Finite Element Modeling of Atherosclerotic Plaque Formation and Evolution

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Abstract— **The appearance of lipid plaques on the walls of blood vessels is called atherosclerosis. According to the World Health Organization's statistics, atherosclerosis can affect blood vessels, regardless of age and occupation of the person. In spite of a number of studies, devoted to the investigation of this disease, the exact factors and their influence on atherosclerotic plaque formation and evolution have not yet been determined. Presented investigation examines the influence of mechanical factors on the evolution of atherosclerosis. In this paper a time-dependent coupled problem of the atherosclerotic plaque formation and evolution in the coronary artery has been presented. Penetration of low-density lipoproteins (LDL) into internal layers of the blood vessel, diffusion of macrophages and deformation of the vessel wall with endothelial defects have been considered. The mathematical model of the arterial wall has been implemented using the finite element (FE) package Comsol Multiphysics. The solution has been obtained by means of the following working modes: Convection/Diffusion (for the LDL penetration process), Diffusion (for the LDL modified by macrophages, or foam cells), and Moving Mesh (for visualizing the wall deformation).**

Index Terms— **Atherosclerotic plaque, Endothelial dysfunction, Foam Cells, Low-density lipoproteins (LDL), Macrophages.**

I. INTRODUCTION

It is established by most authors [1-4] that cerebrovascular events are related to atherosclerotic disease in the carotid arteries and are frequently caused by rupture of a vulnerable plaque. These plaques are characterized by the presence of a large lipid pool covered by a thin fibrous cap with infiltration of macrophages and a scarcity of smooth muscle cells. The progression from asymptomatic atherosclerosis, to a high-risk/vulnerable plaque, to a thrombosed plaque, and to clinical events is detailed described in [1]. The plaque, including its endothelium, is not the only determinant of thrombosis – the loss of the normal thrombotic–thrombolytic equilibrium in the circulating blood, and local flow conditions are also important contributors to thrombosis.

At the present time there is no widely accepted diagnostic method to prospectively identify such "high-risk"/"vulnerable" plaques. But the most detailed evidence concerning the plaques causing coronary thrombosis and rapid lesion progression, or symptomatic disease, is derived from numerous autopsy studies, magnetic resonance and radionuclide imaging, carotid endarterectomy and intravascular ultrasonography, coronary angiography and also from the post-mortem histological studies [1,8-11]. Most researchers have differentiated three main types of plaques [1]. "A ruptured plaque" that is a plaque with deep injury with a real defect or gap in the fibrous cap that had separated its lipid-rich atheromatous core from the flowing blood, thereby exposing the thrombogenic core of the plaque. "A plaque with a calcified nodule" — heavily calcified plaque with the loss and/or dysfunction of endothelial cells over a calcified nodule. "An eroded plaque" — a plaque with loss and/or dysfunction of the lumenal endothelial cells leading to thrombosis. There is no structural defect (beyond endothelial injury) or gap in the plaque, which is often rich in smooth muscle cells and proteoglycans. Here we restrict ourselves to only this type of plaques.

The early steps of atherogenesys have been subjected to numerous reviews, in particular most detailed ones [2, 3], where all the governing mechanisms of the LDL proliferation into susceptible area of vasculature, their uptake by macrophages and efflux, equilibrium and unbalance of macrophage lipid metabolism. In order to simplify these complex mechanisms and then include them into the mathematical descriptions of atherogenesys we use data [4] of lipids and macrophages distributions in intima and media at the different stages of progression of the disease.

Some works [5, 6, 7] study the problem of LDL infiltration into the arterial wall taking into account their pervasion from the blood flowing through a lumen. Such a consideration involves the hydrodynamic description of blood stream into a relatively short segment of the artery (Navier-Stokes equation), bloods moving through porous artery's wall (Darcy or Darcy-Brinkman equation), a transfer of LDL concentration by moving blood, which is combined by the diffusion of LDL (Diffusion equation). In order to simplify this model we use results presented in [3, 9] that confirm predominantly diffusive character of LDL transfer through the layers of a blood vessel. After preliminary study of this problem in a full statement, we excluded the hydrodynamic equations and modeled propagation of LDLs' concentration by using only diffusion equation with parameters of the layers that provide a good agreement with the results of the solving the problem in a full formulation.

