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Plaque progression modeling by using hemodynamic simulation and histological data

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Abstract

Atherosclerosis is a disease of large arteries that is characterized by the accumulation of lipids in the arterial wall. Mechanical forces such as low shear stress are implicated in plaque formation and development. The objective of this work is to examine influence of wall shear stress (WSS) and histological and blood analysis data on the atherosclerosis development. Histological data and blood analysis (cholesterol, HDL, LDL and triglycerides) are available for 18 rabbits fed by atherogenic diet at Cambridge University. WSS data are calculated by using Computer Fluid Dynamic (CFD). Navier-Stokes equations and Darcy`s law were main governing methods for modeling fluid dynamics in the lumen and wall. Convection diffusion equations were used for modeling LDL and oxygen transport. For coupling fluid dynamics and solute dynamics Kedem-Katchalsky equations were used. Two types of finite element model were used. Wall free models were wall is treated only as boundary condition and single layered model where intima and media of the wall is treated as one entity with homogenous transport characteristics.

Keywords: Finite Element Model (FEM), Computer Fluid Dynamic (CFD), Atherosclerosis, Wall Shear Stress, LDL, Lipid Accumulation, Plaque

1. Introduction

Atherosclerosis is a disease of the large arteries characterized by the blood vessel endothelial dysfunction and lipid, cholesterol, calcium and cell elements accumulations inside blood vessel wall. It is commonly referred as plaque formation, vascular remodeling, acute and chronic obstruction of blood vessel lumen, blood flow disorder and lower oxygenation of relevant tissues. Many studies confirmed different risk factor which contributes development and spreading of the atherosclerosis, the most common are hyperlipidemia, higher blood pressure and sugar values, cigarette consumption, age and sex. Great contribution to atherosclerosis development gives mechanical quantities such as low shear stress areas which causes

endothelium dysfunctions and atherogenesis. The main objective of this study is to examine influence of low shear stress and arterial mass transport by modeling the blood flow and solution transport processes in arterial lumen and the wall. Transport processes of the atherogenic species such as low density lipoprotein (LDL) from the bulk blood flow to and across arterial wall contributes to lipid accumulation in the wall.

We modeled relationship between WSS (obtained from computer simulations) and blood analysis data on one hand and plaque size from histology on the other hand. Histological and blood analysis data are available for 18 rabbits fed by atherogenic diet at Cambridge University. Data and geometry are available in two different times (T2 comes three months after T1) for all 18 rabbits. Two different nonlinear models are used for modeling this relationship: third order polynomial regression and quadratic response surface regression [Hill et al. 2006].

2. Mathematical model

Model used here includes fluid dynamics for blood flow and transmural flow and solute dynamics for mass transfer. In order to simulate mass transfer in large arteries and lipid accumulation in the wall following equations were employed.

Hence the fluid is assumed to be steady, incompressible and laminar for modeling fluid dynamics in the lumen Navier-Stokes equations were used (1),(2)

$$-\mu\nabla^2 u_l+\rho\left(u_l\cdot\nabla\right)u_l+\nabla p_l=0 \tag{1}$$

$$\nabla u_l=0 \tag{2}$$

where u_l is blood velocity, p_l is pressure, μ is blood dynamic viscosity and ρ is blood density.

Darcy`s law were used to model mass transfer across the wall (transmural flow) of the blood vessel.

$$u_w-\nabla\left(\frac{k}{\mu_p}p_w\right)=0 \tag{3}$$

$$\nabla u_w=0 \tag{4}$$

where u_w is transmural velocity, p_w pressure in the arterial wall, μ_p is viscosity of blood plasma, and k is the Darcian permeability coefficient of the arterial wall (3), (4). Convective diffusion equations were occupied for modeling mass transfer in the lumen (5)

$$\nabla\cdot\left(-D_l\nabla c_l+c_l u_l\right)=0 \tag{5}$$

where c_l represents blood concentration in the lumen and D_l is diffusion coefficient of the lumen.

Convective diffusion reactive equations (6) were used for modeling mass transfer in the wall which are related to transmural flow.

$$\nabla\cdot\left(-D_w\nabla c_w+Kc_w u_w\right)=r_w c_w \tag{6}$$

where c_w is solute concentration in the arterial wall, D_w is diffusive coefficient of solution in the wall, K is solute lag coefficient and r_w is consumption rate constant.

The coupling of fluid dynamics and solute dynamics at the endothelium was achieved by the Kedem-Katchalsky equations (7),(8).

