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Dependence of leukocyte capture on instantaneous pulsatile flow

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ABSTRACT

Atherosclerosis, an artery disease, is currently the leading cause of death in the United States in both men and women. The first step in the development of atherosclerosis involves leukocyte adhesion to the arterial endothelium. It is broadly accepted that blood flow, more specifically wall shear stress (*WSS*), plays an important role in leukocyte capture and subsequent development of an atherosclerotic plaque. What is less known is how instantaneous *WSS*, which can vary by up to 5 Pa over one cardiac cycle, influences leukocyte capture. In this paper we use direct numerical simulations (DNS), performed using an in-house code, to illustrate that leukocyte capture is different whether as a function of instantaneous or time-averaged blood flow. Specifically, a stenotic plaque is modeled using a computational fluid dynamics (CFD) solver through fully three-dimensional Navier-Stokes equations and the immersed boundary method. Pulsatile triphasic inflow is used to simulate the cardiac cycle. The CFD is coupled with an agent-based leukocyte capture model to assess the impact of instantaneous hemodynamics on stenosis growth. The computed wall shear stress agrees well with the results obtained with a commercial software, as well as with theoretical results in the healthy region of the artery. The analysis emphasizes the importance of the instantaneous flow conditions in evaluating the leukocyte rate of capture. That is, the capture rate computed from mean flow field is generally underpredicted compared to the actual rate of capture. Thus, in order to obtain a reliable estimate, the flow unsteadiness during a cardiac cycle should be taken into account.

1. Introduction

The prevalence and consequences of Cardiovascular Diseases (CVD) make them one of the world's most prominent diseases. CVD are the primary cause of death in the world with more than 17.3 million deaths per year and the total direct and indirect cost of CVD and stroke in 2016 were more than $316.6 billion. Many CVD develop as a result of atherosclerosis, including coronary heart disease, carotid artery disease (stroke), peripheral artery disease (PAD), and angina (chest pain). As defined by the American Heart Association, atherosclerosis is a condition in which plaque builds up inside the arterial wall. Plaque is made of cholesterol, leukocytes and other arterial cells, fatty substances, cellular waste products, calcium, elastin, collagen, and fibrin. The plaque may partially or completely block the blood's flow through an artery, thus influencing blood hemodynamics. In this paper we show how instantaneous pulsatile flow around a plaque influences leukocyte capture to the arterial wall.

Clinical techniques used to measure flow rates in vivo suggest a positive correlation between the hemodynamics and atherosclerotic growth and remodeling. Gibson et al. (1993) found a significant correlation between vessel low wall shear stress (*WSS*) and increased rate of atherosclerosis progression. They used quantitative angiography to calculate the change in coronary arterial diameter over 3 years. *WSS* was calculated by a finite-element model employing the Navier-Stokes equations and assuming a constant coronary flow rate of 8 ml/s. Similarly, others have used in vitro and in vivo studies to show correlations between the *WSS*, leukocyte infiltration and wall composition. In-vivo, plaque regions with average low *WSS* tend to be or become fibrotic (Chatzizisis et al., 2008). Likewise, in vitro studies show low *WSS* is correlated with a higher rate of leukocyte extravasation (Bailey et al., 2007). Conversely, longitudinal studies suggest plaque regions with an average high *WSS* tend to exhibit regression of fibrotic tissue (Timmins et al., 2015; Samady et al., 2011). In-vitro studies also show high *WSS* regions have little leukocyte extravasation (Burns

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et al., 2007; Sheikh et al., 2003; Barreiro et al., 2005; Cinamon and Alon, 2003). It is broadly accepted *WSS* plays an important role in leukocyte extravasation and plaque remodeling; however, it is less known how the instantaneous wall shear stress, which can vary by up to 5 Pa during one cardiac cycle (Hasan et al., 2013), influences leukocyte transmigration and resulting plaque progression. In this paper we show how leukocyte capture as a function of instantaneous flow is significantly different than as a function of time-averaged flow.

Several numerical studies have illustrated the spatiotemporal dynamics of blood flow within the coronary artery, and were used to inform the model presented herein. Hasan et al. (2013) used a computational fluid dynamics model to investigate the effect of cyclic motion (i.e. bending and stretching) on coronary blood flow. In this study, the artery was modeled as an anisotropic nonlinear elastic material (via the five-parameter Mooney-Rivlin hyperelastic model). Blood was assumed as an incompressible Newtonian fluid and flow was solved using continuity and Navier-Stokes equations. Hasan et al. (2013) concluded the bending motion of the coronary artery has little effect on flow properties (i.e., blood flow velocity, blood shear stress and wall shear stress) but greatly affects the stresses within the artery wall. Since we are modeling leukocyte capture as a function of blood hemodynamics, the model presented herein does not account for wall motion. Chaichana et al. (2012) studied the hemodynamic effect of realistic coronary plaques reconstructed based on high-resolution CT data of human coronary plaques. Computational Fluid Dynamics (CFD) analysis revealed the classic features: *WSS* was highest at the peak stenosis (minimum luminal diameter) and recirculation regions occurred post-stenosis. Even though this study used realistic (i.e. non-axisymmetric) plaque geometries the degree of stenosis was the primary factor giving rise to the observed hemodynamic changes. Therefore, our model uses simplified plaque geometries to keep the focus on the effects of instantaneous versus steady flow on leukocyte capture.

