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INFLUENCE OF ARTERIAL PRESSURE ON A MODEL FOR CHOLESTEROL ACCUMULATION AND INTIMAL GROWTH

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Abstract. Cardiovascular diseases are among the first causes of death in the first world countries nowadays, and are expected to be among them in the developing countries in the near future. Atherosclerosis, one of the main cardiovascular diseases, is a chronic inflammatory disease that affects medium and great size arteries by means of an accumulation of fat, cholesterol, cell debris, calcium and smooth muscle cells in the artery wall. This accumulation may lead to the formation of atherosclerotic plaques, called atheromas, which could either grow towards the lumen of the artery or become unstable and rupture, causing a partial or total obstruction of the blood flow. The lack of blood supply to an organ implies the lack of oxygen causing its temporary mal functioning (ischemia) or the death of the tissue (infarct). Since late seventies it has been hypothesized that hemodynamic forces over the endothelium, the innermost layer of arteries, are very important to the formation and development of atheromas. This hypothesis suggests that atheromas grow in regions of complex flow patterns, such as bifurcations or regions of marked curvature, where recirculation and/or secondary flow develops. Among others, arterial pressure and cholesterol concentration in blood are some important known factors that influence the development of the atherosclerotic plaques. In this work we study the influence of the arterial pressure on the intimal growth rate predicted by a model developed by the authors and presented in previous works. We selected for this study a model of the carotid bifurcation in the carotid artery, which has received and continues to receive a lot of attention for it supplies blood to some parts of the brain. Atheromas that develop in this bifurcation may cause a stroke, which is one of the major causes of death. In the present work we use this model, combined with Finite Volume simulations of the blood flow through the artery, to study the influence of arterial pressure on the time evolution and shape of an atheroma developed in this bifurcation.

1 INTRODUCTION

Atherosclerosis is an inflammatory disease that affects large and medium-sized arteries (Ross, 1999). The atherosclerotic lesion, 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. Atheromas may cause a temporary or permanent lack of blood and oxygen supply to some organ, and this is the reason why there has been a big effort devoted to learn and understand its genesis and to find the main risk factors for the atherosclerotic disease (Jensen-Urstad et al., 1999; Altman, 2003; Hinderliter and Caughey, 2003).

Atheromas develop in arterial bifurcations, junctions or region with marked curvature. Four decades ago, it was 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 (Fry, 1969; Caro et al., 1971). Nowadays, researchers agree that atheromas develop in areas with complex flow patterns such as recirculation and/or secondary flows, where the endothelium is subjected to low and oscillating shear stresses, which are thought to be the cause of the location of the plaques (Friedman and Giddens, 2005; Ku, 1997). Due to these low and oscillating stresses the permeability of the endothelium would be altered, favoring extracellular low density lipoproteins (LDL) transport and accumulation, part of which suffers an oxidative reaction.

Another important event in the initiation of the atheroma is the leukocyte recruitment. Monocytes and T lymphocytes tend to accumulate in the early atherosclerotic lesion. The monocytes become macrophages in the artery wall and ingest the oxidized LDL turning into foam cells, commonly found in atheromas (Braunwald et al., 2001). The evolution of the atheroma into more complex plaque, involves SMC migration and proliferation, as well as accumulation of molecules and other substances. It is the extracellular matrix rather than the cells themselves that makes up much of the volume of an advanced atherosclerotic plaque. The vascular smooth muscle cells produce this excessive extracellular matrix macromolecules, such as collagens and proteoglycans (Braunwald et al., 2001).

Lately, there has also been a few works that simulated a coupled transport of LDL in blood and through the artery wall (Stangeby and Ethier, 2002; Sun et al., 2006). These works intend to predict the variation of the transendothelial LDL flux along the artery axial direction, as well as the LDL concentration in the wall, especially before and after the stenosis caused by the growing atheroma.

The majority of these works model blood flow in a two dimensional geometry and assume blood as a Newtonian fluid. The Newtonian model reproduces with good agreement the blood flow in arterial regions where high shear rates are dominant. However, in areas where the flow patterns are such that shear rates are low, non-Newtonian models such as the Casson model or the power law model, give a better approximation to the apparent viscosity and the shear stresses generated by the blood flow (Chen and Lu, 2006; Basombrio et al., 2002). This is the situation found in bifurcations such as the carotid artery, where helical flow patterns develop (Zarins et al., 1983).

