Identification of Atherosclerotic Lesion-Prone Sites through Patient-Specific Simulation of Low-Density Lipoprotein Accumulation

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Abstract. We present a patient-specific model of low-density lipoprotein (LDL) transport from blood into arterial walls. To this end, the arterial endothelium is represented by a shear-stress dependent three-pore model taking into account blood plasma and LDL passage through the vesicular pathway, normal junctions and leaky junctions. We virtually remove atherosclerotic plaque from an in-vivo left coronary artery computed tomography (CT) dataset to obtain an approximation of the artery anatomy in its healthy state. By applying our model, we show that the location of the plaque in the diseased state corresponds to one of the two sites with predicted high LDL concentration in the healthy state. We further show that in the diseased state, the site with high LDL concentration has shifted distally, which is in agreement with the clinical observation that plaques generally grow in downstream direction.

1 Introduction

Atherosclerosis, a progressive disease characterized by the accumulation of lipids in the arterial walls, is the primary cause of heart disease and stroke [1]. Locally elevated concentrations of low-density lipoprotein (LDL) are considered to be the initiator of atherosclerotic plaque formation [1]. Therefore, transport of LDL into arterial walls has been the subject of various experimental [2, 3] and computational [4-6] investigations.

In this study, we have modeled the transport of LDL from the artery lumen into the arterial wall in a three-dimensional (3D) left coronary artery with and without the presence of a calcified plaque. The interface between the artery lumen and the arterial wall, i.e. the endothelium, is represented by a three-pore model taking into account mass transport through the vesicular pathway, normal junctions and leaky junctions. Spatial shear stress distribution at the endothelium is determined through the reconstruction of the arterial blood flow field using computational fluid dynamics (CFD) based on anatomy data acquired through computed tomography (CT) scans of a patient with coronary artery disease. A constant thickness arterial wall is obtained by the extrusion of the segmented artery lumen surface.

Most of the prior 3D computational studies include LDL transport in the artery lumen only and do not give any information on LDL transport through the endothelium and into the arterial wall [4]. One recent study by Koshiba et al. [5] included LDL transport in both artery lumen and arterial wall of a curved 3D artery, however only employing a constant permeability for the endothelium with a single pathway approach. The novelty of our work lies in the modeling of LDL transport in a 3D patient-specific coronary artery in which the endothelium is represented by a three-pore model that enables the inclusion of the effects of local wall shear stress on various pathways of blood plasma and LDL flux. The previous studies on the prediction of localization of atherosclerotic plaques rely on low wall shear stress as their base indicator [7]. In comparison, the model at hand allows for the direct identification of LDL accumulation sites, which are generally accepted as prerequisites for plaque formation.

2 Methods

2.1 Acquisition and Processing of Anatomy Data

A 74 year old female patient with atypical anginal pain was scanned with a dual-source CT scanner (Somatom Definition, Siemens Medical Solutions, Forchheim, Germany) following a standard cardiac contrast-enhanced scan protocol described in [8]. The in-plane resolution was 0.256 mm (512 x 512 voxels) and 170 slices were reconstructed with a slice thickness and slice spacing of 0.5 mm.

The coronary arteries were automatically segmented with a progressive region growing technique [9]. The resulting binary segmentation mask enclosed calcified plaques and was converted into a mesh with a marching cube algorithm. A calcified

Fig. 1. Superposition of the surfaces of the patient's coronary arteries with and without plaque. The difference between the two geometries, i.e. the calcified plaque, is shown in the insert (note rotated coordinate axes). LMA, LCX, LAD and FDB stand for left main coronary artery, left circumflex artery, left anterior descending artery and first diagonal branch of the left anterior descending artery, respectively.

plaque was detected in the proximal part of the left anterior descending artery (segment 6 according to the model of the American Heart Association [10]). The plaque was manually segmented and all voxels belonging to the plaque were then removed from the segmentation mask before a second mesh - this time without the plaque - was computed as described above. The two initial 3D surface-based meshes of the patient's coronary arteries were subsequently converted to NURBS (non-uniform rational B-spline) surfaces in order to ensure adequate smoothing of the domain, which is essential for the generation of a high-quality computational grid. Figure 1 shows the surfaces of both NURBS representations with and without plaque.

