THE PRESENCE OF RED BLOOD CELLS IN THE PLASMA LAYER INFLUENCES NITRIC OXIDE AND O_2 TRANSPORT

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Abstract: Using computer modeling, we studied the effects on nitric oxide (NO) and oxygen (O_2) transport in the microcirculation when a small number of red blood cells (RBCs) are present in the outer plasma layer of the bloodstream, as reported in the literature [3]. The model contains six concentric layers: the RBC-rich core, the plasma layer containing a small number of RBCs, the endothelial surface layer (ESL, also known as the glycocalyx) [2], [6], the endothelium, the vascular wall, and the surrounding tissue. Our results indicate that the presence of RBCs in the plasma layer causes a significant decrease in NO in the endothelium and in the vascular wall. Only a small increase in endothelial and vascular wall O2 is suggested by the simulations.

The Model

The model geometry is shown in Figure 1.

General mass transport equations in a cylindrical arteriolar segment were used to calculate radial and axial gradients for NO and O_2 in each of these layers.

$$\begin{cases} \dfrac{\partial C_{NO}}{\partial t} = D_{NO}\nabla^2 C_{NO} - \vec{v}\cdot\nabla C_{NO} \pm \sum_{i=1}^{n} R_{NO}{}^{i} \\ \dfrac{\partial C_{O_2}}{\partial t} = D_{O_2}\nabla^2 C_{O_2} - \vec{v}\cdot\nabla C_{O_2} \pm \sum_{j=1}^{m} R_{O_2}{}^{j} \end{cases}$$

where C_{NO} and C_{O_2} represent NO and O_2 concentration respectively, D_{NO} and D_{O_2} represent the diffusion coefficient for NO and O_2 respectively, and $\vec{v}$ represents the blood velocity vector. For both equations, the first term on the right side represents diffusion and the second represents convective transport. The final term is the summation of all reactions, i.e., production (+) or consumption (-) of the corresponding species.

The luminal transport mechanisms of O_2 were assumed to be governed by diffusion and convection, and binding to oxyhemoglobin. The luminal transport mechanisms of NO were assumed to be governed by diffusion and convection and scavenging by hemoglobin.

The glycocalyx was assumed to be a stagnant layer with the same properties as blood plasma. Both NO and O2 diffuse radially and axially through this layer.

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NO production (RNO) by eNOS is dependent on endothelial O2 availability, and the amount of O2 consumed is equal to the amount of NO synthesized, i.e., RO2 = RNO.

NO consumption by the vascular wall and surrounding tissue was assumed to obey a first order reaction

The vessel hematocrit was assumed to be constant in the RBC-rich core and to decrease in the plasma layer, reaching zero at the interface with the ESL. Information regarding the hematocrit profile in the plasma layer is limited [5], [4]. We tested two RBC profiles: in one, we assumed a linear function and in the other, a parabolic function. The parabolic function results in a lower number of RBCs in the plasma layer than with the linear function.

The ESL was assumed to have the same properties as stagnant plasma. NO was assumed to be synthesized in the endothelium and since NO production depends on O_2 availability, the amount of NO produced was set to be equal to the amount of O_2 consumed.

The NO production rate was described by Michaelis-Menten kinetics [1]. Both NO and O_2 are consumed by the vascular wall and the surrounding tissue and the O_2 consumption in these layers was inhibited by NO using modified Michaelis-Menten kinetics. The mass flux at the centerline of the arteriole and at the outermost surface of the tissue cylinder was assumed to be zero for both O_2 and NO, except at the inlet of the bloodstream. A parabolic PO_2 and an exponential C_{NO} radial profiles were assumed at the inlet of the bloodstream. This eliminates the effect of an abrupt boundary change in the numerical computations. The concentrations of NO and the O_2 partial pressure were assumed to be continuous at the interface between layers.

Finite element methods, using FlexPDE 4, (PDESolutions, Antioch, CA), were used to solve the set of coupled non-linear partial differential equations.

Calculations were performed for different velocity profiles, with varying ESL and plasma layer thicknesses, and different NO production rates. We also calculated the relative importance of various mechanisms on the luminal transport of NO.

