model. Elevated flow shear stress is observed in the stenotic region where vessel wall is thick. Figure 6 gives 6 matching slices (out of 11) of the plaque sample from Y21. Only the 5 ICA slices (40 points/slice, 200 data points from lumen surface) were selected for our correlation analysis. Figure 6-(c) plots WTI vs. Stress- P_1 at Time 2 using results from the 3D FSI model. The PC value was -0.528 ($p < 0.0001$) which is highly statistically significant. For the 5 individual slices, we have PC = -0.651 ($p < 0.0001$), -0.457 ($p = 0.0031$), -0.453 ($p = 0.0033$), -0.640 ($p < 0.0001$), -0.778 ($p < 0.0001$), respectively. The linear approximation given by the least squares method is:

$$\text{WTI (cm)} = 0.0637 - 0.000897 \sigma \text{ (KPa)}, \quad (14)$$

A 95% confidence interval for the population correlation is $(-0.6622, -0.421)$. The daily WTI (scan interval 304 days) is given by:

$$\text{dWTI (cm/day)} = 0.000210 - 2.95 \times 10^{-6} \sigma \text{ (KPa)}. \quad (15)$$

To compare 2D and 3D FSI models, Fig. 6-(d) presented WTI vs. Stress- P_1 (at Time 2) using results from 2D models which gave PC = -0.497 , $p < 0.0001$. The error between 2D and 3D PC values is only 5.87%, with 3D model giving stronger correlation.

It is known that stress values from 2D and 3D plaque models can be different because 3D model includes longitudinal stretch and slices are bonded together (Tang et al., 2004b). Greater axial stretch leads to increased 3D Stress- P_1 values. At the same time, 2D model expands more in radial direction because it has no axial stretch and no bonding effect from neighboring slices. That leads to higher Stress- P_1 value at inner wall (lumen) and lower Stress- P_1 values at outer portion of the wall as shown by Fig. 5-(e) & (f). 3D maximum Stress- P_1 (Time 1) from all slices was 426 KPa found from the bifurcating slice. This is 58% higher than that (269KPa)

from the 2D models. Average 3D Stress- P_1 values from all nodal points for the slice shown in Fig. 6-(e) was 33.64 KPa, while the 2D average was 19.42KPa. While 2D and 3D models do give different Stress- P_1 values, Fig. 6 shows that they have similar distribution patterns and the majority of those values differ in a proportional way. 2D models could be used as a first-order approximation for our correlation analysis purposes. Our 3D example supported the correlation results given by 2D models.

4. Discussion

4.1 Correlation between WTI and Flow Maximum Shear Stress (FMSS)

The purpose of this paper is to report our findings of the negative correlations between plaque progression and plaque wall stress which is of general interest to the cardiovascular research community. To investigate the effect of flow shear stress on plaque progression, Fig. 7-(a) plots WTI vs. FMSS (maximum of the shear components of fluid stress acting on lumen surface, see Fung, 1994) using results from the 3D FSI model at T1. A negative correlation between WTI and FMSS was observed, even though wall thickness showed positive correlation with FMSS (Fig. 7(b)). The PC value (WTI vs. FMSS at T1) was -0.525 , $p < 0.0001$. A 95% confidence interval for the population correlation was $(-0.619, -0.417)$. For individual slices, we had PC = -0.623 ($p < 0.0001$), -0.766 ($p < 0.0001$), -0.784 ($p < 0.0001$), 0.303 ($p = 0.057$), and 0.283 ($p = 0.077$), respectively. Variations of PC values from slice to slice were very noticeable which may be related to local flow behaviors such as flow re-circulation regions. The linear approximation for WTI given by the least squares method is:

$$\text{WTI (cm)} = 0.0619 - 0.000578 \tau \text{ (dyn/cm}^2\text{)}. \quad (16)$$

Noticing WTI has statistically significant negative correlations with both Stress- P_1 at Time 2 and FMSS at Time 1, multiple regression analysis was performed using both variables which led to the following formula with noticeable improvement on R^2 value ($R^2 = 0.279$, PWS only; $R^2 = 0.276$, FMSS only):

$$\text{WTI} = 0.111 - 0.00103 \sigma \text{ (KPa)} - 0.000663 \tau \text{ (dyn/cm}^2\text{)}, (R^2 = 0.637). \quad (17)$$

The daily WTI (scan interval 304 days) is given by:

$$\text{dWTI (cm/day)} = 0.000365 - 3.39 \times 10^{-6} \sigma \text{ (KPa)} - 2.18 \times 10^{-6} \tau \text{ (dyn/cm}^2\text{)}. \quad (18)$$

We are currently constructing 3D FSI models for more cases and updated results including both PWS and FMSS will be reported in our future papers.