In this paper, a direct numerical simulation (DNS) of pulsatile blood flow in a branch-less circular cylindrical coronary artery is implemented. Incompressible, pulsatile flow of blood as a Newtonian fluid is solved using an in-house parallel code. *WSS* is computed from the transient fully 3D velocity field at the wall. The stenotic wall of the artery is introduced using the immersed boundary method (Orlandi and Leonardi, 2006). Calculated spatiotemporal fields from the DNS are then compared to, and agree well with, those obtained using a commercial program, COMSOL. In the second part of the paper, *WSS* computed from the DNS is coupled with a leukocyte capture model as presented by Bhui and Hayenga (2017). We then compare the total value of leukocyte capture during time-averaged and instantaneous flow. The instantaneous *WSS* plays a critical role in leukocyte capture and thus vascular remodeling of the stenotic artery.

2. Numerical method

We consider an artery as a rigid circular cylinder with a length-to-diameter ratio $L/D = 32$. The Navier-Stokes equations for a Newtonian incompressible fluid are assumed as the governing equations:

$$\nabla \cdot \mathbf{u} = 0 \tag{1}$$

$$\frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u} \cdot \nabla)\mathbf{u} = -\frac{1}{\rho}\nabla p + \nu \nabla^2 \mathbf{u} \tag{2}$$

Here $\mathbf{u}$ is the velocity vector, p the pressure, $\rho = 1060\ \mathrm{kg/m^3}$ is the blood density, $\nu = 3.3 \cdot 10^{-6}\ \mathrm{m^2/s}$ is the blood kinematic viscosity, and t is time. The inlet velocity profile is assumed to be axisymmetric and parabolic:

$$u = 2\,u_{\mathrm{bulk}}(t) \cdot \left[1 - \frac{r^2}{(D/2)^2}\right] \tag{3}$$

where u_{bulk} is the pulsatile bulk velocity, r is the radial distance from the artery axis. The amplitude of the bulk velocity follows the triphasic waveform signal modified from He and Ku (1996) (shown in Fig. 2a). The period is 0.8 s ($T = 0.8$ s), which gives a Womersley number of $\alpha = (D/2)\sqrt{2\pi/(\nu T)} \approx 2.3$.

A Gaussian function is used to model the stenotic region of the arterial wall:

$$r_w(x, \vartheta) = \frac{D}{2} - h \exp\left[-a_1 \left(\frac{x}{D}\right)^2\right] \cdot \exp\left(-a_2 \vartheta^2\right) \tag{4}$$

where x and ϑ are the streamwise and azimuthal coordinates, respectively. The maximum height of stenosis is h, and a_1 and a_2 are the shape parameters. We have considered both axisymmetric and three-dimensional geometries. In the first case, the azimuthal shape parameter, a_2, is set to $a_2 = 0$; for the three-dimensional case, $a_2 = 2.68$. In both cases, the axial shape parameter is kept fixed to $a_1 = 8.41$. To assess the effect of different degrees of flow obstruction, we varied the height of the stenosis. For the axisymmetric geometry, we have considered three cases: $h/D = 0.1, 0.2, 0.3$. Two further simulations with the three-dimensional geometry ($a_2 = 2.68$) have been performed using $h = 0.1D$ and $h = 0.2D$. Fig. 1 illustrates the geometries of the stenotic wall used in this study.

Eqs. (1) and (2) can be non-dimensionalized by appropriately normalizing all the variables by reference values of velocity, length and density. Herein, the mean bulk velocity u_{mean}, the arterial diameter D, and the blood density are the selected reference values. Scaling the variables in (1) and (2) yields the non-dimensional Navier-Stokes equations:

$$\nabla_* \cdot \mathbf{u}_* = 0 \tag{5}$$

$$\frac{\partial \mathbf{u}^*}{\partial t^*} + (\mathbf{u}^* \cdot \nabla_*)\mathbf{u}^* = -\nabla_* p^* + \frac{1}{Re}\nabla_*^2 \mathbf{u}^* \tag{6}$$

where quantities denoted by a superscript $*$ refer to non-dimensional variables:

$$\mathbf{u}^* = \frac{\mathbf{u}}{u_{\mathrm{mean}}}, \qquad t^* = \frac{t u_{\mathrm{mean}}}{D}, \qquad p^* = \frac{p}{\rho u_{\mathrm{mean}}^2}$$

and

$$[\nabla_*]_i = \frac{\partial}{\partial x_i^*} \quad \text{with} \quad x_i^* = \frac{x_i}{D}$$

The non-dimensional momentum Eq. (6) explicitly depends on the Reynolds number. The Reynolds number, based on the artery diameter $D = 2.9$ mm and on the mean bulk velocity u_{mean}, is $Re = u_{\mathrm{mean}} D/\nu \approx 340$, where:

$$u_{\mathrm{mean}} = \frac{1}{T}\int_0^T u_{\mathrm{bulk}}(t)\,\mathrm{d}t = 0.384\ \mathrm{m/s} \tag{7}$$

The in-house numerical code solves the non-dimensional equations. Eqs. (5) and (6) are discretized using a finite differences scheme on a Cartesian grid. The numerical scheme is described in detail in Orlandi (2000). Central finite differences are used for the spatial derivatives, which yield a second-order conservative scheme. Time-advancement is performed with a hybrid third-order low-storage Runge-Kutta scheme with the non-linear terms treated explicitly, and the linear terms implicitly. A fractional step

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