Here we present a simple model for the plaque initiation and growth combined with Finite Element simulations of the blood flow to predict the evolution of the shape of an atheroma in a three dimensional model of the human carotid bifurcation. The plaque growth rate model is based on the accumulation of oxidized LDL in the artery wall, the blood flow is assumed stationary, blood is modeled using the Casson model (Fung, 1997), and we include a depen-

dence of the endothelial permeability on the shear stresses as proposed by LaMack, Himburg, X.M., and Friedman (2005) and on the LDL blood concentration as proposed by Stangeby and Ethier (2002). We also analyzed the response of the model to different values of blood pressure, studying its influence on the time evolution and shape of an atheroma developed in this bifurcation.

2 THE MODEL

The growth model proposed is based on an LDL shell mass balance within the intima (Bird, Stewart, and Lightfoot, 2001) expressed by

$$\frac{dm}{dt} = (J_{in} - J_{out})\, A - \dot{m}_{ox} - \dot{m}_{cons}, \tag{1}$$

where m is the mass of LDL within the intima, J_{in} is the LDL flux that goes into the intima from the lumen, J_{out} is the LDL flux that goes out of the wall through the media and to the lymph system, A is the lumen-intima interphase area, $\dot{m}_{ox}$ and $\dot{m}_{cons}$ are the sinks of this model, which represent the consumption of LDL due to the oxidative reaction and the physiologic ingestion of LDL by the wall cells. All other reactions were neglected. Since blood transports the cholesterol, LDL goes into the intima mainly carried by plasma that goes through the endothelium in the radial direction. It was assumed that there is no plasma moving in the axial or tangential direction within the wall and LDL diffusion in these directions was also neglected. The endothelium is treated as a semi permeable membrane. LDL goes into the intima driven by both, a convective flux of plasma or filtration velocity, J_v, and a diffusive flux proportional to the transmembrane LDL concentration, ΔC. The model for these fluxes is known as the Kedem-Katchalsky equations, (Kargol and Kargol, 2003), and are given by

$$\begin{aligned} J_v &= L_p \left(\Delta p - \sigma^{end} \Delta \pi\right), \\ J_{in} &= P_d \Delta C + \left(1 - \sigma^{end}\right) J_v \Delta C, \end{aligned} \tag{2}$$

where L_p is the hydraulic conductivity of the endothelium, P_d is the endothelial permeability to LDL Michel and Curry (1999), σ^{end} is the endothelial reflection coefficient, Δp and $\Delta \pi$ are the transmembrane hydrodynamic and osmotic pressure differences respectively. In this model Δp it is assumed to be $70 mmHg$ for physiologic conditions, when blood systolic pressure is $120 mmHg$. The hydrodynamic and osmotic transmembrane pressure differences are of similar values in the capilaries, but in medium and large-sized arteries, Δp is higher than $\Delta \pi$. For physiologic conditions, $\Delta \pi$ was calculated using the Vanť Hoffś formula $\delta \pi = \frac{R}{M_{LDL}} T \Delta C$, where R is the gas universal constant, M_{LDL} is the LDL molecular weight and T is the solute temperature (i.e.: body temperature, $37°C$), and it results to be about 30% of the hydrodynamic transmembrane pressure, so it was modeled as $\Delta \pi = 0.3 \Delta p$. We also assumed $\sigma^{end} = 0.9979$ and $L_p = 3 \times 10^{-12} m s^{-1} Pa^{-1}$ as found in the literature (Sun et al., 2006; Yang and Vafai, 2006). The influence of the hemodynamic forces is represented by the dependence of the endothelial permeability P_d on the wall shear stress τ_w. Although it is not clear how is τ_w sensed by the cell, there are a few models proposed in the literature (Rappitsch et al., 1997; Hazel et al., 2003; Friedman and Fry, 1993). The model adopted here for P_d is

$$P_{\mathrm{d}} = P_{d0} e^{2.75 C_{bl}/C_0} \mid \tau_w \mid^{-0.11}, \tag{3}$$

where $P_{d0} = 1.15 \times 10^{-11} Pa^{0.11} m s^{-1}$ was scaled so that the permeability is $2 \times 10^{-10} m s^{-1}$ at the inlet of the artery, which is considered a normal or reference value in the literature (Prosi

et al., 2005), and $C_0 = 1.2kgLDL/m^3$ is the LDL concentration in blood recommended by physicians. Eq. (3) includes a dependence on τ_w as proposed by LaMack, Himburg, X.M., and Friedman (2005) and on the LDL concentration in blood C_{bl} as proposed by Stangeby and Ethier (2002). Analysis made by Tarbell (2003) and Hodgson and Tarbell (2002) show that the Damkholer number, Da, which is the dimensionless endothelial permeability, is much lower than the Sherwood number, Sh, that is the dimensionless mass transfer coefficient. This implies that the endothelium is the major resistance to LDL transport to the intima and the mass transport boundary layer on the lumen side will be thin. Based on this analysis, the LDL concentration in blood was assumed constant. The LDL oxidation in the intima is assumed an irreversible first order reaction and, since it was also assumed that all LDLox accumulates in the intima, the rate of LDL oxidation and accumulation is km, where $k = 1.4 \times 10^{-4}s^{-1}$ is the oxidative reaction rate coefficient used by Sun et al. (2006).

