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Influence of arterial geometry on a model for growth rate of atheromas

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Abstract. Atherosclerosis is a disease that affects medium and large size arteries and it can partially or totally obstruct blood flow through them. The lack of blood supply to the heart or the brain can cause an infarct or a stroke with fatal consequences or permanent effects. This disease involves the proliferation of cells and the accumulation of fat, cholesterol, cell debris, calcium and other substances in the artery wall. Such accumulation results in the formation of atherosclerotic plaques called atheromas, which may cause the obstruction of the blood flow. Cardiovascular diseases, among which atherosclerosis is the most frequent, are the first cause of death in developed countries. The published works in the subject suggest that hemodynamic forces on arterial walls have influence on the localization, initial development and growth rate of atheromas. This paper presents a model for this growth rate, and explores the influence of the bifurcation angle on the blood flow patterns and on the predictions of the model in a simplified carotid artery. The choice of the carotid bifurcation as the subject for this study obeys the fact that atheromas in this artery are often responsible for strokes. Our model predicts a larger initial growth rate in the external walls of the bifurcation and smaller growth area and lower growth rates as the bifurcation angle is increased. The reason for this seems to be the appearance of helical flow patterns as the angle is increased.

1. Introduction
Atherosclerosis is an inflammatory disease that affects large and medium-sized arteries [1]. The atherosclerotic lesion or atheroma is a focal thickening of the innermost layer of the artery wall, called intima. These lesions consist mainly of accumulation of lipids, endothelial and vascular smooth muscle cells (SMC), connective tissue and debris [2]. The evolution of the atheroma is not constant in time; on the contrary it can have both chronic and acute manifestations. Few human diseases have a longer incubation period than atherosclerosis, which begins to affect arteries during the second and third decades of life and yet, its symptoms do not appear until several decades later [3]. The atheroma...
will evolve causing a temporary or permanent lack of blood and oxygen supply to some organ, which can result in its malfunction or the infarct of the organ tissue. These manifestations could be classified in three groups, based on the organ they affect: cerebrovascular disease, ischemic heart disease and peripheral vascular disease.

Despite the efforts made to reduce it, cardiovascular diseases continues to be the principal cause of deaths in North America, Europe and a big part of Asia [1], and is expected to be so in every country within the next two decades [4]. This is the reason why, in the past few decades, there has been a big effort devoted to learn and understand its genesis [2] and to find the main risk factors.

In the late 60’s and the early 70’s, the first theories about the focal nature of lesion initiation came to light [5,6]. These theories proposed that the hemodynamic forces exerted by the blood flow on the artery wall, more specifically on the vascular wall endothelial layer, have a major influence on the location where the atherosclerotic plaques will develop. Researchers agree that atheromas develop in areas where there are complex flow patterns such as recirculation and/or secondary flows, which occur in arterial bifurcations, junctions or regions with marked curvature. The endothelium in these areas is subjected to low and oscillating shear stresses due to the flow patterns, which is thought to be the cause of the location of the plaques [7, 8]. However, there are different theories about why this is so. Some research focus their effort on studying the blood cholesterol transport to find out how the concentration varies along the vessel wall [9, 10], while others propose that there is a malfunction of the endothelium caused by these shear stresses and concentrate on looking for a dependence of the permeability of the endothelium on the shear stress [11].

Lately, there has also been a few works that simulated a coupled transport of low density lipoproteins (LDL) in blood and through the artery wall [12, 13]. These works intend to predict the variation of the transendothelial LDL flux along the artery axial direction, especially before and after the stenosis caused by the growing atheroma.

This work presents a simple model for the plaque growth rate based on the accumulation of oxidized LDL in the artery wall, including a dependence of the endothelial permeability on the shear stresses, as proposed by LaMack [14], and on the LDL blood concentration, as proposed by Stangeby [12]. The model is tested in a stationary blood flow in the carotid artery bifurcation, figure 1, modeled with six different bifurcation angles to study the effect of this angle on the formation of the atheroma. The wall shear stresses were obtained from a Finite Volume Simulation of the blood flow using an open source CFD toolbox, OpenFoam [15], assuming the blood as homogeneous and Newtonian.