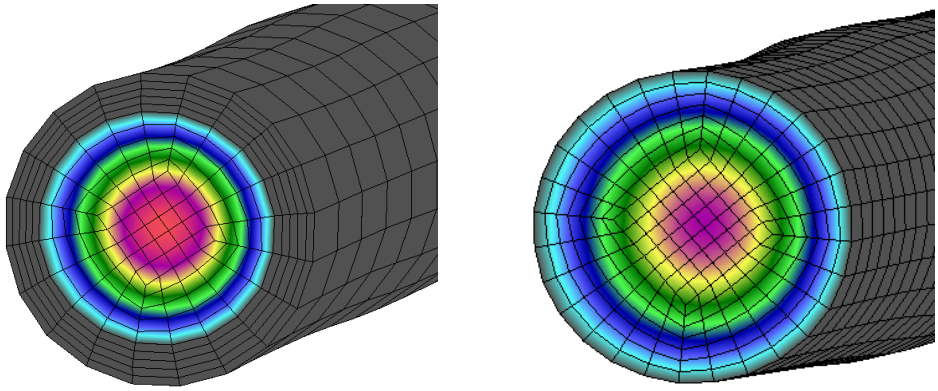
$$J_v = L_p\left(\Delta p - \delta_d \Delta\pi\right) \tag{7}$$

$$J_s = P\Delta c + \left(1-\delta_f\right) J_v \bar{c} \tag{8}$$

where L_p is the hydraulic conductivity of the endothelium, Δc is the solute concentration difference across the endothelium, Δp is the pressure drop across the endothelium, $\Delta\pi$ is the oncotic pressure difference across the endothelium, σ_d is the osmotic reflection coefficient, σ_f is the solvent reflection coefficient, P is the solute endothelial permeability, and $\bar{c}$ is the mean endothelial concentration [Nanfeng et al. 2006].

3. Simulation

As mentioned above, arterial mass transport is influenced by the mechanical forces especially wall shear stress which is present on the arterial wall as effect of blood flow through the blood vessel. As mass transport problem, solute permeability (Fig. 1a) must be considered. Also in this study wall free finite element (FE) model is used (Fig. 1b) without considering transport in the arterial wall.



(a) (b)

Fig. 1. Single layered and wall free model

Computer finite element model used here for performing simulations were generated using medical images (IVUS) [Filipovic et al. 2006] and represents rabbit`s carotids [Holzapfel et al. 2000]. Wall free model were used for simulating blood flow and mass transport in the lumen. These models treats wall as rigid and boundary conditions are all nodes that represents the wall and inlet of the artery are totally constrained. Also initial velocities are prescribed at inlet nodes. Modeling transport processes in the wall is not possible. Unlike the wall free models single layered models provides detailed description of the arterial wall because it takes fluid and tissue phase transport. This type of the model treats intimal and medial parts as one single layer porous medium with homogenous transport characteristics [Kojic et al. 2008]. Plaque growth simulations were performed with these type models where lumen and the wall are part of the

same FE mesh but they are recognized as different entities [Nanfeng et al. 2006], [Filipovic et al. 2011], [Parodi et al. 2011]. Constraining phase uses a few mesh nodes groups. The inlet wall and lumen nodes, representing artery lumen, artery endothelium, wall nodes and shell nodes. All those groups are constrained in the appropriate way in order to simulate behavior in the realistic conditions. In the prescribing loads phase besides the prescribing velocities at the lumen inlet, the prescribing fluxes at specific elements and the prescribing concentrations are necessary in order to simulate plaque propagation processes. Plaque propagation simulation provides, also LDL, Cytokines, Macrophage, and Wall LDL distributions.

4. Simulation results

Different result for different simulation types may be presented (Fig. 2). Blood flow simulations provides velocity, pressure and shear stress distribution.