Results

An example, demonstrating the sensitivity of mean PO_2 and peak NO in the endothelium to changes in plasma layer thickness, and thus in the number of RBCs in the plasma is shown in figure 2.

The simulation used a parabolic flow velocity profile with RNO = 150 μM/s. The glycocalyx thickness was 0.5 μm and the presence of RBCs in the plasma layer was represented by a linear hematocrit profile. Note the significant rise in peak NO and the fall in mean O_2 as the plasma layer thickness increases.

Discussion

RBCs in the bloodstream are the most important NO scavenger, therefore the RBC profile is expected to have a key influence on NO transport. At the same time, the presence of RBCs in the plasma layer near the endothelium has an effect on O2 transport since the RBCs provide an additional source of O2, with an increase in O2 delivery from blood to the surrounding tissue. Our results indicate that the mean endothelial PO2 for simulations with RBCs in the plasma layer is higher than without RBCs. At the same time, the elevated availability of O2 in the endothelium increases NO production. However, since RBCs in the plasma layer also act as NO scavengers, the net effect is to significantly decrease the bioavailability of NO in the surrounding tissue. Our computer simulations suggest that the presence of RBCs in the plasma layer causes a significant decrease in NO in the endothelium and in the vascular wall while resulting in only a small increase in endothelial and vascular wall O2. We conclude that the presence of RBCs in the plasma has a much larger effect on NO than on O2 transport.

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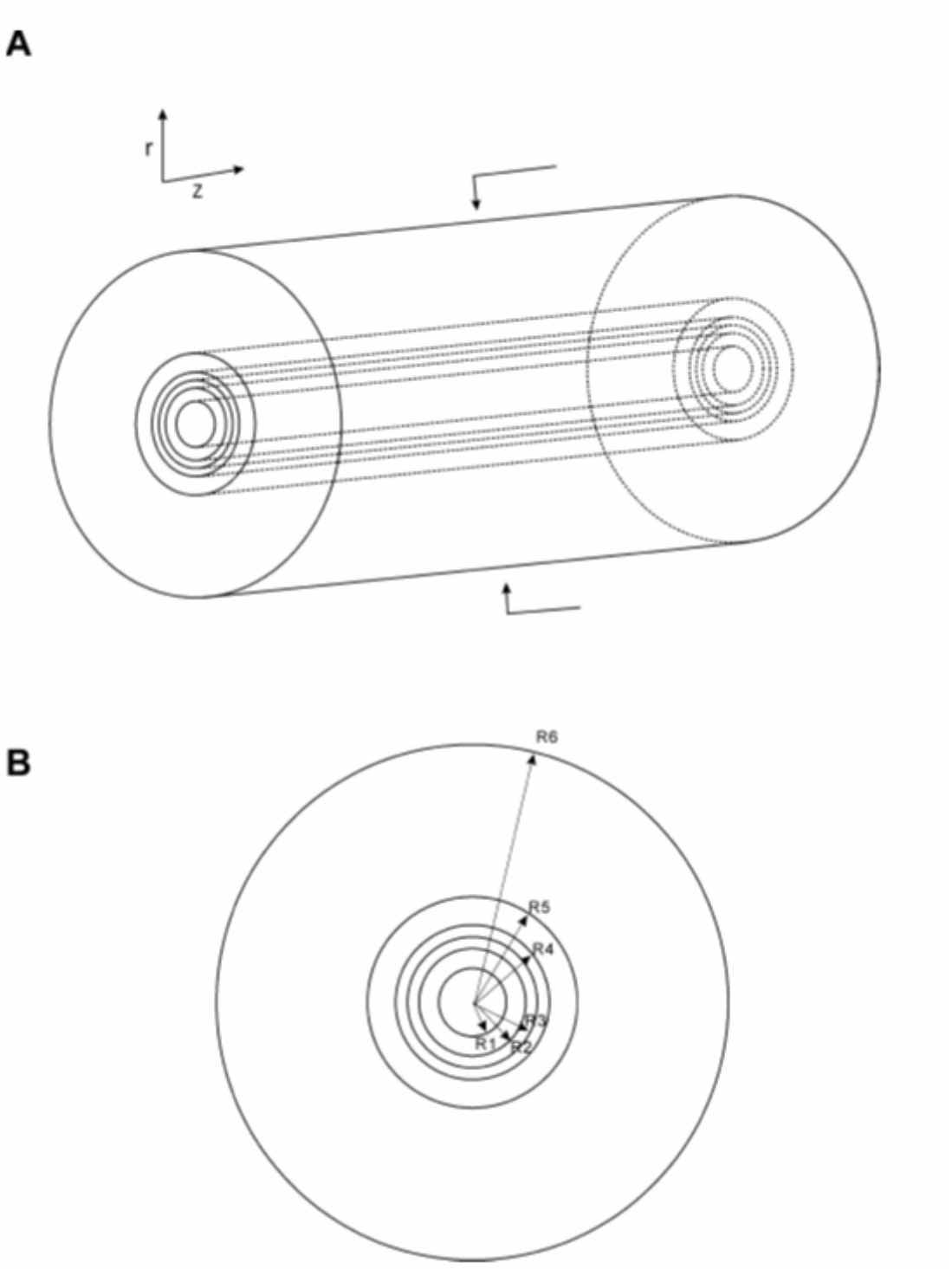