2. Atherosclerotic Plaque Growth

2.1. Atherogenesis and plaque evolution

Although it is not known what the major determinant is for plaque onset, it seems that the relevant factor that influence the LDL mass flux to the artery wall in these specific locations are the complex flow patterns developed there due to bifurcations and high curvature regions [16]. These seem to cause extracellular LDL accumulation, part of which suffers an oxidative reaction, LDLox. Another important event that is distinguished in the initiation of the atheroma is leukocyte recruitment. Monocytes and T lymphocytes tend to accumulate in the early atherosclerotic lesion. The monocytes, which become macrophages in the artery wall, ingest the oxidized LDL, turning into foam cells, commonly found in atheromas [3].

The evolution of the atheroma into more complex plaque, involves SMC migration and proliferation. On the other hand, it is the extracellular matrix rather than the cells themselves that makes up for much of the volume of an advanced atherosclerotic plaque. The vascular smooth muscle cells produce this excessive extracellular matrix macroolecules, such as collagens and proteoglycans [3].
2.2. The model

The growth model we propose in this work is based on the concept of conservation of LDL mass, expressed as

$$\frac{DC_{LDL}}{Dt} = -\nabla \cdot J_{LDL} + \dot{N}_{LDL},$$

(1)

where $C_{LDL}$ is the concentration of LDL in the intima, $J_{LDL}$ is the LDL flux vector and $\dot{N}_{LDL}$ is the consumption of LDL due only to the oxidative reaction, because all other reactions were neglected.

The LDL is mainly transported by the blood; therefore, all the convective and diffusion fluxes in the axial and tangential direction in the artery wall were neglected, compared to the LDL flux that goes through the endothelium into the intima ($J_{LDL,\text{in}}$). It was also assumed that this flux either goes through an oxidative reaction ($\dot{N}_{LDL}$) or goes out of the wall to media and the lymph system ($J_{LDL,\text{out}}$), as equation (2) shows.

$$\frac{dC_{LDL}}{dt} \approx -\frac{J_{LDL,\text{out}} - J_{LDL,\text{in}}}{e_0} + \dot{N}_{LDL} = 0$$

(2)

Here, $e_0$ is the intima initial thickness.

The endothelium is treated as a semi permeable membrane. The LDL that goes into the intima is driven by both a convective flux of plasma, $J_v$, and a diffusive flux proportional to the trans-membrane LDL concentration difference, $\Delta C_{LDL}$. The model for these fluxes is shown in equations (3), known as the Kedem-Katchalsky equations [17]

$$J_v = L_p (\Delta p - \sigma \Delta \pi),$$

$$J_{LDL,\text{in}} = P_d \Delta C_{LDL} + (1 - \sigma) J_v \bar{C}_{LDL},$$

(3)

where $L_p$ is the hydraulic conductivity of the endothelium, $P_d$ is the endothelial permeability to LDL, $\sigma$ is the endothelial reflection coefficient, $\Delta p$ and $\Delta \pi$ are the trans-membrane hydrodynamic and osmotic pressure differences, respectively, and $\bar{C}_{LDL}$ is the mean endothelial concentration [18]. In this model, the trans-membrane hydrodynamic pressure difference is assumed constant, $\Delta p = 70$ mmHg, and the osmotic pressure difference is calculated using the van’t Hoff’s formula, $\bar{C}_{LDL}$, where $R = 8.3145 \text{ J/mol.K}$ is the universal gas constant, $M_{LDL}$ is the LDL molecular weight and $T$ is the absolute temperature (i.e.: body temperature, 37 ºC). The reflection coefficient and the hydraulic conductivity where also assumed constant, $\sigma = 0.9979$ and $L_p = 3 \times 10^{-12} \text{ m.s}^{-1} \text{ Pa}^{-1}$ as found in the literature [13, 19].

