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Predicting bifurcation angle effect on blood flow in the microvasculature

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ABSTRACT

Since blood viscosity is a basic parameter for understanding hemodynamics in human physiology, great amount of research has been done in order to accurately predict this highly non-Newtonian flow property. However, previous works lacked in consideration of hemodynamic changes induced by heterogeneous vessel networks. In this paper, the effect of bifurcation on hemodynamics in a microvasculature is *quantitatively* predicted. The flow resistance in a single bifurcation microvessel was calculated by combining a new simple mathematical model with 3-dimensional flow simulation for varying bifurcation angles under physiological flow conditions. Interestingly, the results indicate that flow resistance induced by vessel bifurcation holds a constant value of approximately 0.44 over the whole single bifurcation model below diameter of 60 μm regardless of geometric parameters including bifurcation angle. Flow solutions computed from this new model showed substantial decrement in flow velocity relative to other mathematical models, which do not include vessel bifurcation effects, while pressure remained the same. Furthermore, when applying the bifurcation angle effect to the entire microvascular network, the simulation results gave better agreements with recent *in vivo* experimental measurements. This finding suggests a new paradigm in microvascular blood flow properties, that vessel bifurcation itself, regardless of its angle, holds considerable influence on blood viscosity, and this phenomenon will help to develop new predictive tools in microvascular research.

1. Introduction

Understanding the hemodynamics in the human microvasculature has long been a subject of study. In the middle twenties, several experiments *in vitro* and *in vivo* were performed to measure the blood viscosity in various tube diameters. As a result, it was found out that the apparent viscosity in a microvessel is highly dependent on the vessel diameter. This phenomenon, known as the Fåhræus-Lindqvist effect (Fåhræus and Lindqvist, 1931), changed the general concept of blood viscosity as a material property to be a system property. Meanwhile, in the experiments *in vivo* (Lipowsky et al., 1978, 1980), it was reported that *in vivo* viscosity is relatively high when compared to the experimental results obtained *in vitro*, especially at diameters below 20 μm. In subsequent years, the *in vivo* viscosity law (Pries et al., 1990, 1994) was developed by using indirect network-based approach. Also, it was discussed about the possible reasons for the discrepancy between apparent viscosity of blood *in vitro* and *in vivo* (Pries et al., 1994; Secomb and Hsu, 1997). Related to the difference, Pries et al. suggested that Endothelial Surface Layer (ESL) is the main source of discrepancy, and proposed a modified *in vivo* viscosity law considering its effects (Pries and Secomb, 2005). More recently, there have been various attempts to develop more advanced experimental techniques using Microviscometry and Doppler Optical Coherence Tomography, and to apply them for measuring microvascular hemodynamic flow properties *in vivo* (Long et al., 2004; Gagnon et al., 2015). Further details on microvascular hemodynamics are available in many excellent review articles (Pries et al., 1996; Pries and Secomb, 2008; Secomb and Pries, 2013; Sochi, 2015).

On the other hand, direct experimental measurement of pressure drops in individual microvessels is still challenging, and detailed validation of the theoretical viscosity laws remains to be achieved. For this reason, numerical simulations of microvascular hemodynamics started to be considered as a feasible alternative, particularly due to its robustness, accuracy, and non-invasive character. At network level, numerical experiments (Pries et al., 1990) were conducted *via* linear analysis by combining experimentally measured topological data of a microvascular network with the Poiseuille's law (Poiseuille, 1846). It was extended to the scope of network based numerical simulation by developing an indeterminacy resolving algorithm for cases with incomplete boundary conditions (Fry et al., 2012). A number of studies were conducted at microscale level by computationally modelling individual red blood cells (RBCs) in order to study its physical properties and influence of cell to cell interaction in microvascular blood flow (Bagchi, 2007; Fedosov et al., 2011; Secomb, 2011; Lee et al., 2013; Katanov et al., 2015). In parallel with numerical simulations, several researchers attempted to establish theoretical models for microvascular networks (Frame and Sarelius, 1993; Kassab et al., 1993; Zamir, 1999; Takahashi et al., 2009; Lee et al., 2014), and reproduce them computationally without the need to carry out elaborate experiments. J. A. Adam, in particular,

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described the mathematical relationship between bifurcation angles and radii of bifurcating blood vessels (Adam, 2011).

Previous works, however, lacked in consideration of three-dimensional (3D) hemodynamic effects in multiple connections of microvessel segments. Majority of the studies were either based on a single microvascular tube or on the assumption that the microvascular network is a collection of individual vessel segments without complex geometries such as bifurcating regions. While there have been both experimental (Stehbens, 1975) and numerical (Perktold et al., 1991; Tadjfar, 2006; Li et al., 2012; Razavi and Shirani, 2013; Jones, 2014) researches to understand the effect of vessel bifurcation on blood flow, no clear discussions were made regarding the effect of bifurcation angles on microvascular blood flow at such a low speed. Previous works were only focused on the accurate measurement of blood viscosity *in vivo*, calculated from the measured flow velocities and pressure drops. However, considering that blood viscosity is a system property influenced by microvasculature geometry, its effects must be analysed in order to further understand and also to improve the *in vivo* viscosity law. In this paper, 3D *in silico* model is used to quantitatively capture the effect of bifurcation in the microvasculature under physiological flow conditions. The resistance at junctions of bifurcating microvessel is determined by combining detailed Computational Fluid Dynamics (CFD) with a simple mathematical model. The blood flow considering bifurcation effect in the microvasculature is fully discussed with the *in vitro* and *in vivo* viscosity laws, and the recent experimental observations.