In this paper we present a sequence of mathematical models and their finite-element implementation for the low-density lipoproteins (LDL) proliferation into the wall of both intact blood vessel and vessel with local dysfunction of endothelium, for the macrophages/LDL metabolism, and also for the growth of atherosclerotic plaques. By using results of these models simulations, which were compared with the results of clinical studies, we have found the values

of parameters that determine the atherosclerotic plaques evolution until a high-risk state of their disruption.

II. COUPLED PROBLEM OF LDL-PROPAGATION AND MACROPHAGE LIPID METABOLISM

The blood vessel is modeled as a straight axially-symmetric tube with the length of $L = 20mm$ and luminal radius of $Rl = 3.1mm$. The arterial wall is considered as a three-layered structure, consisted of the endothelial layer, intima and media, as shown in Fig.1. The thickness and properties of each layer are listed in Table 1.

The full equation system involving the propagation of LDL and the macrophage lipid metabolism includes:
— Navier-Stokes and continuity equations

$$\rho\left(\overline{u}\nabla\overline{u}\right) + \nabla p - \mu\Delta\overline{u} = 0 , \qquad (1)$$
$$\nabla \cdot \overline{u} = 0$$

where $\overline{u}$ is the velocity vector, p is a blood pressure, μ is a blood dynamic viscosity;
—Flow in porous media (Brinkman equation)

$$\frac{\mu_l}{K_l}\overline{u_l} = -\nabla p_l + \frac{\mu_l}{\varepsilon_l}\nabla^2\overline{u_l} , \qquad (2)$$
$$\nabla^2\overline{u_l} = 0$$

where $\overline{u_l}$ and p_l are the velocity and the pressure vectors, respectively; ε_l and K_l are the porosity and the permeability of respective layers of the vessel wall;
—Convection/diffusion equations for the concentration of low-density lipoproteins c^{LDL}

$$\delta_{ts}\partial c^{LDL}/\partial t + \nabla \cdot \left(-D\nabla c^{LDL}\right) = R^{LDL} - \mathbf{u}\cdot c^{LDL} , \qquad (3)$$

where $c^{LDL}(r,z)$ is a local LDL concentration and δ_{ts} are the time-scaling coefficients, differ for all layers (see Table 1). All above equations fully correspond to those used in [5, 6], but LDL removal reaction rate R^{LDL} in the intimal layer and media was considered as a variable that depends on the macrophage lipid metabolism

$$R^{LDL} = R_{norm}^{LDL} + R_{crash}^{LDL} \qquad (4)$$

and consists of two parts, which describe the normal LDL removal in a healthy blood vessel

$$R_{norm}^{LDL} = -\frac{k\_remlip}{c\_lip0}\cdot H(c^{LDL} - cthr_{norm}, dev_{norm}) \qquad (5)$$

and intensive LDL uptake at infraction of metabolism due to elevated of LDLs concentration

$$R_{crash}^{LDL} = -k\_act\_mphags\cdot\frac{\partial c\_prod\_mphags}{\partial t} . \qquad (6)$$

Hereinafter H is a smoothed Heaviside function, equal to zero at a concentration less than its threshold value, and 1 at a greater concentration, c_lip0 is the value of a stable LDL concentration in healthy blood vessels, k_remlip is the LDL assimilation parameter at the normal macrophage lipid metabolism, dev_{norm} is a fitting parameter (see Table 1).

