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Microvascular blood flow resistance: Role of red blood cell migration and dispersion

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ABSTRACT

Microvascular blood flow resistance has a strong impact on cardiovascular function and tissue perfusion. The flow resistance in microcirculation is governed by flow behavior of blood through a complex network of vessels, where the distribution of red blood cells across vessel cross-sections may be significantly distorted at vessel bifurcations and junctions. In this paper, the development of blood flow and its resistance starting from a dispersed configuration of red blood cells is investigated in simulations for different hematocrit levels, flow rates, vessel diameters, and aggregation interactions between red blood cells. Initially dispersed red blood cells migrate toward the vessel center leading to the formation of a cell-free layer near the wall and to a decrease of the flow resistance. The development of cell-free layer appears to be nearly universal when scaled with a characteristic shear rate of the flow. The universality allows an estimation of the length of a vessel required for full flow development, $l_c \lesssim 25D$, for vessel diameters in the range 10 μm < D < 100 μm. Thus, the potential effect of red blood cell dispersion at vessel bifurcations and junctions on the flow resistance may be significant in vessels which are shorter or comparable to the length l_c. Aggregation interactions between red blood cells generally lead to a reduction of blood flow resistance. The simulations are performed using the same viscosity for both external and internal fluids and the RBC membrane viscosity is not considered; however, we discuss how the viscosity contrast may affect the results. Finally, we develop a simple theoretical model which is able to describe the converged cell-free-layer thickness at steady-state flow with respect to flow rate. The model is based on the balance between a lift force on red blood cells due to cell-wall hydrodynamic interactions and shear-induced effective pressure due to cell–cell interactions in flow. We expect that these results can also be used to better understand the flow behavior of other suspensions of deformable particles such as vesicles, capsules, and cells.

Introduction

Flow resistance of a full cardiovascular system is mainly attributed to the resistance of blood flow within microvasculature or microcirculation (Lipowsky et al., 1980; Popel and Johnson, 2005; Pries and Secomb, 2008; Secomb and Pries, 2011), which is comprised of the smallest vessels (e.g., arterioles, capillaries, venules) with diameters up to about 100 μm. In particular, the flow resistance in microvasculature is governed by the flow behavior of blood through a complex network of vessels, and therefore, the knowledge about bulk blood properties is far from sufficient to predict the behavior of blood and its flow resistance in microcirculation. For instance, experimental measurements (Lipowsky et al., 1980; Pries et al., 1994; Pries and Secomb, 2005) of blood flow resistance in vivo have shown that it may be several times larger than that in in vitro experiments on blood flow in glass tubes (Reinke et al., 1987; Pries et al., 1992). Several potential contributions to an increased blood flow resistance in vivo have been suggested. These include vessel irregularities, bifurcations, and junctions, which may affect the distribution of red blood cells (RBCs) in a vessel cross-section (Pries et al., 1994; Secomb and Hsu, 1997; Pries et al., 1989), the presence of endothelial surface layer (or glycocalyx) (Vink and Duling, 1996; Weinbaum et al., 2007) at the vessel walls (Pries and Secomb, 2005; Pries et al., 1997), and the length of vessel sections between bifurcations and junctions (Popel and Johnson, 2005; Pries et al., 1996).

The endothelial surface layer resembles a polymeric brush at a vessel wall with an estimated thickness of about 0.5 — 1.5 μm (Pries et al., 2000; Yen et al., 2012). Its effect on an increased flow resistance can be interpreted as an effective reduction of the vessel diameter due to the glycocalyx, and a large enough thickness of this layer (~2 μm) provides a plausible explanation for the discrepancy of experimentally measured blood flow resistances in vivo and in vitro (Pries and Secomb, 2005; Pries et al., 1997). However, contribution of the other effects has not been rigorously studied. As an example, RBCs in microvessels migrate away from the walls leading to a layer near a