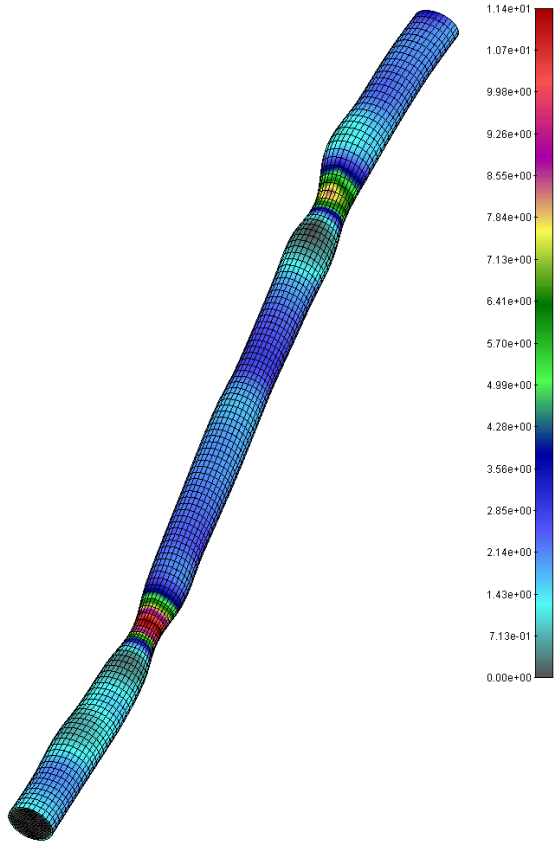
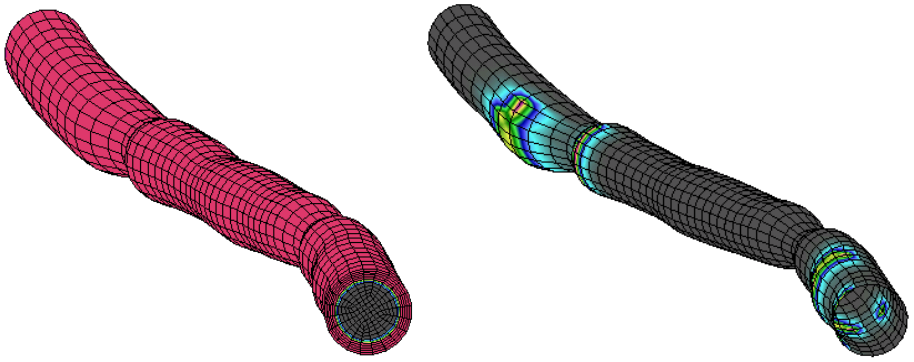
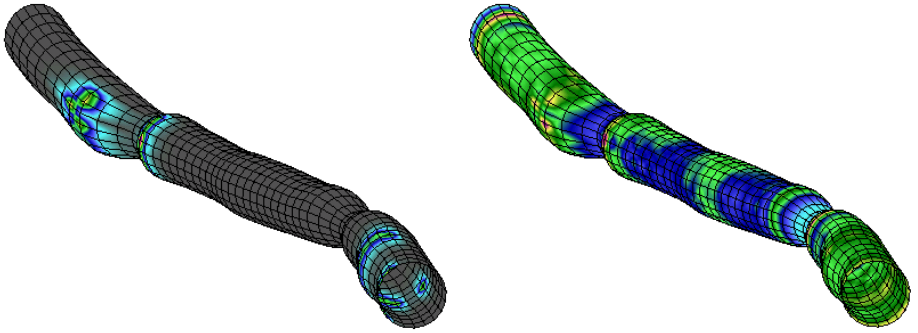


Fig. 2. Blood flow simulation – Shear stress distribution on the wall of the model generated from reconstructed IVUS medical images of rabbits carotid

Plaque propagation simulation, in advance, provides, besides other results, LDL, Cytokines, Macrophage, and Wall LDL distributions (Fig. 3).



Wall pressure distribution b. Oxidized LDL distribution



c. Macrophages distribution d. Cytokine distribution

Fig. 3. Plaque propagation simulation results

5. Fitting data

In this section we try to model relationship between histological data (cholesterol, HDL, LDL and triglycerides) and WSS on one side and plaque progression on the other side. Tables 1 and 2 contain INPUT-OUTPUT data for two different times (T2 comes three months after T1).

	INPUTS					OUTPUTS	
	WSS [Pa]	Cholesterol [mmol/L]	HDL [mmol/L]	LDL [mmol/L]	Triglycerides [mmol/L]	$\frac{A_{endothelial}}{A_{intima}+A_{media}}$ [%]	$\frac{A_{wall}}{A_{intima}+A_{media}}$ [%]
Rabbit 2	2.91	12.7	0.66	11.9	0.3	12.7	29.9
Rabbit 3	1.39	8.1	0.98	6.6	1.1	8.77	36.2
Rabbit 4	4.82	21.8	1.47	17.8	5.6	2.73	58.76
Rabbit5	2.74	21.5	0.90	20.0	1.3	8.84	41
Rabbit 6	3.68	17.5	0.91	7.0	1.1	1.62	53.65
Rabbit 7	5.09	20.2	1.10	17.8	2.9	0.85	55.94
Rabbit 8	4.62	17.2	0.80	16.0	0.8	6.2	26.92