2.2 Reconstruction of the Flow Field in the Artery Lumen

For the flow field reconstruction, the arterial blood was regarded as an incompressible Newtonian fluid. Four sets of nonuniform unstructured grids respectively consisting of approximately 376,000, 686,000, 976,000 and 1,382,000 tetrahedral and prismatic elements were evaluated to carry out the CFD calculations with the finite-volume code ANSYS CFX 11.0 (ANSYS, Inc., Canonsburg, PA, U.S.A.) using an Algebraic Multigrid scheme with pressure-velocity coupling adapted from [11]. Grid independence tests showed that 976,000 elements were sufficient to resolve all flow features and to accurately calculate local wall shear stress with less than 2.5% deviation from the finest grid solution. The flow field was then reconstructed with the respective grid under steady-state conditions with an inlet mass flow rate of 57 ml/min, which is the time-averaged blood inflow into the left main coronary artery (LMA) based on the pulsatile volume inflow profile given in [12]. Constant pressure boundary conditions of 70 mmHg [6] were used at the three outlets and a no-slip boundary condition was utilized at the endothelium.

2.3 Determination of Blood Plasma and LDL Flux through the Endothelium

The blood plasma and LDL flux through the endothelium is governed by a three-pore model as discussed in detail by Olgac et al. in [6]. The three-pore model represents the vesicular pathway, normal junctions and leaky junctions. Blood plasma flux occurs through normal and leaky junctions, whereas LDL flux occurs via the vesicular pathway and through leaky junctions [6].

It has been shown that in low shear stress regions, cells are roundly shaped and they proliferate more compared to high shear stress regions, where they are elongated in the flow direction [2, 13]. It has also been shown that 80.5% of total mitotic cells are leaky [3]. In the current study, we calculate the local fraction of leaky junctions, ϕ , which is defined as the ratio of the area of leaky cells to the area of all cells [6], as a function of local wall shear stress obtained by the above CFD model. The following correlations derived in [6] are used to this end:

$$SI = 0.380e^{-0.790WSS} + 0.225e^{-0.043WSS}, \quad (1)$$

$$\#MC = 0.003797e^{14.75SI}, \quad (2)$$

$$\#LC = 0.307 + 0.805 \cdot (\#MC), \quad (3)$$

$$\phi = \frac{\#LC \times \pi R_{cell}^2}{unit\ area}, \quad (4)$$

where WSS, SI, #MC and #LC are the wall shear stress, shape index of cells (equals one for a circular cell and approaches zero for a highly elongated cell [13]), number of mitotic cells and number of leaky cells, respectively, R_{cell} and *unit area* are the radius of a single endothelial cell ($15\ \mu m$) and a unit area of $0.64\ mm^2$, respectively. The calculated local fractions of leaky junctions are used in the pore theory [14] to estimate the transport properties, i.e. hydraulic conductivity, diffusive permeability and reflection coefficient, of the leaky junction pathway.

The endothelium and the arterial wall exhibit a combined resistance against inflow from the artery lumen. We use an electrical analogy for the fluid dynamics in which the flow, analogous to current in an electric circuit, is driven by the pressure difference, which is analogous to potential difference. According to the electrical analogy, the filtration velocity can be expressed as

$$J_v = \frac{p_l^{end} - p_{adv}}{R_T}, \quad (5)$$

where R_T is the combined flow resistance of the normal junctions, leaky junctions and the arterial wall, and p_l^{end} and p_{adv} are the lumen side pressure at the endothelium and the pressure at the media-adventitia interface, respectively. The solute flux J_s through the endothelium is given by

$$J_s = (P_v + P_{app,lj})c_l^{end}, \quad (6)$$

where P_v , $P_{app,lj}$ and c_l^{end} are the apparent permeability coefficients for the vesicular pathway and the leaky junctions, and the lumen side concentration of LDL at the endothelium, respectively. LDL concentration in the artery lumen is taken to be constant ($1.0 \times 10^{-3}\ mol/m^3$), as it was shown by Olgac et al. that the maximum spatial LDL concentration variation in the artery lumen is under 1.0% [6].

2.4 Reconstruction of the Flow and LDL Concentration Field in the Arterial Wall

The arterial wall was regarded as a single layer porous medium with constant thickness of 0.34 mm, the combined thickness of intima and media of the human left anterior descending coronary artery [15]. The transmural velocity field in the arterial wall is calculated using Darcy's Law, where the permeability of the arterial wall is taken as $1.2 \times 10^{-18}\ m^2$ [6]. The lumen side pressure at the endothelium, as obtained with the CFD model of the artery lumen, is used in Eq. (5) to calculate the local blood plasma flux at the endothelium, which is then applied as inlet boundary condition for

the artery wall domain. A constant pressure boundary condition of 17.5 mmHg is applied at the media-adventitia interface and at the longitudinal ends of the wall, zero flux boundary conditions are used [6].

LDL transport in the arterial wall is governed by the convection-diffusion-reaction equation, which takes into account the degradation of LDL in the arterial wall. The LDL flux, locally calculated with Eq. (6), is applied at the endothelium and a constant nondimensional concentration of 0.005 is imposed at the media-adventitia interface [6]. At the longitudinal ends of the wall, isolation boundary conditions are used.