The LDL flux that goes out of the intima, J_{out}, was assumed to leave the intima only in the radial direction toward the media, where the mass of LDL, and concequently its concentration, C_m, was assumed to be negligible at $\delta r = 0.1mm$ from the intima. This is based on studies made by Prosi et al. (2005), who showed that the value and the gradient of LDL concentration within the intima are not sensible to the conditions assumed at the media. The LDL flux leaving the intima was calculated as $J_{out} = J_{diff} + J_{conv}$ with

$$\begin{aligned} J_{diff} &= -D^m \frac{\partial C}{\partial r} \approx D^m \frac{C - C_m}{\delta r}, \\ J_{conv} &= J_v \left(1 - \sigma^{int}\right) C, \end{aligned} \tag{4}$$

where $D^m = 5 \times 10^{-14} m^2/s$ is the diffusion coefficient of the media layer, $\sigma^{int} = 0.8272$ is the reflexion coefficient of the intima and C is the LDL concentration within the intima (Yang and Vafai, 2006; Prosi et al., 2005). This last variable is related to the mass of LDL within the intima using $C = \frac{m}{V_{pl}^{int}}$, where V_{pl}^{int} is the volume of the intimia occupied by plasma. Asuming the intima as a porous media and that plasma fills all the porous then $V_{pl}^{int} = V_{int}\phi^{int}$, where ϕ^{int} is the porosity of the intima, $\phi^{int} = V_{porous}/V_{int}$ comes from porous media theory. Aproximating the lumen-intima interphase area, A, as constant, we can obtain $V_{int} = e_{int}A$ and replacing all this it results: $C = \frac{m}{e_{int}A\phi^{int}}$.

The last term of Eq. (1) represents a sink of LDL due to physiologic LDL consumption by the wall cells. Not surprisingly, the results obtained with the model without this term, predict accumulation of LDL even in zones where it is unlikely to occur under physiologic conditions, i.e., in the straight portions of the arteries. The physiologic cell consumption was therefore calculated as:

$$\dot{m}_{cons} = \left(J_{in} - J_{out}\right)_{refcond} A, \tag{5}$$

where the reference conditions mendioned in the subscript are: $C_{bl} = 1.2kg/m^3$, blood systolic pressure is $120mmHg$ and the value of τ_w used was the lowest value obtained among the straight portions of the carotid bifurcation.

Finally, the LDLox mass accumulation is related to the rate of intimal thickenning, i.e. plaque growth rate, through the LDLox density, ρ_{ox} and the lumen-intima interphase area. Eq.(6) assumes that the LDLox density is aproximately the same is the LDL density, $\rho_{LDL} = 1006 - 1063kg/m^3$ (Blanco, 1997) and that the interphase area remains constant. Since this model is applied on finite volume model of the intima, the variation in the interphase area of each cell is small compared with its thickness variation. Therefore, the plaque growth rate

results:

$$\frac{de_{int}}{dt} \approx \frac{1}{\rho_{LDL}A}\dot{m}_{ox} = \frac{km}{\rho_{LDL}A}. \tag{6}$$

It is importat to note that at this stage, the volume of the LDL accumulated within the intima is of the same order as the volume of LDLox, however, the mechanism of plaque formation is more complex and involves accumulation of other molecules such as Smooth Muscle Cells and the extracellular matrix secreted by these cells. The migration and proliferetion of these cells is influenced by the concentration of LDLox in the intima and not by the concentration of LDL. And in the end, this other molecules are the ones that build up most of the volume of the lesion. That is the reason why, we are not including the mass of LDL to the growth of the lesion, since they will not be relevant to the growth when these other molecules are included in the model, which will be than in a near future.

To calculate the blood flow through the artery we solve numerically the equations of momentum balance and the equation of continuity adopting the rheological blood Casson model given by Fung (1997),

$$\mu = \left(\sqrt{\frac{\tau_y}{\dot{\gamma}}} + \sqrt{\mu_\infty}\right)^2 \tag{7}$$

where μ is the viscosity of the whole blood, τ_y is the yield stress, μ_∞ is the infinite viscosity and $\dot{\gamma}$ is the shear rate. The Casson coefficients, τ_y and τ_y depend on the hematocrite, H, given by Wells and Merrill (1961); Copley (1963).

$$\mu_\infty = \left(\frac{\mu_p}{(1-H)^\alpha}\right) and \sqrt{\tau_y} = \beta\left[\left(\frac{1}{(1-H)}\right)^{\alpha/2} - 1\right] \tag{8}$$

where $\mu_p = 1.2mPa.s$ is the viscosity of human plasma, and the fited parameters for human blood are $\alpha = 2$ and $\beta = 0.3315Pa^{1/2}$ (Wells and Merrill, 1961; Copley, 1963).