The influence of the hemodynamic forces is represented by the dependence of the endothelial permeability of the wall shear stress, $\tau_w$. Although it is not clear how the shear stress is sensed by the cell, there are a few models proposed in the literature [16, 20]. The model adopted here for the endothelial permeability includes a dependence on the wall shear stress as proposed by LaMack et al. [14], which assumes that the permeability depends on the absolute value of the wall shear stress, as in (4). It also accounts for the influence of the LDL concentration in blood, $C_{LDL,blood}$, using a model proposed by Stangeby [12].

$$P_d = P_{d0} e^{2.75 C_{LDL,blood}/C_0} \left| \tau_w \right|^{-0.11}$$

(4)

The constant $P_{d0} = 1.15 \times 10^{-11} \text{ Pa.m.s}^{-1}$ was scaled so that the permeability is $2 \times 10^{-10} \text{ m.s}^{-1}$ at the inlet of the artery, which is considered a normal or reference value in the literature [21] and $C_0$ is the LDL concentration in blood recommended by physicians, $1.2 \text{ kg LDL/m}^3$. The LDL concentration in blood was assumed constant in the circulation, based on the relation between the Sherwood number,
\[ Sh_d = \frac{h_{LDL} d}{D_{blood}^{LDL}}, \] that is the dimensionless mass transfer coefficient (calculated with the arterial diameter, \( d \), the mass transport coefficient in blood, \( h_{LDL} \), and the LDL diffusion coefficient in blood, \( D_{LDL}^{blood} \), and the Damkohler number,

\[ Da_{end} = \frac{P_e d}{D_{blood}^{LDL}}, \] which is the dimensionless endothelial permeability based on the effective endothelial permeability, \( P_e \). Analysis made by Tarbell [22] and Hodgson [23] show that the \( Da_{end} \) is much lower than the \( Sh_d \), which implies that the endothelium is the major resistance to LDL transport to the intima.

The last term of equations (1) and (2) represent the LDL oxidation in the intima, which is assumed an irreversible first-order reaction. And, since it was also assumed that all the LDL that goes though the oxidative reaction, LDL\text{o}x, accumulates in the intima, then

\[ \dot{N}_{LDL} = -k C_{LDL} \] is the rate of LDL\text{o}x accumulation, where \( k = 1.4 \times 10^{-4} \text{ s}^{-1} \) is the oxidative reaction rate used by [13].

Last but not least, the LDL flux that goes out of the intima \( \left( J_{LDL,\text{out}} \right) \) is assumed to leave the intima only in the radial direction toward the media, where the concentration of LDL is assumed to be negligible at a distance of 0.1 mm from the intima. This is based in studies made by other authors [21], who showed that both the value and the gradient of concentration in the media are not sensible to the conditions assumed at the adventitia. The LDL flux leaving the intima is calculated as a diffusive flux \( \left( J_{LDL,\text{diff}} \right) \) plus a convective flux \( \left( J_{LDL,\text{conv}} \right) \) as in (5), where \( \gamma = 1.728 \) and \( \phi = 0.983 \) are the hindrance and porosity of the intima (assumed constant), \( D_{LDL}^{\text{in}} = 5 \times 10^{-14} \text{ m}^2 \text{ s}^{-1} \) is the diffusion coefficient, and \( C_{LDL}^{\text{media}} \) is the LDL concentration in the media at a distance \( \delta r \) from the intima [19,21]:

\[
\begin{align*}
J_{LDL,\text{conv}} &= \frac{J}{\phi \gamma} C_{LDL}, \\
J_{LDL,\text{diff}} &= -D_{LDL}^{\text{in}} \frac{\partial C_{LDL}}{\partial r} \approx -D_{LDL}^{\text{in}} \frac{C_{LDL}^{\text{media}} - C_{LDL}}{\delta r} 
\end{align*}
\]

Using the model just described, the initial evolution of the concentration of LDL in the intima can be obtained. Quite unsurprisingly, the results obtained in this way predict accumulation of LDL even in zones where that is unlikely to happen, i.e., in the straight portions of the arteries. This is so because the model is still lacking a sink of LDL due to outflow and due to consumption of cells other than foam cell formation. In this paper, for the sake of simplicity, we just opted for renormalizing the solution by simply subtracting the minimum value from the whole field, so that null or very low growth is predicted in the straight portion of the arteries, as expected.

Finally, once the rate of accumulation of LDL\text{o}x is obtained, the initial growth rate can be calculated as:

\[
\frac{d e}{d t} = \frac{V_{LDL}}{M_{LDL} e_0 N_a k C_{LDL}}, \]

where \( V_{LDL} \) is the volume of the LDL molecule, and \( N_a \) is the Avogadro number.