Figure 1: Model geometry. A: Side view of the 250 µm long tissue cylinder; B: Cross-sectional view: RBC-rich core (0<r<r1), RBC-poor boundary layer (r1<r<r2), endothelial surface layer (ESL or glycocalyx layer, r2<r<r3), endothelium (r3<r<r4), vascular wall (r4<r<r5) and tissue (r5<r<r6).

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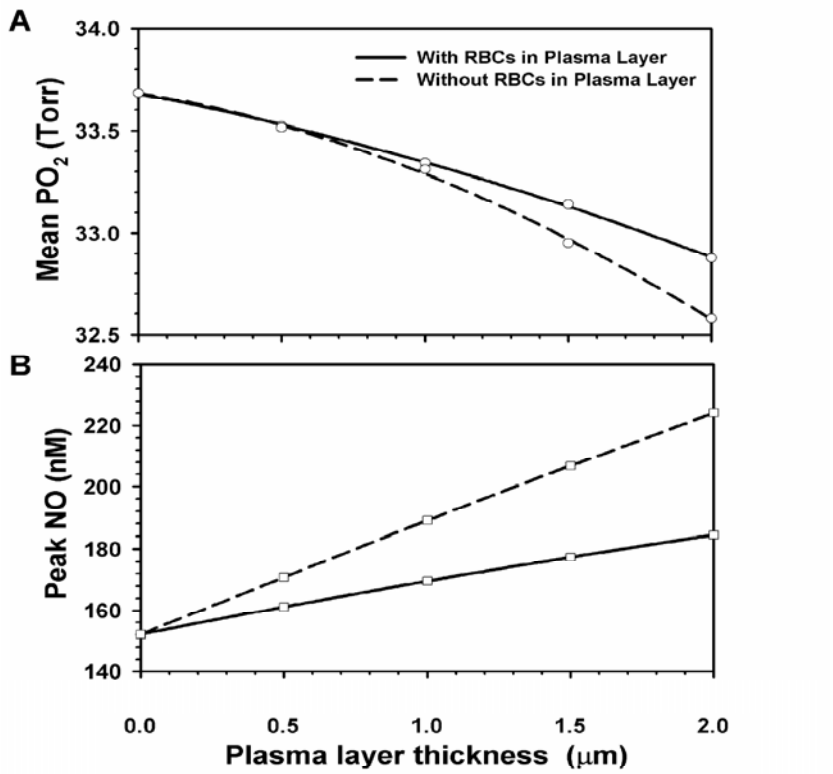

Figure 2: An example comparing the Peak NO and mean PO_2 with and without red blood cells in the plasma layer as a function of the thickness of the glycocalyx layer

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