3 SOLUTION AND IMPLEMENTATION

Blood flow and the growth model simulations were uncoupled and implemented in OpenFoam v1.4.1 (OpenFoam, 2007). From flow simulations the wall shear stress distribution was the input parameter used for the growth model simulation, which predicts the modified geometry for the following time step.

Figure 1 shows the initial carotid bifurcation geometry used for the flow simulations using a mesh with 209000 tetrahedral elements and a parabolic stationary profile with $Re_d = 440$ used as the inlet boundary condition at the common carotid artery, CCA. A tension free condition was used as the outlet boundary condition on the internal carotid and a fix flat velocity profile was used on the external carotid to achieve an exit volumetric flow relation of 70:30 between the internal and external carotid arteries, ICA and ECA. 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. OpenFoam uses a Finite Volume technique to transform the flow equations into algebraic and a SIMPLE algorithm was used to solve them.

For the growth model, the intima was modeled as a shell of an initial thickness $e_0 = 50\mu m$ and the discreatization in the axial and tangential direction were coincident with the surface elements of the flow mesh. The whole thickness of the intima was modeled as one volume element. The growth model was implemented to predict a discrete growth velocity for each cell on the surface of the mesh, which was use as an input for the Dynamic Motion Solver

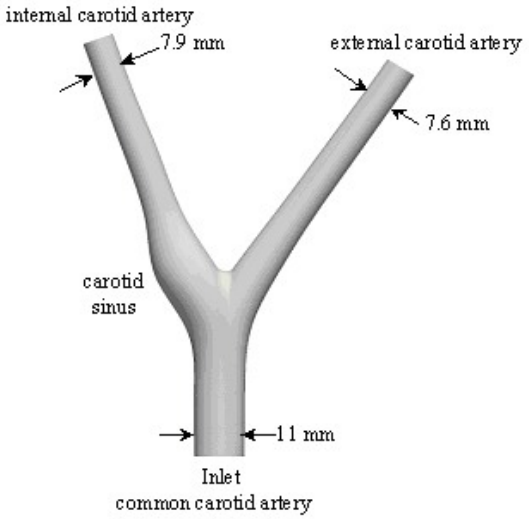

Figure 1: Geometric model of the carotid bifurcation used for the simulations

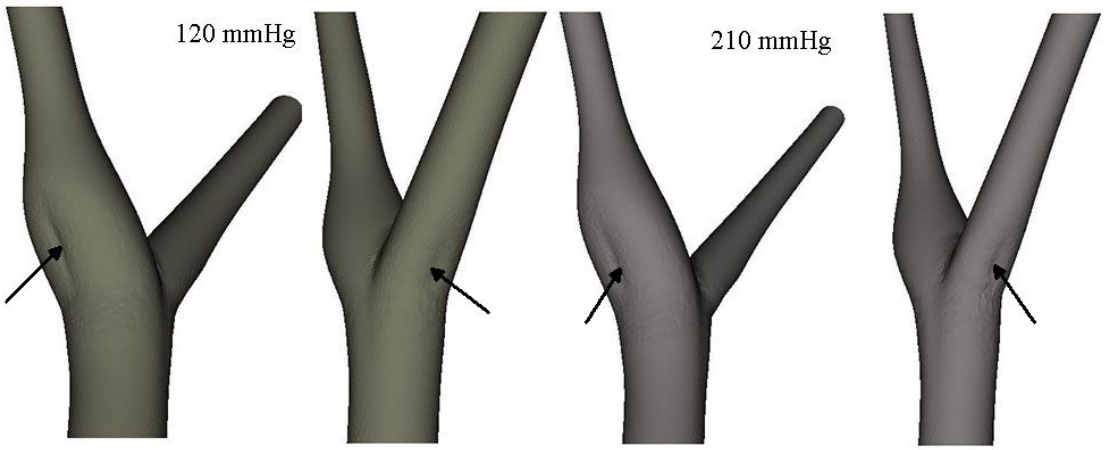

Figure 2: Deformed geometry after 60 time steps for 120 mmHg(left) and 210 mmHg(right) blood pressures. The arrows mark the formation of the atheroma.

available in OpenFoam, which moves the surface mesh nodes based on the velocity provided and accommodates the rest of the mesh using a Laplacian transformation.