The metabolism dysfunction, caused by a significant increase of LDL in the blood or a damage of the endothelium, leads to an increased LDL infiltration into intima and media. After that a mechanism of rapid macrophages penetration into the vessel wall starts with the formation of macrophage foam cells. Due to an absence of substantiated quantitative estimations of the growth

parameters for such tumors on the LDL concentration or other system characteristics, we assumed that an excess of the local LDL concentration above a certain threshold $cthr_{crash} = 0.0025$ leads to an increased concentration of the foam cells, which promotes the growth of atherosclerotic plaque. In the reaction rate of LDL assimilation (6) k_act_mphags is a macrophage activity parameter, and the partial derivative with respect to time is taken from the concentration of foam cells, which is proportional to the LDL concentration in excess of the 0.0025 value

$$c\_prod\_mphags = c^{LDL}\cdot H(c^{LDL} - cthr_{crash}, dev_{crash}) \,(7).$$

Diffusion equation describes the accumulation process of the concentration c_{phags} of LDL modified by macrophages, or so-called foam cells (diffusion coefficient equals to zero)

$$\delta_{ts}\partial c_{phags}/\partial t = R_{phags}; \quad R_{phags} = c\_prod\_mphags . \quad (8)$$

Defect of endothelial layer has been modeled by its locally reduced permeability and increased diffusion coefficient.

In order to reduce computational complexity, blisequential simplifications of thesh model have been performed, as a result, the Navier-Stokes and Brinkman equations were excluded from consideration.

The initial and boundary conditions for the simplified model have been specified as follows. Both the initial concentrations of low-density lipoproteins in all the arterial layers and the concentration of foam cells in the intima and media have been assumed to be zero.

The boundary conditions for the Convection/Diffusion equations:
Initial concentration of LDL on the boundary **1** that is an interface between the endothelium and lumen (Fig.1) - $c_0 = 0.0286nmol/mm^3$.

In the Diffusion mode for the foam cells concentration the outer boundaries of endothelium (**1-3**), and the boundary between the intima and media (**7**) are inactive (Fig.1). On the rest boundaries the Insulation/Symmetry conditions were specified.
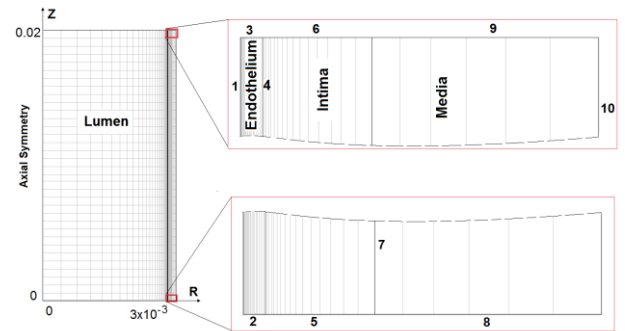

Figure 1. The scheme and numbered boundaries of the considered blood vessel

Along the vertical boundaries a linear distribution of edge elements was given, the number of finite elements was taken to be 100. An exponential distribution method was applied along the horizontal boundaries; number of FE is equal to 20 for the endothelium, when the distribution coefficient equals to 0.2; for the intima the number of elements is 16, the distribution ratio is 0.1; for the media are 20 and 0.1, respectively. FE-mesh and numbers of the vessel's wall boundaries are shown in Fig. 1.

TABLE I.   CONSTANTS AND PARAMETERS

Name	Expression	Description
Rend	2e-6[m]	Thickness of endothelial layer
Rint	10e-6[m]	Thickness of intimal layer
Rmedia	200e-6[m]	Thickness of media
D_e	1.8167e-17[m^2/s]	LDL diffusion coefficient in endothelial layer
D_int	3.7e-12 [m^2/s]	LDL diffusion coefficient in the intima
D_med	4.3e-14 [m^2/s]	LDL diffusion coefficient in the media
c_threshold	0.0025	Threshold lipid concentration at which the macrophage growth starts
delta_int	3.5e7	The time constant of the macrophage lipid metabolism in the intima
delta_med	3.5e7	The time constant of the macrophage lipid metabolism in the media
active_phags	9	Parameter of macrophage activity
clipint0	0.005	Stationary concentration of lipids in the intima of a healthy vessel
clipmed0	0.003	Stationary concentration of lipids in the media of a healthy vessel
k_remlip	4e-12	LDL assimilation rate at the normal macrophage-lipid metabolism

The mapped mesh parameters have been specified individually for each boundary. Mesh statistics is given in Table 2.

