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A computational model of oxygen delivery by hemoglobin-based oxygen carriers in three-dimensional microvascular networks

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Abstract

A detailed computational model is developed to simulate oxygen transport from a three-dimensional (3D) microvascular network to the surrounding tissue in the presence of hemoglobin-based oxygen carriers. The model accounts for nonlinear O_2 consumption, myoglobin-facilitated diffusion and nonlinear oxyhemoglobin dissociation in the RBCs and plasma. It also includes a detailed description of intravascular resistance to O_2 transport and is capable of incorporating realistic 3D microvascular network geometries. Simulations in this study were performed using a computer-generated microvascular architecture that mimics morphometric parameters for the hamster cheek pouch retractor muscle. Theoretical results are presented next to corresponding experimental data. Phosphorescence quenching microscopy provided PO_2 measurements at the arteriolar and venular ends of capillaries in the hamster retractor muscle before and after isovolemic hemodilution with three different hemodilutents: a non-oxygen-carrying plasma expander and two hemoglobin solutions with different oxygen affinities. Sample results in a microvascular network show an enhancement of diffusive shunting between arterioles, venules and capillaries and a decrease in hemoglobin's effectiveness for tissue oxygenation when its affinity for O_2 is decreased. Model simulations suggest that microvascular network anatomy can affect the optimal hemoglobin affinity for reducing tissue hypoxia. O_2 transport simulations in realistic representations of microvascular networks should provide a theoretical framework for choosing optimal parameter values in the development of hemoglobin-based blood substitutes.

Keywords: HBOC; Oxygen diffusion; Microcirculation; Blood substitutes

1. Introduction

The microvasculature is the site of oxygen transport to tissue and regulation of local blood flow, and therefore has been studied extensively. Motivated by experimental observations in skeletal muscle, Krogh (1919) presented a simple mathematical model for oxygen transport in capillary-perfused tissue. The model assumed uniformly spaced parallel capillaries, each receiving the same convective O_2 supply and delivering O_2 to the same amount of tissue. The uniformity of the capillary/tissue configuration allowed a single capillary and the surrounding 'tissue cylinder' to be considered; several other simplifying assumptions then made an exact solution possible. The Krogh model has provided many valuable insights into O_2 transport; however, over the last two decades it has been substantially extended to include many physiologically important aspects of microvascular O_2 delivery. In particular, it is now known that the complexity of microvascular geometry and hemodynamics (Pittman, 1995), as well as blood transport properties (Hellums et al., 1996; Popel et al., 2003), can significantly affect O_2 delivery to tissue.

Given the physiological importance of microvascular O_2 delivery, it is of interest to obtain a better quantitative understanding than is possible with the Krogh model.

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However, the complex nature of microvascular oxygen transport has posed difficulties. Experimentally, it has been difficult to measure the main quantity of interest, the tissue O_2 concentration (or partial pressure, PO_2), in three dimensions with a micron resolution. This has motivated theoretical work to enable calculation of tissue PO_2 distributions (Popel, 1989). Modeling studies in skeletal muscle have shown the importance of many features neglected in the Krogh model, including heterogeneity of parallel capillary spacing (Hoofd and Turek, 1996), heterogeneity of capillary convective O_2 supply (Ellsworth et al., 1988; Popel et al., 1986), diffusive shunting between capillaries (Ellsworth et al., 1988; Wieringa et al., 1993), capillary tortuosity and anastomoses (Goldman and Popel, 2000), interactions between capillaries and arterioles (Secomb and Hsu, 1994), and intravascular transport resistance (Federspiel and Popel, 1986). In addition, it is known that O_2 transport from pre- and post-capillary vessels (arterioles and venules) can be significant in resting muscle (Kuo and Pittman, 1988; Swain and Pittman, 1989). Therefore, these features are desirable for realistic modeling of O_2 transport in skeletal muscle, as well as in other tissues (e.g., brain (Hudetz, 1999; Kislyakov and Ivanov, 1986), heart (Beard and Bassingthwaighte, 2001; Beard et al., 2003; Wieringa et al., 1993), tumors (Secomb et al., 1993, 2004)).