The growth model presented in the previous section results in a set of two non linear ordinary differential equations to solve for the mass of LDL within the intima and its thickness as a function of time. Assuming the time it takes for the intima to become thicker is much longer than the time involve in the variation of the LDL oxidation and accumulation, an analytical solution wass obtained. The accumulation of LDLox is an exponential function that, if boundary conditions remain constant, tend to a constant value and the thickeness grow exponentially. The assumption was verified comparing the settling time of the mass function with the time it takes for the intima to grow only 5% of the initial value, for two extreme values of τ_w. For both cases, ther settling time is many orders of magnitude lower, which validates the assumption made.

4 RESULTS

Four different blood pressure conditions were simulated: $120mmHg, 150mmHg, 180mmHg$ and $210mmHg$. Since this is a stationary model, this condition represent systolic blood pres-

sures and result in transmembrane pressure gradients of $70, 100, 130$ and $160 mmHg$ respectively, which causes a higher plasma flow through the vascular wall (2). Figure 2 shows the deformed geometry after 60 time steps for the lowest(a) and highest(b) blood pressures simulated. It is important to note that, while for the lowest pressure case the atheroma grows in the external walls of the bifurcation, marked with arrows in the Figure, for all the other cases, and specially for the highest pressure, not only the atheromas form in the external walls at the bifurcation, but also there is LDLox accumulation in all other parts of the model. We use here the number of time steps as a time reference, because the real time each time step represents, which is actually 10 years, is not a representative time scale for the plaque growth since LDLox accumulation is not the mail component that builds up the volume of the plaque.

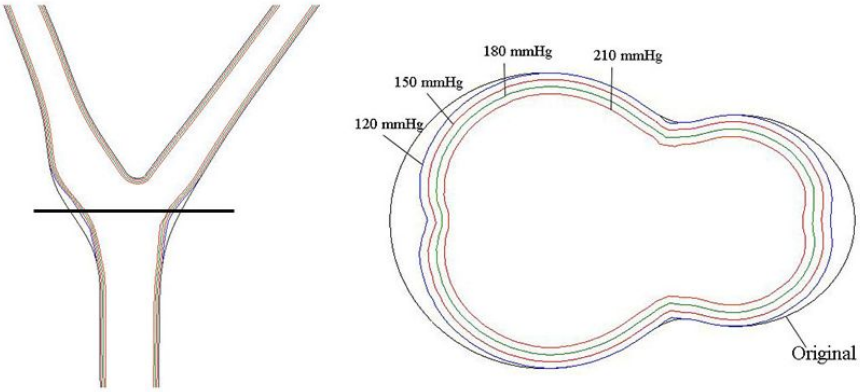

Figure 3: Lumen-intimal initial interphase and its modification after 60 time steps for the different pressure conditions. On the left the sagital cut; the horizontal line shows the position of the axial cut shown on the right.

Figure 3 shows two cuts of the bifurcation with the lumen-intimal interphase for the initial geometry and its deformation after 60 time steps for the different pressure conditions. A sagital cut is on the left, the horizontal line on this cut shows the position of the axial cut shown on the right. This Figure confirms that this model predicts intimal thickening not only where the atheroma forms but also everywhere in the carotid wall, for all the cases simulated except for the case of 120 mmHg. This is because the consumption rate included in 1 is obtained based on the fluxes for the 120 mmHg case.

Figure 4 shows the percentage of area reduction of the axial cross-sections shown in 3 for the four blood pressures simulated. As it was expected, the higher the pressure the faster the area reduction. The actual area reduction rate predicted by the model varies from 0.16% each time step or every 10 years for the physiologic pressure condition to $0.57\%/timestep$. However, the fact that this model predicts intimal thickening in the internal and external walls of the bifurcation for all the cases except the physiologic case, what is actually not seen very often, may result in an overestimation of the real area reduction for the higher pressure conditions.

To have a more realistic idea of the relative plaque growing rate, it may be usefull to look at the actual growth rate in the area where the real plaque is developing. This is shown in Figures 5 and 6; which show anterior and posterior views of the bifurcation respectively, for 5 different time steps (indicated in the Figure) and using the same growth rate scale for all cases shown. The lesions that develop on the anterior and posterior walls in the case hight pressure, as marked with arrows in Figure 2, grow at about twice the speed for the first 40 time steps, and it seems to grow at similar speed after 60 time steps.