2. Methods

2.1. Modelling of 1D and 3D single bifurcation microvessels

Perfectly symmetric bifurcation was assumed, and the vessel diameters were determined by (Sherman, 1981)

$$d_1^{\gamma} = d_2^{\gamma} + d_3^{\gamma}. \tag{1}$$

Here, d_1 is the parent vessel diameter, $d_{2,3}$ are the daughter vessel diameters, and γ is the bifurcation exponent. In this study, $d_{2,3}$ are effectively identical due to symmetric bifurcation, and d_1 was set to be 60 μm. $\gamma = 3$ was used based on the Murray's law (Murray, 1926) so as to mimic the naturally optimised microvessels. The lengths of each vessel segments were determined based on length to diameter ratio (β):

$$\beta = L/d \tag{2}$$

This ratio varies depending on numerous factors including species, their health condition and vessels' functionality. Due to varying β from organ to organ (Zamir, 1999; Yang and Wang, 2013; Heinzer et al., 2008; Hughes et al., 2009; Lauwers et al., 2008), two cases were considered: $\beta = 7$ and 25. Finally, four different bifurcation angles (ψ) were considered in this study: 30, 60, 90, and 120 degrees. For 3D modelling, each vessel tubes were located equidistant from a fixed point in the bifurcating region (*e.g.* origin) such that the geometric variation in the bifurcating region is minimised for different angles.

2.2. Blood flow calculation in 1D single bifurcation model

Each vessel segment followed the Poiseuille's law (Poiseuille, 1846). The volumetric flow rate, Q, depends on tube geometry and fluid viscosity for a given driving pressure drop, ΔP:

$$Q = \frac{\pi d^4}{128\mu L}\Delta P \tag{3}$$

where d is the tube diameter, L is the tube length, and μ is the dynamic viscosity of the fluid flowing through the tube. The sum of volumetric flow rate of the parent and two daughter vessels at the bifurcation junction should be zero due to the conservation of mass, $\Sigma Q_i = 0$. Based on the Poiseuille's law and conservation of mass, the pressure at the junction and three flow rates for one parent and two daughter vessel segments were determined.

2.3. Blood flow simulation in 3D single bifurcation model

The blood flow in 3D single bifurcation model was computed by using ANSYS Fluent. All the boundary conditions were the same with the mathematical model for single bifurcation. Its built-in mesh generator was used, and the flow was assumed to be incompressible, single phase, and homogeneous without considering any particles or deformable bodies such as the RBCs. Velocities were extracted from each vessel with constant diameter by taking the average velocity values from the whole volume of the corresponding vessels. See also SI.

2.4. Boundary conditions for single bifurcation models

Only the pressure values were defined at both the inlet and the outlet. Physiological pressure drop of 15 mmHg was applied from the inlet to the outlet of the 1D and 3D single bifurcation models. This pressure boundary condition was set based on the *in vivo* observation on pressure drop in the diameter range of artery to capillary vessels (Pries et al., 1992, 1994). Refer to Fig. 1A for schematic view of the boundary conditions. Here, the *in vitro* viscosity law (Pries et al., 1994) at the parent vessel was used for parent and daughter vessel segments (See SI for full viscosity model). For more realistic viscosity modelling, it is essential to determine the viscosity as a function of diameter, shear rate and hematocrit. The viscosity in the 1D and 3D single bifurcation models was fixed at a certain value based on the diameter of parent vessel since they were utilised only for determining the flow resistance by bifurcation angle in the viewpoint of fluid dynamics. The hematocrit for determining the blood viscosity was fixed at 0.45.

2.5. Calculation of the bifurcation angle induced flow resistance, $k_R\psi$

Blood flow in 1D single bifurcation model was simply calculated with the Poiseuille's law and the conservation of mass. The solution of this 1D mathematical model is not changed even if the bifurcation angle is changed. Hence, the solution in 1D single bifurcation case was set as a reference of blood flow at a single bifurcation without loss of energy during the bifurcation process. Unlike the 1D model case, blood flow in 3D single bifurcation model is changed by varying the bifurcation angle. From the difference between the flow solutions in the 1D and 3D models, the bifurcation angle induced flow resistance can be quantitatively estimated. Since the flow resistance by bifurcation angle causes reduction of blood flow, the following modified Poiseuille's law is suggested:

$$Q = \frac{\pi d^4}{128\mu L}(1 - k_R\psi)\Delta P \tag{4}$$

where k_R is the flow resistance coefficient arising from vessel bifurcation and ψ is the local bifurcation angle. If the vessel of interest is a straight vessel without bifurcation, k_R should be zero, effectively becoming the Poiseuille's law. However, if the vessel segment of interest is a parent vessel with two daughter vessels (vessel with bifurcation), the pressure drop for the parent vessel will be altered when compared to a straight vessel with the same diameter and length. This is due to the fact that the blood flow is impeded near the bifurcation producing certain level of resistance, which is related to the bifurcation angle. Similarly, the inlet flow in the daughter vessel is also changed due to the bifurcation process. Additional flow resistance effectively implies increment in viscosity, and hence decrement in flow conductance. By comparing the flow solutions from the 1D mathematical model with the solutions from the 3D computational model with single bifurcation, the effect of vessel bifurcation was