Rabbit 9	2.58	14.9	0.78	13.9	0.5	9.1	54.35
Rabbit 10	9.05	2.0	0.79	0.7	1.1	6.81	30.7
Rabbit 11	2.87	1.7	0.81	0.6	0.5	13.35	12.88
Rabbit 12	3.32	0.9	0.51	0.2	0.4	4.44	39.05
Rabbit 13	3.49	1.5	0.55	0.6	0.7	24	20.77
Rabbit 14	2.92	8.4	0.91	7.3	0.5	4.68	21.88
Rabbit 15	4.38	12.0	1.32	10.3	0.8	7.5	44.6
Rabbit 16	5	34.6	0.70	32.4	3.2	5.33	59.24
Rabbit 17	1.42	6.9	0.70	6.0	0.4	6.18	26.8
Rabbit 18	2.04	4.5	1.13	3.1	0.5	7.51	6.67
Rabbit 19	2.47	7.5	0.87	6.4	0.5	7.62	31.1

Table 1. Input-output Data at Time T1

	INPUTS					**OUTPUTS**	
	WSS [Pa]	Cholesterol [mmol/L]	HDL [mmol/L]	LDL [mmol/L]	Triglycerides [mmol/L]	$\frac{A_{endothelial}}{A_{intima}+A_{media}}$ [%]	$\frac{A_{wall}}{A_{intima}+A_{media}}$ [%]
Rabbit 2	2.61	12.7	0.66	11.9	0.3	5.1	10.18
Rabbit 3	3.18	8.1	0.98	6.6	1.1	8.5	37.7
Rabbit 4	1.62	21.8	1.47	17.8	5.6	5.26	24
Rabbit 5	1.55	21.5	0.90	20.0	1.3	15.26	27.3
Rabbit 6	7.62	17.5	0.91	7.0	1.1	4.12	19.74
Rabbit 7	5.8	20.2	1.10	17.8	2.9	6.19	20.48
Rabbit 8	2.66	17.2	0.80	16.0	0.8	16.92	10.2
Rabbit 10	8.34	2.0	0.79	0.7	1.1	5.55	33.98
Rabbit 11	1.8	1.7	0.81	0.6	0.5	9	18
Rabbit 12	2.12	0.9	0.51	0.2	0.4	4.71	21.5
Rabbit 13	1.72	1.5	0.55	0.6	0.7	12.45	6.54
Rabbit 14	3.87	8.4	0.91	7.3	0.5	6.58	30.1
Rabbit 15	2.22	12.0	1.32	10.3	0.8	7.3	8.6
Rabbit 16	6.58	34.6	0.70	32.4	3.2	23.06	5.76
Rabbit 17	2.76	6.9	0.70	6.0	0.4	9.74	23.73

Table 2. Input-output Data at Time T2

In order to model plaque progression we used WSS, cholesterol, HDL, LDL and triglycerides as input data. As a measure of plaque progression we used $\frac{A_{\text{endothelial}}}{A_{\text{intima}}+A_{\text{media}}}$ on one hand and $\frac{A_{\text{wall}}}{A_{\text{intima}}+A_{\text{media}}}$ on the other (Fig. 4).

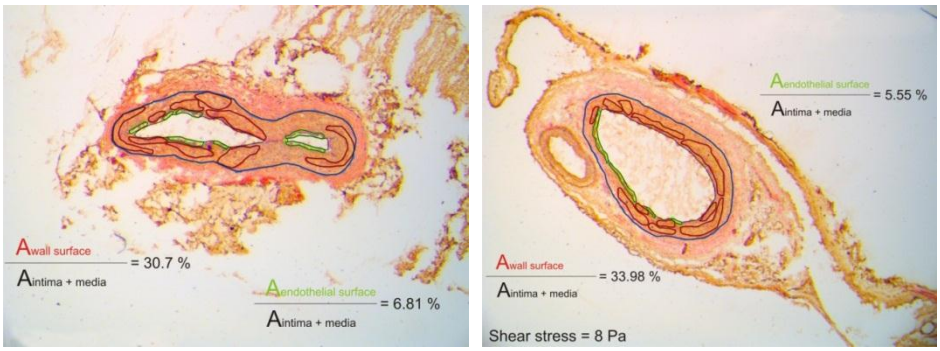


Fig. 4. Carotid artery cross section for rabbit 10 (left T1, right T2)

The following regression models gave the best results:

- Third order polynomial regression:

$$OUTPUT = a_0 + \sum_{i=1}^{5}\left(a_{i,1}\cdot INPUT_i + a_{i,2}\cdot INPUT_i^2 + a_{i,3}\cdot INPUT_i^3\right)$$

- Quadratic response surface regression:

$$OUTPUT = a_0 + \sum_{i=1}^{5}\left(a_i\cdot INPUT_i\right) + \sum_{i=1}^{5}\left(b_i\cdot INPUT_i^2\right) + \sum_{i=1}^{5}\sum_{j=1}^{5}\left(c_{i,j}\cdot INPUT_i\cdot INPUT_j\right); \forall i \le j : c_{i,j} = 0$$

where

$$INPUT = \begin{bmatrix} WSS \\ Cholesterol \\ HDL \\ LDL \\ Triglycerides \end{bmatrix}$$

And $OUTPUT$ is $\frac{A_{\text{endothelial}}}{A_{\text{intima}}+A_{\text{media}}}$ or $\frac{A_{\text{wall}}}{A_{\text{intima}}+A_{\text{media}}}$.

