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Modeling neutrophil transport in pulmonary capillaries

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ABSTRACT

Neutrophils can be retained in the pulmonary microvasculature due to their low deformability, resulting in having a higher concentration there than in the systemic circulation, even in normal lungs. It is thought that this high concentration of the cells facilitates their effective recruitment to sites of inflammation. Thus, in order to understand their role in the immune system in the lungs, where blood comes in contact with outer air via thin septa of alveoli, it is important to clarify their flow characteristics in the pulmonary capillary bed. However, in contrast to erythrocytes in systemic capillaries, little research has been performed on the flow of neutrophils in pulmonary capillaries. This may be partly because no complete rheological model of the cell has been established yet, and partly because pulmonary capillaries are very short and closely interconnected, forming a complicated three-dimensional network, in addition to difficulty in *in vivo* experimental observations. Moreover, the neutrophils change their mechanical properties and show active motion in response to some chemoattractants. In this article, various proposed rheological models of the neutrophil, flow models of a cell through a single capillary segment, and alveolar capillary network models are introduced, aiming at the numerical simulation of neutrophil transport in the pulmonary microvasculature.

1. Introduction

It is well known that blood is a solid–liquid two-phase fluid which consists of liquid plasma and solid blood cells. The blood cells are of several types: erythrocytes (red blood cells), leukocytes (white blood cells) and platelets. Since erythrocytes account for most of the blood cells, they strongly determine the rheological characteristics of blood. In human blood, the number of leukocytes is about 1/1000 of that of erythrocytes (Fung, 1993), ranging from 6000 to 9000 cells/μl according to the literature (Table 1). Constituting such a minority of the blood cell population, they have little influence on the rheological properties of blood, but play a major role in the immune system for host defense.

Leukocytes are roughly classified into five types: neutrophils, eosinophils, basophils, lympocytes and monocytes, neutrophils being the most common. The number of neutrophils is 60–70% of the total number of leukocytes (Mashima, 1996), or 5400 cells/μl on average (range 3000–6000 cells/μl) (Mazumdar, 1992). They increase in number in the case of acute infection and exhibit amoeba-like migration resulting in accumulation at the sites of inflammation. Individual leukocytes can obstruct capillary blood flow, the so-called leukocyte plugging phenomenon (Nicoll and Webb, 1946; Schmid-Schönbein, 1987), and in the case of an abrupt increase of neutrophils due to some diseases such as acute leukemia, blood flow through a microvascular bed is severely compromised due to the numerous occlusions (Braide et al., 1984; Blixt and Bagge, 1984; Fenton et al., 1985).

Many reports have mentioned that neutrophils are far less deformable than erythrocytes, and thus, more than a half (50–80%) of them can be delayed in passing through the pulmonary capillary bed (Hogg, 1987; Gebb et al., 1995). For their passage through 40–100 capillary segments from an arteriole to a venule (Staub and Schultz, 1968; Doerschuk, 2000; Huang et al., 2001), the transit time of individual neutrophils widely varies from <2 s to >1200 s, while such passage of erythrocytes requires only a few seconds (Lien et al., 1987; Hogg et al., 1988, 1994). Thus the resultant concentration of neutrophils in the pulmonary capillary bed exceeds that in the large vessels of the systemic circulation by a factor of 20–60 (Doerschuk, 2000), 40–80 (Hogg and Doerschuk, 1995) or 60–100 (Hogg et al., 1994) due to their low deformability. Hence, the pulmonary capillary bed can be considered to be a neutrophil reservoir or marginated pool for the defense of the host against infection (Hogg et al., 1994; Schwab et al., 2003), in contrast to the systemic circulation where the marginated pool resides essentially within the postcapillary venules (Kubes et al., 1995).

The function of the lung is to oxygenate the blood and to remove carbon dioxide. The lung consists of an aggregate of about 300 million small alveoli, whose diameter is 250 μm ± 5–10%, so that the blood–gas interfacial area becomes very large (West, 1977). In an adult human lung, the pulmonary capillary blood–gas exchange

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Table 1
Number of leukocytes and neutrophils in blood

Number of leukocytes	Number of neutrophils	Reference
7000 cells/μl	60–70% of leukocytes	Mashima (1996)
6000–8500 cells/mm^3 (=cells/μl)		Oka (1984)
9000 cells/μl (range 4000–11,000 cells/μl)	5400 cells/μl (range 3000–6000 cells/μl)	Mazumdar (1992)[a]

[a] The unit used in this book is "cells/ml." However, it should be "cells/μl.".

area is in the order of 60 m^2 (Hogg, 1987) or 70 m^2 (Fung, 1997). The pulmonary capillary segments surrounding individual alveoli are highly interconnected to form a dense network, and the capillary network is identified with the alveolar septa. The capillaries of single-layered endothelial cells are held between alveolar respiratory epithelial cell layers of alveolar sacs together with the interstitium to form an interalveolar septum, the thickness of the membrane that separates the blood from the air being less than 1 μm (Fung, 1997). Since the membranes are so thin, they serve not only as a window for gas exchange, but can also act as a window for invasion of the host by pathogenic substances. As previously mentioned, however, the highly concentrated neutrophils are effectively recruited to the sites of inflammation. Therefore, it is essential to determine how neutrophils travel in pulmonary capillaries, not only in order to understand microcirculatory flow dynamics, but also to understand the functions and behavior of neutrophils in the immune system.