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wall void of RBCs (Goldsmith et al., 1989; Cokelet and Goldsmith, 1991). This layer is called cell-free layer (CFL) or RBC-free layer, and its thickness is directly associated with the blood flow resistance (Popel and Johnson, 2005; Reinke et al., 1987; Fedosov et al., 2010a). In the microvasculature, blood flow and in particular the distribution of RBCs in a vessel cross-section can be significantly disturbed at bifurcations and junctions resulting in a reduced CFL thickness and an increased flow resistance (Ong et al., 2012). After the RBC distribution is distorted at a vessel bifurcation, in the following vessel segment RBCs will migrate toward the vessel center leading to a dynamic development and recovery of the CFL thickness. Thus, the flow resistance in microcirculation is affected by the degree of RBC dispersion at vessel junctions and the length of the CFL recovery after the distortion in comparison to a characteristic length of vessel segments between bifurcations in microvascular networks.

RBC migration and the development of CFL are governed by hydrodynamic interactions of RBCs with channel walls (Cantat and Misbah, 1999; Abkarian et al., 2002; Coupier et al., 2008) and cell–cell interactions or collisions in flow (Kumar and Graham, 2012; Grandchamp et al., 2013). The former RBC-wall interaction is usually referred to as a lift force (Cantat and Misbah, 1999; Abkarian et al., 2002; Coupier et al., 2008; Messlinger et al., 2009), while the latter one is called shear-induced diffusion or shear-induced normal stress (Grandchamp et al., 2013; Leighton and Acrivos, 1987). The lift force drives RBCs away from the vessel walls, while the cell–cell interactions lead to an effective dispersion of RBCs. The balance between these two contributions at steady flow results in a converged thickness of the RBC flow core and CFL. Clearly, the CFL development and its final thickness are functions of a number of parameters including hematocrit (volume fraction of RBCs), flow rate, vessel diameter, and aggregation interactions between RBCs. There exists a diffusion-based model (Carr, 1989; Carr and Xiao, 1995), which predicts a recovery length of CFL symmetry after it is distorted behind vessel bifurcations. However, the model has several adjustable parameters.

The main focus of this paper is a systematic investigation of CFL development in microvessels for a number of blood flow conditions using mesoscopic simulations (Fedosov et al., 2014a, 2014b). We use the smoothed dissipative particle dynamics method (Español and Revenga, 2003) to study the development of blood flow for various flow conditions starting from a fully-dispersed configuration of RBCs. Following the migration of RBCs away from the walls, the CFL thickness is dynamically monitored until it converges to a constant value of a fully-developed flow. The time evolution of CFL thickness appears to be nearly universal with respect to the flow rate for physiological hematocrit level $H_t \leq 0.45$; this range of hematocrit level is also directly relevant for healthy microcirculatory blood flow (Lipowsky et al., 1980; Pries et al., 1986). This allows us to define a length l_c for the development of CFL, which is nearly independent of the flow rate and shorter than or equal to $25D$, for vessel diameters in the range $10\ \mu m < D < 100\ \mu m$. Thus, the effect of RBC dispersion at vessel bifurcations and junctions on the flow resistance may be significant in vessels which are shorter or comparable to the length l_c, while in longer vessel sections it can be practically neglected. Aggregation interactions between RBCs result in a reduction of blood flow resistance, since they aid to maintain a more compact RBC flow core.

Finally, we also develop a simple theoretical model which describes well the final CFL thickness when the flow has converged. The model considers the balance between a lift force on RBCs due to cell-wall hydrodynamic interactions and shear-induced effective pressure due to cell–cell interactions in flow. This model supports the idea that these are the two main mechanisms which govern the final CFL thickness. Similar ideas have also been applied to describe dispersion of RBCs after injection (Grandchamp et al., 2013). We hope that our results will help to better understand also the flow behavior of other suspensions of deformable particles such as vesicles, capsules, and cells, and will trigger new investigations in this area.

The paper is organized as follows. In the second section, we briefly introduce the simulation techniques employed for RBC and flow simulations and describe the simulation setup. The third section presents simulation results and the theoretical model, while in the fourth section implications of the results are discussed. We conclude in the fifth section with a brief summary.