Coefficients a, b and c are determined by using INPUT-OUTPUT data (Tables 1 and 2). We used a simplex optimization method developed by John Nelder and Roger Mead [Nelder et al. 1965] to reach the best fit. This method involves only function evaluations (no derivatives).

As a measure of accuracy we calculated relative mean squared error:

$$RMSE = \frac{(p_1 - t_1)^2 + \cdots + (p_n - t_n)^2}{(t_1 - \bar{t})^2 + \cdots + (t_n - \bar{t})^2}$$

where p_i is i-th predicted value of the output, t_i is i-th target value of the output and $\bar{t}$ is average value of the output

$$\bar{t} = \frac{1}{n}\sum_{i=1}^{n} t_i$$

The RMSE represent the ratio between total squared error of our model and total squared error of default predictor (i.e. a model which always predicts an average output value). The value of RMSE less than 1.0 indicates that the model is useful. The lower the RMSE, the more accurate is the model.

Table 3 shows relative squared error values for both, polynomial regression and response surface regression models for time T1.

OUTPUT	Polynomial regression	Response surface regression
$\frac{A_{\text{endothelial}}}{A_{\text{intima}} + A_{\text{media}}}$	0.008652	0.00057
$\frac{A_{\text{wall}}}{A_{\text{intima}} + A_{\text{media}}}$	0.09218	0.010291

Table 3. Relative Squared Errors of Polynomial Regression and Response Surface Regression Models at Time T1

Table 4 shows relative squared error values for both, polynomial regression and response surface regression models for time T2. In this table we can see that both models gave almost perfect fit.

OUTPUT	Polynomial regression	Response surface regression
$\frac{A_{\text{endothelial}}}{A_{\text{intima}} + A_{\text{media}}}$	$8.58\text{x}10^{-26}$	$9.07\text{x}10^{-28}$
$\frac{A_{\text{wall}}}{A_{\text{intima}} + A_{\text{media}}}$	$9.51\text{x}10^{-25}$	$3.95\text{x}10^{-28}$

Table 4. Relative Squared Errors of Polynomial Regression and Response Surface Regression Models at Time T2

From Tables 3 and 4 we can conclude that both regression models are useful (RMSE<1). Also, we can conclude that Response Surface Regression model gave slightly better results than Polynomial Regression model.

6. Conclusions

In this paper we tried to model relationship between WSS, cholesterol, HDL, LDL and triglycerides on one hand and plaque size on the other hand. Among many tested, two nonlinear

models: third order polynomial regression and quadratic response surface regression gave the best results. Those two models showed that there is a strong connection between plaque size and input data. The achieved results represent progress in the assessment of stroke risk for a given patient's geometry and blood analysis data.

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Извод

Моделирање прогресије плака коришћењем хемодинамичке симулације и хистолошких података

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Резиме

Атеросклероза је болест великих артерија која је карактеристична по акумулацији липида у зиду артерије. Механичке силе као што су ниски смичући напони су заслужни за формирање и развој плака. Циљ овог рада је да испита утицај смичућег напона зида, хистолошких слика и анализа крви на процес развоја атеросклерозе. Хистолошки подаци заједно са анализама крви (холестерол, HDL, LDL и триглицериди) су урађени на 18 зечева који су били подвргнути атерогеној дијети на Кембриџ Универзитету (Енглеска). Вредности смичућих напона на зида су рачунати коришћењем компјутерске динамике флуида. Навије-Стоксове једначине и Дарсијев закон су коришћене за моделирање динамике флуида у лумену и зиду. Конвективно дифузне једначине су коришћене за моделирања транспорта LDL-а и кисеоника. Примењена су два различита модела. Слободно зидни (wall free) модел где је зид третиран само као гранични услов и једнослојни модел где су инитима и медија крвног суда третирани као један ентитет са карактеристикама хомогеног транспорта.

Кључне речи: Модел Коначних Елемената (МКЕ), Компјутерска Динамика Флуида (КДФ), атеросклероза, смичући напон зида, LDL, нагомилавање липида, плак

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