TABLE II.   MESH STATISTICS

Number of degrees of freedom	67024
Number of mesh points	5757
Number of quadrilateral elements	5600
Number of triangular elements	512
Number of vertex elements	8

III. LDL ACCUMULATION PROCESS IN A VASCULAR WALL WITH DAMAGED ENDOTHELIAL LAYER

In order to simulate the shape evolution of the region with a high concentration of the LDL, modified by macrophages, we used the *Moving Mesh* mode. Local deformation of the grid has been associated with a concentration value c_{phags}.

This method assumes the definition of explicit expressions for mesh deformations induced by the *Diffusion* mode, with the spread of moving borders displacements towards the interior region. Getting the smooth mesh deformation within the region is realized by solving a system of partial differential equations (PDEs) for the mesh displacements. According to the selected Laplace method of smoothing the deformed mesh coordinates x, y are the additional degrees of freedom, obeying the equations (non-stationary case):

$$\frac{\partial^2}{\partial X^2}\left(\frac{\partial x}{\partial t}\right) + \frac{\partial^2}{\partial Y^2}\left(\frac{\partial x}{\partial t}\right) = 0; \quad \frac{\partial^2}{\partial X^2}\left(\frac{\partial y}{\partial t}\right) + \frac{\partial^2}{\partial Y^2}\left(\frac{\partial y}{\partial t}\right) = 0 \quad (9)$$

for describing the spatial coordinates of these nodes (x, y) after deformation we used the functions $x = x(X,Y,t); y = y(X,Y,t)$, which include time t; spatial

coordinates in the fixed system (spatial frame) are indicated by (x, y), and the (X, Y) coordinates are the coordinates of the grid nodes in their initial configuration, or the reference frame.

In this problem, the z-displacements in intima and media are taken to be 0, and the radial components – equal to

$$dr = -kr \cdot c\_phags \cdot mmesh(R), \quad (10)$$

where the function

$$mmesh(R) = -\left(\left(-R + 3.112 \cdot 10^{-3}\right)/0.2 \cdot 10^{-3}\right)^2 + 1 \quad (11)$$

controls the mesh displacement towards the lumen; it accepted vanished at the outer boundary of media. The assumption of such a mesh deformation function is due to the lack of reliable clinical data on the nature of walls deformations toward the vessel lumen and outside. In order to bring the simulation result in line with the available clinical data we have entered a correction factor $kr = 0.03$, which concatenates the concentration of the LDL modified by macrophages with a thickening of the vessel walls.

For all areas the initial values of spatial coordinates $r(t_0) = rinit\_ale$ and $z(t_0) = zinit\_ale$ have been set, where the boundary variables $rinit\_ale = R$ and $zinit\_ale = Z$ are the initial r- and z-coordinates of all the subdomains' points, respectively.

The upper and lower boundaries of the endothelium (**2,3**) and the intima (**5,6**) are fixed, i.e. mesh displacements in r and z directions are taken to be zero. The outer boundaries of the media (**8-10**) and the boundary between the intima and the endothelium (**4**) are inactive. On the outer vertical edge of the endothelium (**1**) and the boundary between the intima and media (**7**) a condition of free mesh displacement is given.

The transient analysis has been performed by means of Convection and Diffusion, Diffusion and Moving Mesh modes, using time-dependent solver and the Direct (UMFPACK) linear system solver.