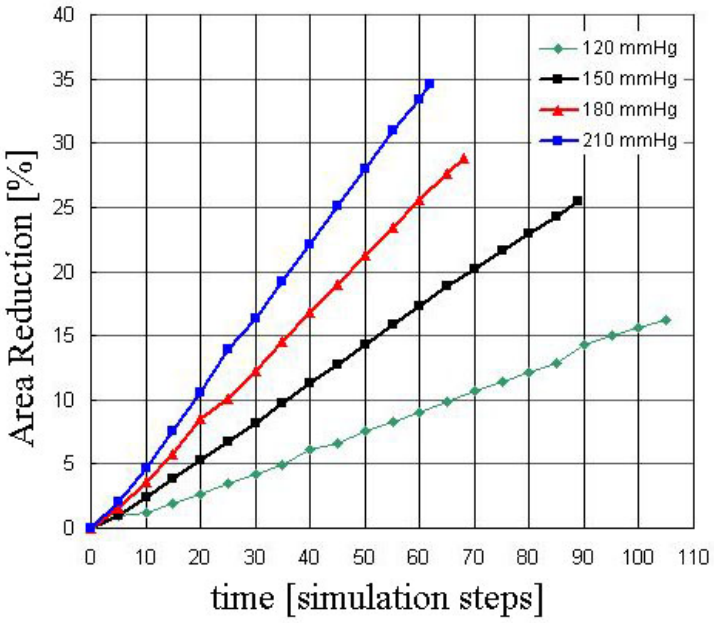

Figure 4: Percentage of area reduction of the axial cross-sections shown in 3 for the four blood pressures simulated

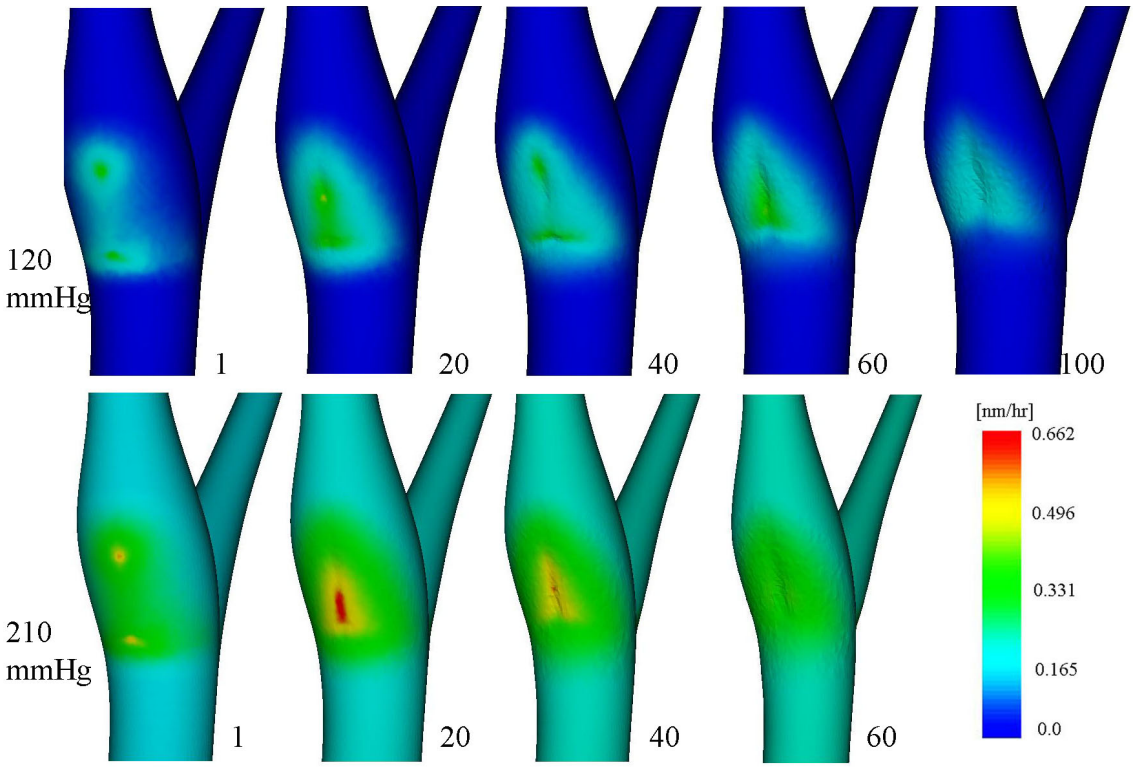

Figure 5: Growth rate predicted by the model. Anterior view of the bifurcation. Top: 5 simulation steps for 120 mmHg. Bottom: 4 simulation steps for 210 mmHg