It should be noted that when using FMSS values at Time 2, the PC value (WTI vs. FMSS) became PC = -0.260 , $p < 0.0001$. Using both Stress- P_1 and FMSS at Time 2, we have:

$$\text{WTI} = 0.124 - 0.00108 \sigma \text{ (KPa)} - 0.00127 \tau \text{ (dyn/cm}^2\text{)}, (R^2 = 0.447). \quad (19)$$

4.2. Possible Hypothesis for Plaque Progression, Mechanical and Other Related Factors

Plaque progression is a multi-faceted process. Other than mechanical factors, plaque type, component size and location, cell activities, blood conditions such as cholesterol level, diabetes, changes caused by medication such as statin, and other chemical conditions, inflammation and lumen surface condition may all have impact on plaque progression. Investigations and findings from all the channels, modalities and disciplines could be integrated together to obtain better and more thorough understanding of the complicated atherosclerotic progression process.

We are trying more complex function forms and using more time steps to better predict plaque growth. It was found that by using Stress- P_1 , WT at T2 (WT2) and WTI, much better

predictions could be made for wall thickness at Time 3. Using a sample slice (S4) from Y1, the predicting function for WTI-23 (WT at T3 – WT at T2) for Slice 4 is given by:

$$\text{WTI} - 23 = 0.0349 + 0.0003 \text{ Stress} - P_1 + 0.0012 \text{ WTI} \cdot \text{Stress} - P_1 - 0.0076/\text{WT2} - 0.1461 \text{ WTI}/\text{WT2}, \quad (20)$$

where $\text{Stress} - P_1$ at T2 was used. Coefficients in (20) were determined using the least-squares method to fit the MRI data. The R^2 values for the 7 slices of Y1 were 0.63, 0.81, 0.78, 0.85, 0.78, 0.50, and 0.54 respectively, much better than the linear correlation results. We are still sorting things out and results will be reported in our future papers.

The purpose of our study was to quantify patient-specific plaque growth functions which will be used to simulate plaque progression using computational models. Using a progression model, plaque geometry will be updated at each numerical time step using the growth function determined based on MRI data. Since plaque grows very slowly and MRI scans are normally done on a yearly basis (18 months for participants in this paper), the most recent scan is closer to our numerical steps. That is a reason why Time 2 values were used in our correlation results reported in Table 1. More scans (MRI time points) will improve accuracy of our growth functions as indicated by (20).

4.3. Choosing WTI as measure for plaque progression

WTI and $\text{Stress} - P_1$ at the inner boundary of the vessel are the natural choices of quantities for a first-order approximation to investigate plaque progression. It is true that tissue type (various plaque components), plaque component shape and size are all contributing factors. How each plaque component would grow in 3D setting depends on detailed local 3D stress/strain environment not available from 2D models. A first-order plaque growth function as defined in this paper (dWTI) will be a good starting point for future more challenging 3D investigations.

4.4. Locations of plaque thickening and thinning

Because thicker wall leads to lower stress level (ignoring plaque components for the time being), the negative correlation between WTI and $\text{Stress} - P_1$ implies that plaque thickening tends to happen where the wall is thicker. That is further evidenced by the positive correlation between WTI and WT at time 2 and the growth function given by (20) which included wall thickness effect. All data points were treated equally (without referring to their locations) in this paper as required by statistical correlation analysis assumptions. Further analysis for localized plaque growth behaviors will need to include detailed location specific 3D flow and plaque stress/strain data and more accurate predictions will become possible.

4.5. Plaque progression and plaque vulnerability

The long term goal of the current work is that patient-specific quantitative plaque growth functions can be determined based on multiple annual MRI scans and used to simulate plaque progression, i.e., how the plaque would grow and would become in future years. “Future” plaque vulnerability can be assessed based on predicted future plaque morphologies by the progression models. We are adding the “time dimension” into plaque assessment technology to improve the predicting power and accuracy.