IV. NUMERICAL RESULTS AND ANALYSIS

Two types of blood vessels have been considered - a healthy vessel and a vessel with locally damaged endothelial layer in its midsection ($z = 0.01m$). The analysis was carried out in the time interval of 24 months. The interval has been chosen in accordance with the results of clinical researches [1-2] and our preliminary calculations, showed that, without loss of accuracy the hydrodynamic effects may be excluded from consideration, and the time interval may be limited by the moment of the plaque destruction caused by blood pressure jumps.

The graphs below show the calculation results of the average LDL concentrations in the layers of a healthy vessel (Fig.2) and the vessel with a local endothelial dysfunction (Fig.3). Fig.4 and Fig.5 demonstrate the average foam cells concentrations in both healthy and locally damaged vessel, respectively. Radial distributions of local LDL concentrations and concentrations of foam cells in the damaged vessel are shown in Fig.6 and Fig.7, respectively.

An LDL infiltration into the damaged vessel wall is simulated according to the coupled scheme of diffusion,

macrophage lipid metabolism and the wall deformation (Fig.8).
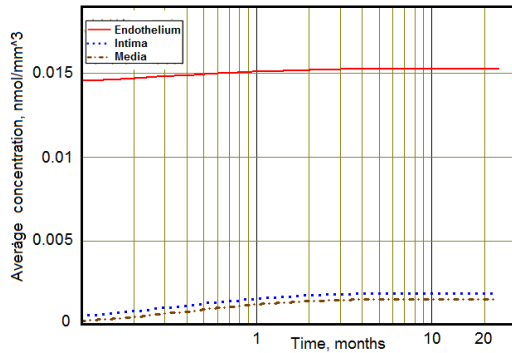

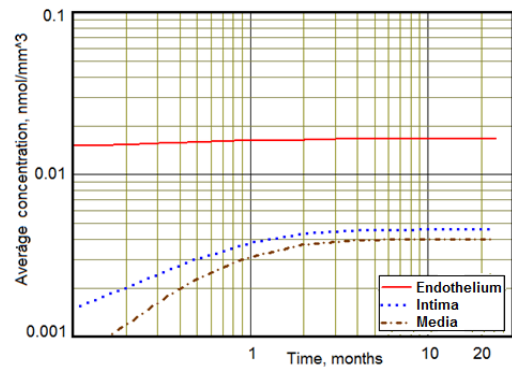Figure 2. Average LDL concentration, healthy vessel

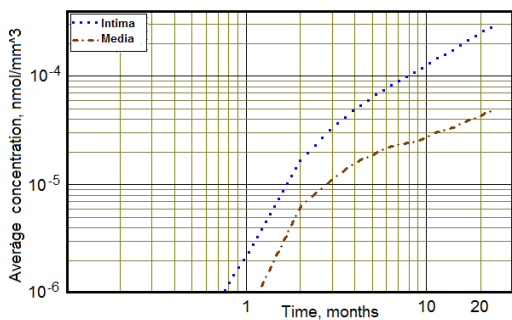Figure 3. Average LDL concentration, locally damaged vessel

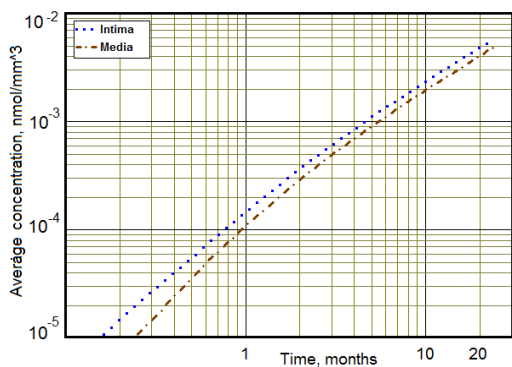Figure 4. Average foam cells concentration, healthy vesse