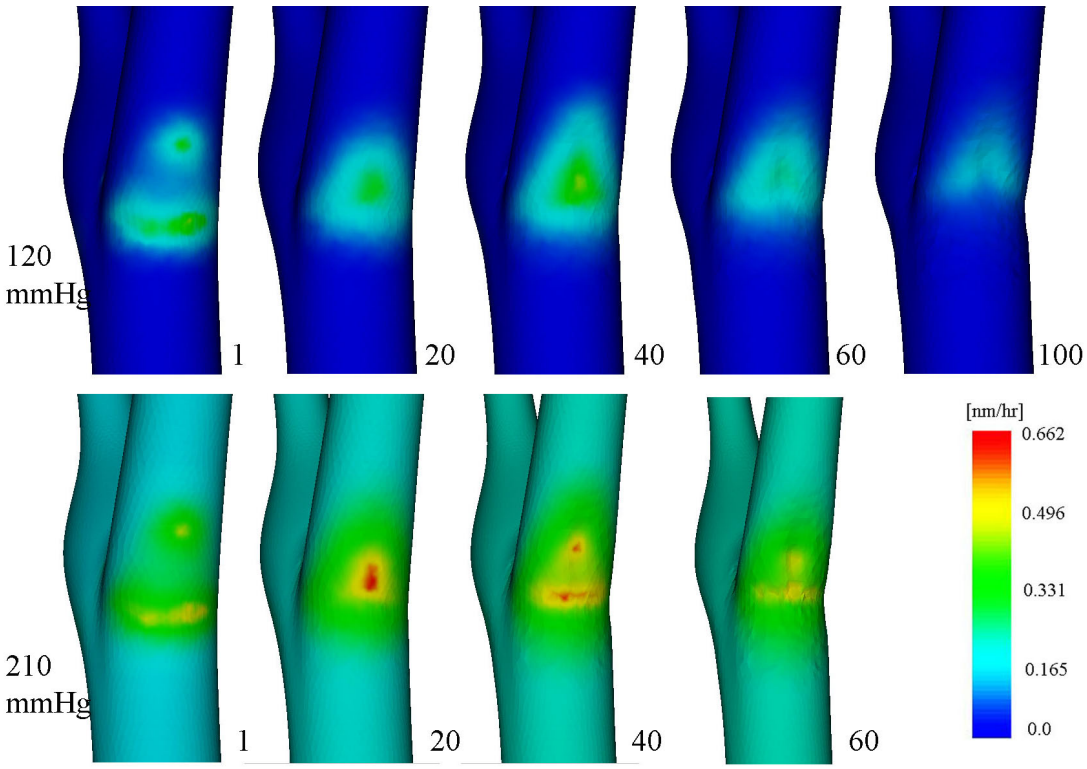

Figure 6: Growth rate predicted by the model. Posterior view of the bifurcation. Top: 5 simulation steps for 120 mmHg. Bottom: 4 simulation steps for 210 mmHg

5 CONCLUSIONS

The proposed model predicts cualitatively good the lesion formation on the external walls of the bifurcation 2, however, it also predicts lesion formation for a physiologic pressure condition and intimal thickening all over the model for all pressures higher than the physiologic case. This may be consequence of the estimation of the cell consumption rate,(eq.5), which was made to prevent intimal thickening for the physiologic condition in the straight portions of the artery.

Another important parameter to keep in mind is that in real life, high pressure conditions cannot last too long. Therefore, it may be possible that for high pressure conditions lasting hours, LDL accumulates and oxidates at higher speed everywhere in the wall, but since the accumulation in the straigh portions is not too high, other mechanisms of consumption that are not modeled here, prevent the lesion formation there. For example, monocyte recruitment is necessary for the foam cell form. This model assumes all LDL that oxidates is accumulating and is not considering the presence of monocytes. This might be a factor that prevents for plaque formation in the straight portions of the artery.

Also the growth that our model is predicting in the straigh portions of the artery is influencing the actual resulting shape of the lesion; consequently, the real cross-section of the artery is different and the resulting flow patterns may be different. This will cause different forces over the endotelium and different permeabilities. However, since the period of time is actually much shorter that the one simulated here, we considered that this will not really affect the actuall relative value of lesion formation at initiation, which is actually of interest.

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REFERENCES

Altman R. Risk factors in coronary atherosclerosis athero-inflammation: The meeting point. *Thrombosis Journal*, 1(1):4, 2003.

Basombrio F., Dari E., Buscaglia G., and Feijoo R. Numerical experiments in complex hemodynamic flows. non-newtonian effects. *International Journal of Computational Fluid Dynamics*, 2002.

Bird R.B., Stewart W.E., and Lightfoot E.N. *Transport Phenomena*. John Wiley and Sons, Inc, New York, second edition, 2001.

Blanco A. *Química biológica*. El Ateneo, Buenos Aires, sexta edition, 1997.

Braunwald E., Ziper D.P., and Libby P. *The vascular biology of atherosclerosis*. Heart disease: A textbook of cardiovascular medicine. Saunders W.B.C.O, 2001.

