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Original Research Article

Non-uniform viscosity caused by red blood cell aggregation may affect NO concentration in the microvasculature

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ABSTRACT

Aggregation of red blood cells in the micro vasculature may affect blood viscosity in the vessel. The purpose of this study was to investigate the potential effect of non-uniform viscosity caused by red blood cell (RBC) aggregation on nitric oxide (NO) concentration and distribution. A 3-D multi-physics model was established to simulate the production, transport and consumption of NO. Two non-uniform viscosity models caused by RBC aggregation were investigated: one assuming a linear and the other a step hematocrit distribution. In addition, the effect of the thickness of the plasma layer was tested. Simulation results demonstrate that non-uniform viscosity caused by RBCs aggregation influences NO concentration distribution. Compared with the uniform viscosity model, NO concentration using non-uniform viscosity is lower than that using uniform viscosity. Moreover, NO concentration calculated from the step hematocrit model is higher than that calculated from the linear hematocrit model. NO concentrations in the endothelium and the vascular wall decrease with the decline of the thickness of the plasma layer. The relative decrease differs between the linear and the step model. Our results suggest that non-uniform viscosity caused by red blood cell aggregation affects nitric oxide distribution in the micro vasculature. If uniform viscosity is assumed when performing numerical simulations, NO concentration values may be overestimated.

1. Introduction

Endogenously-produced nitric oxide (NO) has important physiological effects in the vasculature, nervous systems and respiratory system [1,2]. There has been considerable research effort to better understand the functionality of NO which is closely related to its level of concentration. NO released by the endothelium diffuses into the lumen and the surrounding tissue, and when the amount of NO which

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reaches the smooth muscle cells is high enough to activate soluble guanylate cyclase (sGC) through binding to the heme, the guanosine triphosphate (GTP) is converted into cyclic guanosine monophosphate (cGMP), causing smooth muscle relaxation and vasodilation [3,4].

Numerous studies have been conducted on the possible factors affecting NO concentration. NO concentration is related to the production and the scavenging reactions. Kavdia's mathematical model predicted that the release of NO by the endothelium is linearly dependent on wall shear stress (WSS) [5]. Most NO is scavenged by hemoglobin in the Red blood cells (RBC), and the NO concentration could be affected by the radial hematocrit distribution [6].

In small vessels with diameter in the range of 10–300 μm, the RBCs move toward the center of the vessel, leaving a plasma layer at the wall of the vessel (the Fahraus–Lindquist effect) [7]. Blood hematocrit has attracted major attention as an important factor affecting NO concentration. Current investigations focus mainly on the effect of uneven distribution of red blood cells and the presence or absence of a plasma layer on NO scavenging reaction [8]. Pries' suggested that in small vessels blood viscosity is related to the Hematocrit [9]. However, most studies about NO concentration assume the viscosity in the lumen to be uniform and have not considered the effect of non-uniform viscosity on the production and distribution of NO.

In the present study we hypothesized that the uneven RBC distribution in the blood lumen affects not only NO scavenging reaction, but also the blood viscosity distribution. Furthermore, we assumed that it has influence on wall shear stress (WSS) which affects NO production in the endothelium, ultimately changing the NO concentration in the microcirculation. We used a three-dimensional multi-physics simulation model to perform this study. The model was used to calculate the change in viscosity when a linear or a step distribution of RBCs across the vessel lumen was assumed. The different values of viscosity as well as changes in the plasma layer thickness were then used to calculate the concentration of NO in the vessel and to compare it to the concentration of NO when a uniform viscosity is assumed.

2. Method

The 3-D model for a 350 μm long segment of vessel is depicted in Fig. 1. It represents the lumen ($0 < r < R2$), vascular wall ($R2 < r < R4$) and tissue ($R4 < r < R5$). The lumen was divided into two zones: RBC rich zone ($0 < r < R1$) and RBC poor zone ($R1 < r < R2$), the thickness of the RBC poor zone is δ_P. The endothelial layer ($R2 < r < R3$) is a part of the vascular wall having a thickness δ_e of 1um.

Blood flow in the lumen was assumed to be steady, and steady-state incompressible Navier–Stokes equations (Eq. (1)) were used to simulate the Hemodynamics in the lumen. NO is released by the endothelium, and diffuses into both lumen and the surrounding tissues. In the lumen, mass transport equations including convection and diffusion were used to simulate NO distribution, where scavenging reaction of NO is included (Eq. (2)).

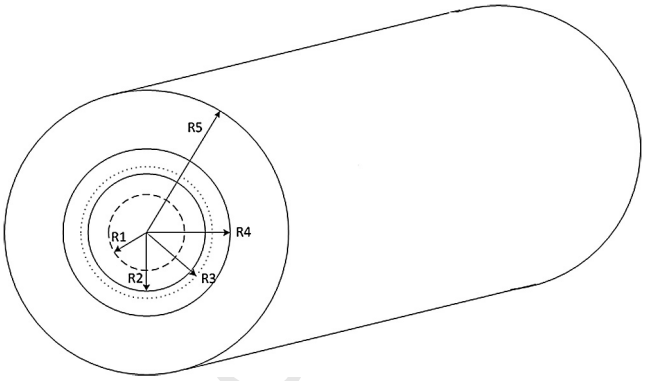

Fig. 1 – A schematic diagram of the model geometry. It includes a RBC rich core ($0 < r < R1$), RBC poor layer ($R1 < r < R2$), endothelium layer ($R2 < r < R3$), vascular wall ($R3 < r < R4$) and tissue ($R4 < r < R5$).

$$\begin{cases} \rho(u\cdot\nabla)u = \nabla\cdot(-p + \mu(\nabla u + (\nabla u)^T) \\ \rho\nabla\cdot(u) = 0 \end{cases} \quad (1)$$

$$\nabla\cdot(-D\nabla C_{NO}) + u\cdot\nabla C_{NO} = R \quad (2)$$

where u is the fluid velocity vector, p is the pressure, D is the diffusion coefficient of NO, and R is the reaction rate of NO.

The production rate of NO was assumed to be proportional to wall shear stress.

$$R_{NO} = R_{ref}\frac{\tau_w}{\tau_{ref}} \quad (3)$$

where the reference NO rate R_{ref} is 150 μmol/L/s, and the reference WSS is 24 dyn/cm^2 [5,10].

Diffusion and consumption reaction equations were used to simulate NO distribution in the vascular wall and tissue. (There is no convection in the wall and tissue) (Table 1). Q2

$$\nabla\cdot(-D\nabla C_{NO}) = R \quad (4)$$

NO can react with oxygen, hemoglobin, myoglobin and other receptors in cells [11]. The consumption of NO influences its concentration distribution. In the lumen, NO is scavenged by hemoglobin in the RBCs. The scavenging rate of NO was treated as a first-order rate reaction.

$$R = -\lambda C_{NO} \quad (5)$$

where λ stands for the NO scavenging rate. NO scavenging rate in the tissue and the vascular wall was set as 1(s^{-1}). Because of the low reaction rate, the auto-oxidation reactions between NO and O_2 was neglected. The scavenging rate by hemoglobin was determined by the hematocrit.

$$\lambda_{rbc}(r) = \lambda_{rbc\_45}\cdot\frac{H(r)}{0.45} \quad (6)$$

In a small vessel, RBC aggregates in the core. The radial hematocrit function $H(r)$ was represented by a linear (Eq. (7)) or a step function (Eq. (8)).

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