The arterial wall domain was constructed by extrusion of the mesh on the endothelium of the artery lumen domain. Three sets of nonuniform unstructured grids respectively consisting of approximately 91,000, 183,000 and 274,000 prismatic elements were evaluated to carry out the CFD calculations with the finite-element code Comsol Multiphysics, Version 3.3 (COMSOL AB, Stockholm, Sweden) using an Algebraic Multigrid preconditioner with a conjugate gradients iterative solver [16]. Grid independence tests showed that 274,000 elements were sufficient to resolve the flow and concentration field in the arterial wall accurately with less than 2.5% difference compared to the medium grid solution.

3 Results and Discussion

Overviews of the simulation results for the two models with and without plaque are shown at the left and right-hand side of Fig. 2, respectively. We make the assumption that the model in which the plaque was virtually removed corresponds to the state of the patient's artery prior to plaque formation and refer to it as the model of the "healthy" state. The original model with the plaque corresponds to the "diseased" state.

In Fig. 2a, the wall shear stress magnitudes at the endothelium are compared. In the diseased model, at the proximal end of the plaque, we observe high shear stress, whereas distal to the plaque, a recirculation zone causes low endothelial shear stress. Looking at the healthy model, we distinguish a small region of high shear stress at the bifurcation where the LMA branches into the LAD and the LCX, followed by a low shear stress region in the proximal section of the LCX and a low shear stress region in the proximal LAD at the same location where the plaque is found in the diseased model.

Figure 2b juxtaposes the filtration velocities through the endothelium. In the healthy model, we observe increased filtration velocities at the above mentioned two low shear stress regions due to an elevated number of leaky junctions. In the diseased model, distal to the plaque within the recirculation zone, the filtration velocity is increased.

In Fig. 2c, the wall side LDL concentrations at the endothelium are compared. In the healthy model, we observe two high LDL concentration locations downstream of the bifurcation where the LMA branches into the LCX and the LAD. The diseased model has a plaque at one of these two locations, i.e. in the proximal section of the LAD. Additionally, in the diseased model, this high LDL concentration location is

Fig. 2. Comparison of the models representing the healthy, plaque-free, state of the patient’s coronary arteries (left) and the diseased state (right): a) Wall shear stress magnitude, b) filtration velocity through the endothelium and c) non-dimensionalized wall side LDL concentration at the endothelium

shifted immediately distal to the plaque. This is in agreement with the finding of Smedby et al. [17] who, in an angiographic study, observed that atherosclerotic plaques grow significantly more frequently in the downstream direction of stenoses than in the upstream direction.

In both the healthy and the diseased models, the locations of high filtration velocity coincide with those of high LDL accumulation. This is because of the elevated number of leaky junctions in these low shear stress regions. The convective removal of LDL molecules with the increased filtration velocity is not sufficient to overcome LDL accumulation.

We assume in this study that the model in which the plaque is virtually removed by segmentation corresponds to the actual artery geometry of the patient before the plaque was formed. However, this may not always be the case, especially when the plaque grows not only towards the artery lumen but also into the arterial wall. Nevertheless, we think that the assumption is acceptable as a starting point considering that it is difficult to perform a patient follow-up study requiring CT scans of healthy subjects who subsequently develop coronary artery disease. A follow-up study on animals fed with a high-fat diet similar to the one recently published by Chatzizisis et al. [7] would be of interest to validate this assumption.

Another question that may be raised is the reason why only one of the two high LDL accumulation locations in the healthy model developed into a plaque. First, while it is known that atherosclerotic plaque formation requires prior LDL accumulation [1], there is no conclusive evidence that LDL accumulation in the artery wall necessarily leads to plaque formation. Other concurrent factors may be necessary. Second, unsteady flow features (e.g. spatial and temporal shear stress gradients), as often observed at bifurcations could potentially effect the formation of leaky junctions, thus the transport of LDL into the arterial wall. In this study we followed a steady-state approach in which the effects of steady wall shear stress on plasma and LDL flux is taken into account. We believe this to be a reasonable approach, since there is no information up to date about the effects of oscillatory shear stress on the formation of leaky junctions.

4 Conclusion

In the work at hand, we present a patient-specific model of low-density lipoprotein transport from blood into arterial walls. The novelty of this work lies in the representation of the arterial endothelium as a three-pore model with shear stress-dependent transport properties coupled to a patient-specific reconstruction of the luminal blood flow field. This approach, as opposed to prior single pathway models with constant transport properties, allows for a patient-specific localization of arterial wall regions with high LDL concentration, thereby contributing to the identification of potential sites of atherosclerotic plaque formation.

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