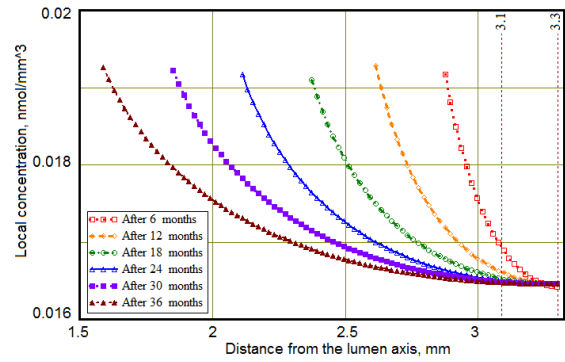Figure 5. Average foam cells concentration, locally damaged vessel

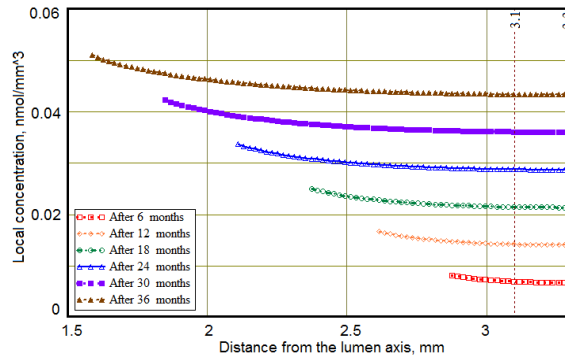Figure 6. Radial distribution of the LDL concentration, locally damaged vessel

Figure 7. Radial distribution of foam cells concentration, locally damaged vessel

Fig.8 demonstrates the simulation results on the three-year evolution of the plaque on the vessel with endothelial dysfunction. The nature and amount of the wall's change in the plaque zone correspond to the results of clinical post-mortem, intravascular ultrasound and catheterization investigations on the damaged blood vessels.
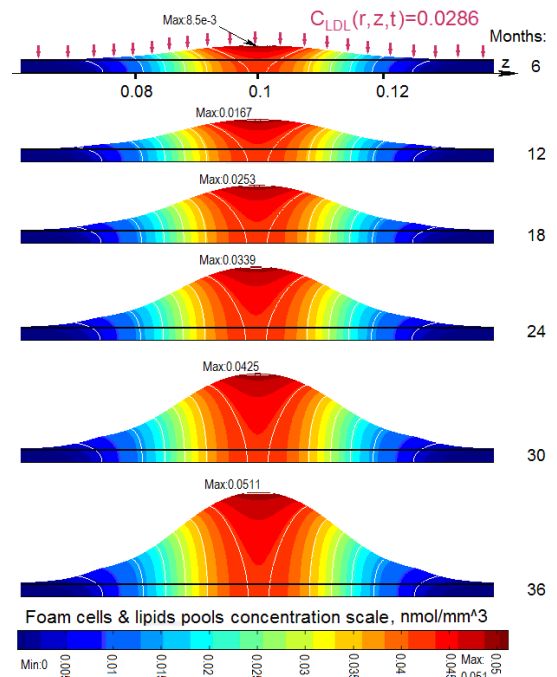

Figure 8. Developing of the atherosclerotic plaque on the wall of a damaged blood vessel during three years

The obtained results have shown that in a relatively stable distribution of LDL, due to the macrophage lipid metabolism, the foam cells are accumulated in the intima and media and reach dangerous value of 0.005 within half a year, while in a healthy vessel this value may not be reached earlier than 80 years.

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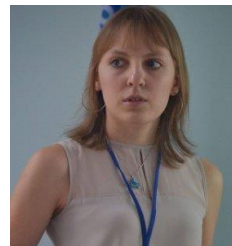

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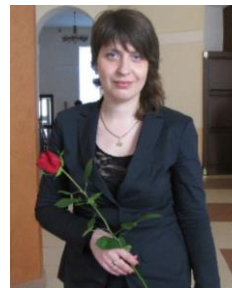
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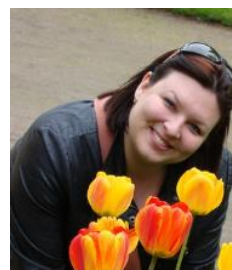
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