5. Conclusion

Our initial results obtained from serial MRI data and 2D models indicated that 18 out of 21 patients studied showed statistically significant negative correlation between PWS at T2 and plaque progression measured by WTI. We believe that this is the first time that quantitative human plaque growth functions (dWTI) were reported which can be used in many further investigations related to plaque progression. Our initial results support the new hypothesis that

plaque progression depends on both structural stress/strain and flow shear stress conditions and that low structure stress and flow shear stress may create favorable environment for continued plaque progression. Including plaque morphological features and more time point data in the growth function may improve accuracy of predicted wall thickness changes. More data and validations are needed to confirm our findings.

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(a) In vivo MR images (T1 weighting) of a human carotid plaque, 10 out of a 24 slice 3D set

(b) Segmented contour plots

(c) 3D geometry, 24 slices

(d) 3D surface view

Figure 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

(a) Progression sample,
Time 1

(b) Progression sample,
Time 2 (18 months)

Figure 2.
A plaque sample showing progression. Red: lumen; Yellow: necrotic core; Dark blue: calcification; Light blue: vessel outer wall.

Figure 3.

Material curves and pressure conditions for the multi-component plaque model. (a) Stress-stretch curves derived from the modified Mooney-Rivlin model. The parameters are ($c_2 = 0$ for all materials): vessel and fibrous tissue: $c_1 = 368000$, $D_1 = 144000$, $D_2 = 2.0$; lipid: $c_1 = 20000$, $D_1 = 20000$, $D_2 = 1.5$; Ca: $c_1 = 3680000$, $D_1 = 1440000$, $D_2 = 2.0$, unit: dyn/cm^2 ; (b) pressure conditions specified at the inlet (CCA) and outlet (ICA and ECA); (c) flow rates obtained from the 3D plaque model solutions corresponding to the pressure conditions.

Figure 4. Human carotid plaque progression measured by wall thickness increase (WTI) correlates negatively with wall maximum principal stress (Stress- P_1). Pearson correlation coefficient $PC = -0.637$ ($p < 0.0001$).

Figure 5. 3D FSI model baseline solution plots showing both structure stress and flow velocity and flow maximum shear stress (FMSS) behaviors.

Figure 6.

Results from 3D FSI model show negative correlation between WTI and plaque wall stress (Stress- P_1), supporting 2D correlation results.

(a) WTI vs. FMSS (5 slices, 200 points)

(b) Wall Thickness vs. FMSS (5 slices, 200 points)

Figure 7.

(a) Wall thickness increase (WTI) correlates negatively with flow maximum shear stress ($PC = -0.525$, $p < 0.0001$); (b) Wall thickness (WT) correlates positively with flow maximum shear stress ($PC = 0.348$, $p < 0.0001$).

Table 1

Eighteen (18) out of twenty-one (21) patients studied showed statistically significant negative correlations between plaque progression measured by wall thickness increase (WTI) and plaque wall stress measured by Stress- P_1 (taken at Time 2) obtained using 2D models. Linear approximations of the daily plaque growth functions by the least squares method are included. 95% confidence interval for correlation of the 21 patients for WTI vs. Stress- P_1 at time 2 is $[-0.443, -0.246]$.