Caro C., Fitz-Gerald J., and Schroter R. Atheroma and arterial wall shear. observation, correlation and proposal of a shear dependent mass transfer mechanism for atherogenesis. *Proceedings of the Royal Society of London. Series B: Biological Sciences*, 177:109–159, 1971.

Chen J. and Lu X.Y. Numerical investigation of the non-newtonian pulsatile blood flow in a bifurcation model with a non-planar branch. *Journal of Biomechanics*, 39(5):812–832, 2006.

Copley A., editor. *The Casson equation and rheology of blood near zero shear*. Interscience Publishers, New York, 1963.

Friedman M. and Giddens D. Blood flow in major blood vessels: Modeling and experiments. *Annals of Biomedical Engineering*, 33(12):1710–1713, 2005.

Friedman M.H. and Fry D.L. Arterial permeability dynamics and vascular disease. *Atherosclerosis*, 104(1-2):189–194, 1993.

Fry D. Certain histological and chemical responses of the vascular interface to acutely induced mechanical stress in the aorta of the dog. *Circulation Research*, 24(1):93–108, 1969.

Fung Y. *Circulation*. Biomechanics. Springer-Verlag, New York, 2nd edition, 1997.

Hazel A.L., Grzybowski D.M., and Friedman M.H. Modeling the adaptive permeability response of porcine iliac arteries to acute changes in mural shear. *Annals of Biomedical Engineering*, 31(4):412–419, 2003.

Hinderliter A. and Caughey M. Assessing endothelial function as a risk factor for cardiovascular disease. *Current Atherosclerosis Reports*, 5(6):506 – 513, 2003.

Hodgson L. and Tarbell J.M. Solute transport to the endothelial intercellular cleft: The effect of wall shear stress. *Annals of Biomedical Engineering*, 30(7):936–945, 2002.

Jensen-Urstad K., Jensen-Urstad M., and Johansson J. Carotid artery diameter correlates with risk factors for cardiovascular disease in a population of 55-year-old subjects. *Stroke*, 30(8):1572–1576, 1999.

Kargol M. and Kargol A. Mechanistic equations for membrane substance transport and their identity with kedem-katchalsky equations. *Biophysical Chemistry*, 103(2):117–127, 2003.

Ku D.N. Blood flow in arteries. *Annual Review of Fluid Mechanics*, 29(1):399–434, 1997.

LaMack J., Himburg H., X.M. L., and Friedman M.H. Interaction of wall shear stress magnitude and gradient in the prediction of arterial macromolecular permeability. *Annals of Biomedical Engineering*, 33(4):457–464, 2005.

Michel C.C. and Curry F.E. Microvascular permeability. *Physiological Reviews*, 79(3):703–761, 1999.

OpenFoam. The open source cfd toolbox. 2007.

Prosi M., Zunino P., Perktold K., and Quarteroni A. Mathematical and numerical models for transfer of low-density lipoproteins through the arterial walls: a new methodology for the model set up with applications to the study of disturbed lumenal flow. *Journal of Biomechanics*, 38(4):903–917, 2005.

Rappitsch G., Perktold K., and Pernkopf E. Numerical modelling of shear-dependent mass transfer in large arteries. *International Journal for Numerical Methods in Fluids*, 25(7):847–857, 1997.

Ross R. Atherosclerosis – an inflammatory disease. *New England Journal of Medicine*, 340(2):115–126, 1999.

Stangeby D. and Ethier C. Computational analysis of coupled blood-wall arterial ldl transport. *Journal of Biomechanical Engineering*, 124(1):1–8, 2002.

Sun N., Wood N., Hughes A., Thom S., and Xu X. Fluid-wall modelling of mass transfer in an axisymmetric stenosis: Effects of shear-dependent transport properties. *Annals of Biomedical Engineering*, 31(1):1–10, 2006.

Tarbell J. Mass transport in arteries and the localization of atherosclerosis. *Annual Review of Biomedical Engineering*, 5(1):79–118, 2003.

Wells Roe E. J. and Merrill E.W. Shear rate dependence of the viscosity of whole blood and plasma. *Science*, 133(3455):763–764, 1961.

Yang N. and Vafai K. Modeling of low-density lipoprotein (ldl) transport in the artery–effects of hypertension. *International Journal of Heat and Mass Transfer*, 49(5-6):850–867, 2006.

Zarins C.K., Giddens D.P., Bharadvaj B.K., Sottiurai V.S., Mabon R.F., and Glagov S. Carotid bifurcation atherosclerosis. quantitative correlation of plaque localization with flow velocity profiles and wall shear stress. *Circulation Research*, 53(4):502–514, 1983.