2. Neutrophil model

Rheological studies of neutrophils are essential for the modeling of their flow through narrow capillaries, especially their entrance into and release from capillaries in the case of large deformation. Much work has been done over the years on designing a correct rheological model for the neutrophil together with elucidation of its structural characteristics and properties. However, measuring deformation and movement of the neutrophils *in vivo* is a difficult task (Hogg et al., 1994), and our understanding of the mechanical behavior of neutrophils has been mostly obtained from *in vitro* experiments or numerical simulations. For experiments, micropipette aspiration and cell indentation by a flexible cantilever of atomic force microscopy (AFM) or by a microbead have been widely used for the development of a rheological model and quantification of the mechanical properties of neutrophils, and numerical reproduction of these experiments have also been performed. Filtration of the cells is another technique for such quantification (e.g., Downey and Worthen, 1988; Inano et al., 1992), although this technique seems to be mainly used for the qualitative investigation of the difference in permeability of the cells due to the effect of some chemoattractants.

The passive neutrophils were initially modeled as a homogeneous sphere composed of a standard viscoelastic material (Fig. 1(a)), which gave the overall shape and time-course of deformation of the cells during micropipette aspiration experiments (Bagge et al., 1977; Schmid-Schönbein et al., 1981). The elastic element G_1 in Fig. 1(a) is thought to impart shape memory that enables the cell to recoil to its resting shape. This model is suitable for data

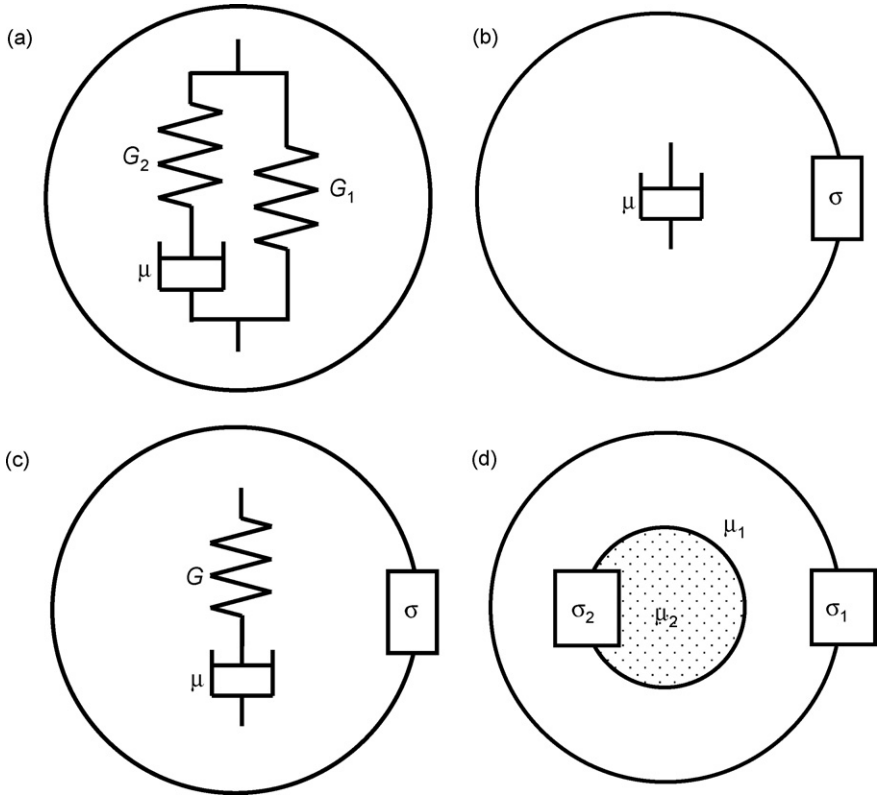

Fig. 1. Four representative rheological models of passive neutrophil. Here, G is the elastic element and μ is the viscous element of the cell interior, and σ is the cortical tension. (a) Standard viscoelastic model, (b) Newtonian liquid-drop model, (c) Maxwell fluid model and (d) compound drop model.