Case	Data Pts	Days	Daily Growth Rate (cm/day) (Unit for Stress: KPa)	Pearson Coeff.	p-value
Y1	700	569	$6.028 \text{ E-}05 - 7.083 \text{ E-}07 \sigma$	-0.497	<0.0001
Y2	400	533	$6.529 \text{ E-}05 - 9.962 \text{ E-}07 \sigma$	-0.381	<0.0001
Y3	600	525	$1.201 \text{ E-}04 - 1.796 \text{ E-}06 \sigma$	-0.637	<0.0001
Y4	500	534	$4.157 \text{ E-}05 - 3.202 \text{ E-}07 \sigma$	-0.244	<0.0001
Y5	300	1097	$4.166 \text{ E-}05 - 4.521 \text{ E-}07 \sigma$	-0.293	<0.0001
Y6	400	403	$1.300 \text{ E-}04 - 1.630 \text{ E-}06 \sigma$	-0.395	<0.0001
Y7	500	557	$-1.278 \text{ E-}05 - 5.206 \text{ E-}08 \sigma$	-0.0414	0.36
Y8	400	565	$6.248 \text{ E-}05 - 5.575 \text{ E-}07 \sigma$	-0.297	<0.0001
Y9	400	565	$2.708 \text{ E-}05 - 3.168 \text{ E-}07 \sigma$	-0.252	<0.0001
Y10	500	558	$9.337 \text{ E-}05 - 1.633 \text{ E-}06 \sigma$	-0.51886	<0.0001
Y11	300	277	$2.363 \text{ E-}04 - 5.206 \text{ E-}06 \sigma$	-0.63663	<0.0001
Y12	400	562	$2.875 \text{ E-}04 - 5.206 \text{ E-}06 \sigma$	-0.50642	<0.0001
Y13	600	631	$-3.082 \text{ E-}05 - 5.206 \text{ E-}06 \sigma$	0.073966	0.07
Y14	300	520	$-1.557 \text{ E-}04 - 5.206 \text{ E-}06 \sigma$	0.21414	0.0002
Y15	500	1126	$7.465 \text{ E-}05 - 5.206 \text{ E-}06 \sigma$	-0.56568	<0.0001
Y16	400	298	$3.074 \text{ E-}04 - 5.206 \text{ E-}06 \sigma$	-0.30653	<0.0001
Y17	500	495	$9.541 \text{ E-}05 - 5.206 \text{ E-}06 \sigma$	-0.31474	<0.0001
Y18	300	549	$2.236 \text{ E-}04 - 5.206 \text{ E-}06 \sigma$	-0.36853	<0.0001
Y19	600	461	$3.668 \text{ E-}05 - 5.206 \text{ E-}06 \sigma$	-0.36071	<0.0001
Y20	600	525	$1.515 \text{ E-}04 - 5.206 \text{ E-}06 \sigma$	-0.39872	<0.0001
Y21	200	304	$1.875 \text{ E-}06 \text{ e}^{-4} - 2.536 \text{ E-}06 \sigma$	-0.497	<0.0001

Correlation analysis results between WTI and Stress- P_1 at Time 1 and Wall Thickness at Time 1 and Time 2. 95% confidence intervals for correlation of WTI vs. Stress- P_1 at Time 1: [0.0986, 0.3306]; WTI vs. wall thickness at Time 1: [-0.367, -0.0956]; WTI vs. wall thickness at Time 2 is [0.3301, 0.578].

Table 2

Case	PC (WTI vs. Stress- P_1 at T1)	p-value	PC (WTI vs. WT at T1)	p-value	PC (WTI vs. WT at T2)	p-value	Baseline Average WTI(cm)
Y1	0.1705	<0.0001	-0.0719	0.0570	0.6435	<0.0001	0.1031
Y2	0.3787	<0.0001	-0.3227	<0.0001	0.2719	<0.0001	0.1384
Y3	0.1278	0.0017	-0.2703	<0.0001	0.8296	<0.0001	0.2226
Y4	0.2672	<0.0001	-0.3524	<0.0001	0.7050	<0.0001	0.1182
Y5	0.2790	<0.0001	-0.3503	<0.0001	0.3933	<0.0001	0.1143
Y6	0.0354	0.4800	-0.0487	0.3300	0.3742	<0.0001	0.1683
Y7	0.5297	<0.0001	-0.4330	<0.0001	0.0960	0.0318	0.1124
Y8	0.1795	0.0003	-0.2660	<0.0001	0.4117	<0.0001	0.1056
Y9	0.4216	<0.0001	-0.7244	<0.0001	0.3770	<0.0001	0.0952
Y10	-0.2126	<0.0001	0.2332	<0.0001	0.6197	<0.0001	0.2084
Y11	-0.1482	0.0100	0.1280	0.0266	0.6928	<0.0001	0.1481
Y12	0.3240	<0.0001	-0.1651	0.0009	0.8953	<0.0001	0.1516
Y13	0.5471	<0.0001	-0.4917	<0.0001	-0.0803	0.0490	0.1767
Y14	0.5239	<0.0001	-0.5400	<0.0001	-0.1360	0.0184	0.2145
Y15	-0.0245	0.5840	0.2465	<0.0001	0.6658	<0.0001	0.1585
Y16	0.0711	0.1560	-0.6268	<0.0001	0.5151	<0.0001	0.1312
Y17	0.4075	<0.0001	-0.3255	<0.0001	0.6329	<0.0001	0.1532
Y18	0.0969	0.0940	0.0632	0.2750	0.5053	<0.0001	0.1936
Y19	0.2339	<0.0001	-0.1292	0.0015	0.2696	<0.0001	0.1565
Y20	0.6017	<0.0001	-0.6454	<0.0001	0.3089	<0.0001	0.1631
Y21	-0.3040	0.0005	0.2370	0.0007	0.5400	<0.0001	0.1899