Models & methods

We employ the smoothed dissipative particle dynamics (SDPD) method (Español and Revenga, 2003) to model fluid flow. SDPD is a mesoscopic simulation technique, where each SDPD particle corresponds to a small volume of fluid instead of individual atoms or molecules. The RBC membrane is represented by a triangulated network model (Discher et al., 1998; Noguchi and Gompper, 2005; Fedosov et al., 2010b; Fedosov et al., 2010c) and coupled to fluid flow using friction forces.

Smoothed dissipative particle dynamics

SDPD (Español and Revenga, 2003) is a mesoscopic hydrodynamics method based on two popular approaches: the smoothed particle hydrodynamics (Lucy, 1977; Monaghan, 1992) and the dissipative particle dynamics (Hoogerbrugge and Koelman, 1992; Español and Warren, 1995) methods. In SDPD, a simulation system consists of N point particles with mass m_i, position $\mathbf{r}_i$, and velocity $\mathbf{v}_i$. The Newton's second law of motion governs the evolution of particle positions and velocities over time as

$$d\mathbf{r}_i = \mathbf{v}_i dt, \quad d\mathbf{v}_i = \frac{1}{m_i}\left(\mathbf{F}_i^C + \mathbf{F}_i^D + \mathbf{F}_i^R\right)dt, \tag{1}$$

where $\mathbf{F}^C$, $\mathbf{F}^D$, and $\mathbf{F}^R$ are conservative, dissipative, and random forces due to inter-particle interactions, respectively. The equations of motion above are integrated using the velocity-Verlet algorithm (Allen and Tildesley, 1991). The three pairwise forces on particle i are defined as follows

$$\begin{aligned}
\mathbf{F}_i^C &= \sum_j \left(\frac{p_i}{\rho_i^2} + \frac{p_j}{\rho_j^2}\right) w_{ij}\mathbf{r}_{ij}, \\
\mathbf{F}_i^D &= -\sum_j \gamma_{ij}\left(\mathbf{v}_{ij} + \left(\mathbf{v}_{ij}\cdot\mathbf{e}_{ij}\right)\mathbf{e}_{ij}\right), \\
\mathbf{F}_i^R &= \sum_j \sigma_{ij}\left(d\overline{\mathbf{W}}_{ij}^S + \frac{1}{3}tr\left[d\mathbf{W}_{ij}\right]\right)\cdot\mathbf{e}_{ij},
\end{aligned} \tag{2}$$

where $\mathbf{e}_{ij} = \mathbf{r}_{ij}/|\mathbf{r}_{ij}|$ and $\mathbf{v}_{ij} = \mathbf{v}_i - \mathbf{v}_j$. p_i and p_j are particle pressures assumed to follow the equation of state $p = p_0(\rho/\rho_0)^\alpha - b$, where p_0, ρ_0, α, and b are selected parameters. Density of particles is calculated locally and determined as $\rho_i = \sum_j W_L(r_{ij})$ with $W_L(r) = \frac{105}{16\pi r_c^3}\left(1+3\frac{r}{r_c}\right)\left(1-\frac{r}{r_c}\right)^3$ being the Lucy function (Lucy, 1977), where r_c is the cutoff radius. Furthermore, $\nabla W_L(r) = -\mathbf{r}w(r)$ such that $w(r) = \frac{315}{4\pi r_c^5}\left(1-\frac{r}{r_c}\right)^2$ and $w_{ij} = w(r_{ij})$. The coefficients γ_{ij} and σ_{ij} define the strength of dissipative and random forces and are defined as $\gamma_{ij} = \frac{5\eta_0}{3}\frac{w_{ij}}{\rho_i\rho_j}$ and $\sigma_{ij} = 2\sqrt{k_BT\gamma_{ij}}$, where η_0 is the desired dynamic viscosity of fluid and k_BT is the energy unit. The notation $tr[d\mathbf{W}_{ij}]$ corresponds to the trace of a random matrix of independent Wiener increments $d\mathbf{W}_{ij}$, and $d\overline{\mathbf{W}}_{ij}^S$ is the traceless symmetric part.

Table 1 presents the fluid simulation parameters in units of the fluid particle mass m, the cutoff radius r_c, and the thermal energy k_BT. Even though SDPD allows one to directly input desired fluid viscosity η_0, the measured dynamic viscosity η of SDPD fluid might be slightly

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