3. Computational Model

Figure 1 shows the carotid bifurcation geometry used for the blood flow simulations and the six different bifurcation angles simulated: 15º, 30º, 45º, 60º, 75º and 90º. The mesh used in each case had approximately 300000 tetrahedral elements and a parabolic stationary profile with a \( Re_d \) of 440 was used as the inlet boundary condition.
A tension-free condition was used as the outlet boundary condition for the blood flow simulation; with different maximum velocities at the exit in order to achieve an exit volumetric flow relation of 75:25 between the internal and external carotid arteries. The wall was assumed rigid and impermeable since the blood flow that permeates the endothelium is many orders of magnitude lower that the arterial flow.

The growth model was implemented as post-processing tool in the OpenFoam toolbox and the same discretization in the axial and tangential direction was used. The intima was not discretized in the radial direction. Therefore, each wall surface element of the carotid bifurcation mesh represented one element of the growth model mesh with an initial thickness $e_0 = 50 \mu m$ used to calculate the rate of LDLox accumulation and the initial growth rate of the intima.

4. Results

Figure 2 on the right shows the streamlines simulated for the carotid bifurcation with a 60° bifurcation angle and figure 2 on the left shows the stationary flow experiment results obtained by Ding et. al. [24] using flow visualization techniques. Although the geometry of our model does not correspond exactly to that of the experiment, it is apparent that both flow patterns are qualitatively similar, and that the main characteristic of the flow is captured by the simulation.

Figure 3 shows the simulated streamlines for three bifurcation angles, 30°, 60° and 90°, to show the different flow patterns developed in the different geometries studied. This Figure shows the formation of secondary flow patterns that become stronger as the bifurcation angle is increased. Moreover, in the bifurcation toward the external carotid side, the 15° bifurcation angle does not show secondary flows. Another thing to notice is that there is no evidence of recirculation, meaning a flow region isolated from the main stream and where fluid particles recirculate and do not mix with the main stream. Other
authors [10] mention explicitly that there is a recirculation region. We are not sure, however, if they found a real recirculation, or if they simply took as that the helical movement of the fluid particles in the bifurcation external walls, where they are seen to change the axial velocity direction twice.

Figure 3: Streamlines obtained numerically for a 30°, 60° and 90° bifurcation angle, from left to right. Blue shows the lowest velocities.

Figure 4 shows the initial growth rate predicted by our model for the 15°, 45° and 90° cases. The image shows three different views of each case, where it can be seen that the initial growth rate on the external carotid is higher and distributed in a bigger area than on the carotid sinus. One of the reasons for this might be that the volumetric flow ratio forced at the exit to attain the physiologic ratio cause much lower velocities on the external carotid and, consequently, lower stresses. The model also predicts a higher initial growth rate on the external walls than on the internal ones.

Figure 4: Initial growth rate for bifurcation angles 15°, 45° and 90° in [m/s].

This is consistent with the fact that, although there is secondary flow toward the external walls, the axial velocity is lower on this side and therefore the shear stresses. The results also show a tendency to decrease the initial growth rate predicted, as the bifurcation angle increase.

This can be explained by the secondary flow patterns, as they become stronger, the shear stresses sensed by the endothelium become stronger as well and, therefore, the permeability decreases and, consequently, the LDL influx decreases. Another important effect of the bifurcation angle variation is that the area where the plaque would initially grow at the bifurcation region is more focalized as the angle is increased.

5. Conclusions

In the results, shown in the previous section, there is evidence of helical flow patterns developed at the bifurcation. The 15° angle case, in which the model predicts the highest initial growth rate on the external carotid external wall, does not show any complex secondary flow pattern in this side. Another important conclusion of this work is that using this permeability model, the initial shape of the atheroma seems to be more concentrated on the sinus wall than on the external carotid wall and this shape becomes more focalized as the bifurcation angle increases.
Finally, another thing to mention is that this model as is, only predicts the initial growth rate, because the actual growth of plaque into the lumen will cause the flow patterns to change and, consequently, the growth rate map will be modified constantly; then, the actual evolution of the plaque might differ from the ones shown here. In this area, work is being done by the authors, and will be presented soon.

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