This need for a high degree of realism is particularly great when situations of relatively low O_2 supply are considered, which is generally the case for applications of blood substitutes (Winslow, 2002). Hemoglobin-based oxygen carriers (HBOC) with different properties (i.e., oxygen affinity, molecular size, NO reactivity) have been developed and hold promise as blood substitutes. Diaspirin cross-linked hemoglobin (DCLHb), for example, is a first-generation artificial oxygen carrier that has O_2 affinity similar to the erythrocytic hemoglobin ($P_{50} = 32$ mmHg; Hill coefficient = 2.4). 3261BR on the other hand, is a genetically cross-linked human hemoglobin that was made by recombinant methods to have a higher O_2 affinity ($P_{50} = 14.6$ mmHg; Hill coefficient = 2.15). However, at this point the optimal values for the design parameters of these products (including their affinity for O_2) have not been established and theoretical studies can assist in this effort.

The purpose of this paper is to extend a previously described mathematical/computational model (Goldman and Popel, 1999, 2000, 2001; Goldman et al., 2004; Popel et al., 2003) so that it can describe oxygen delivery to tissue in the presence and absence of plasma-based hemoglobin. The current work modifies the original model by the addition of arterioles and venules to the geometric component and the addition of plasma hemoglobin to the blood flow and O_2 transport components. This work also contains an approximate derivation of intravascular O_2 transport resistance in the presence and absence of blood substitutes that agrees with, but is much simpler to use than, full-scale intravascular transport calculations. Thus, in this study, we present the methodology for the development of a computational model that can describe O_2 transport in macroscopic tissue volumes after transfusion of HBOC. The study also presents sample results of blood flow and O_2 transport in muscle. Representative theoretical simulations are presented next to corresponding experimental data in three hemodilution scenarios from previous studies. Experimental measurements of PO_2 in the arteriolar and venular end of capillaries from hamster cheek pouch retractor muscle are reported. Sample simulations are also presented at increased O_2 consumption rate that yields hypoxic tissue regions. The model represents a significant advance in theoretical capabilities for studying microvascular O_2 transport, especially when blood substitutes are involved.

2. Methods

Microvascular network: Three-dimensional (3D) microvascular networks from different tissues have been reconstructed using a number of different methods such as scanning electron micrographs of corrosion casts or intravital confocal microscopy (Secomb et al., 2004). In skeletal muscles, most capillaries run approximately parallel to muscle fibers, allowing the construction of a computer-generated approximation of the vascular network by random placement of capillaries around cylindrical muscle fibers of hexagonal arrangement. The computer-generated network in this study was restricted to fit morphological tissue parameters such as fiber diameter, capillary length, density and tortuosity, and number of anastomoses per capillary length (Appendix A). Fig. 1 depicts a network construction representing a tissue block of striated muscle containing capillaries and the supplying arterioles and draining venules. The network is based on morphological parameters for the hamster cheek pouch retractor muscle, which include muscle fibers of 40 μm diameter (Bennett et al., 1991); average arteriole-to-venule length of 400 μm (Dong, 1997; Ellsworth et al., 1988); capillary density (CD) of 1200/mm^2 (Dong, 1997; Ellsworth et al., 1988); 10% tortuosity and 11 anastomoses per tissue module. A tissue module is defined as the tissue block containing capillaries supplied by a single arteriole. For the particular tissue, a module contains an average of approximately 12 capillaries (Berg and Sarelius, 1995). We define a unit tissue block of size $100 \times 100 \times 800$ μm that contains capillaries from two modules feeding arterioles and draining venules. This arrangement allows periodic boundary conditions to be applied in the entrance and exit of the unit tissue block. In the network presented in Fig. 1, the arteriole is placed in the middle of two venules which generates two equidistant modules of approximately $100 \times 100 \times 400$ μm. An alternative arrangement was also constructed with distances between arteriole and neighboring venules 325 and 475 μm, (Fig. 8A).

Network hemodynamics: Network discharge hematocrit (H_D) and blood flow (Q) distribution are estimated from