Microvascular Research 106 (2016) 14–23

Contents lists available at ScienceDirect

Microvascular Research

journal homepage: www.elsevier.com/locate/ymvre

# Recovery of cell-free layer and wall shear stress profile symmetry downstream of an arteriolar bifurcation

Swe Soe Ye [a], Meongkeun Ju [a], Sangho Kim [a,b,*]

[a] Department of Biomedical Engineering, National University of Singapore, 9 Engineering Drive 1, Singapore 117575, Singapore
[b] Department of Surgery, National University of Singapore, 1E Kent Ridge Road, Singapore 119228, Singapore

ARTICLE INFO

*Article history:*
Received 27 November 2015
Revised 23 February 2016
Accepted 7 March 2016
Available online 9 March 2016

*Keywords:*
Flow partitioning
Arteriolar bifurcation
Cell-free layer
Asymmetric flow

ABSTRACT

Unequal RBC partitioning at arteriolar bifurcations contributes to dissimilar flow developments between daughter vessels in a bifurcation. Due to the importance of the cell-free layer (CFL) and the wall shear stress (WSS) to physiological processes such as vasoregulation and gas diffusion, we investigated the effects of a bifurcation disturbance on the development of the CFL width and WSS in bifurcation daughter branches. The analysis was performed on a two-dimensional (2-D) computational model of a transverse arteriole at three different flow rates corresponding to parent branch (PB) pseudoshear rates of 60, 170 and 470 $s^{-1}$, while maintaining a 2-D hematocrit of about 55% in the PB. Flow symmetry was defined using the statistical similarity of the CFL and WSS distributions between the two walls of the vessel branch. In terms of the flow symmetry recovery, higher flow rates caused larger reductions in the flow symmetry indices in the MB and subsequently required longer vessel lengths for complete recovery. Lower tube hematocrits in the SB led to complete symmetry recovery for all flow rates despite the higher initial asymmetry in the SB than in the MB. Arteriolar bifurcations produce unavoidable local CFL asymmetry and the persistence of the asymmetry downstream may increase effective blood viscosity which is especially significant at higher physiological flow rates.



## 1. Introduction

The microvascular network consists of successive bifurcations with corresponding reductions in vessel diameters that optimize the surface area for gas exchange while maintaining low systemic resistance for the pumping heart (Murray, 1926b). In this network architecture, the distribution of plasma and cellular components of blood are often non-uniform and this phenomenon has been termed 'plasma-skimming', 'hematocrit-separation' or 'RBC-partitioning'. Notably, arteriolar bifurcations often result in an uneven RBC-flux fraction biased towards one daughter. This bias has been determined by experimental studies to be related to the total flow fraction by a non-linear function that depends on morphological and hydrodynamical conditions at the branch point (Carr and Wickham, 1991; Dellimore et al., 1983; Enden and Popel, 1994; Fenton et al., 1985; Klitzman and Johnson, 1982; Pries et al., 1989; Schmid-Schonbein et al., 1980). Computational studies have also contributed to the research by examining the dynamics of cell–cell interactions and cellular migration at arteriolar bifurcations (Barber et al., 2011; Secomb et al., 2007) and the role of parameters difficult to define in experiments, such as the parent vessel tube hematocrit, RBC stiffness and aggregability (Xiong and Zhang, 2012; Yin et al., 2013).

While these early studies have given us better appreciation of the parametric factors leading to heterogeneous RBC-partitioning, little investigation has been made into understanding the developing cell-free layer (CFL) downstream of the bifurcation. Instead, several studies have discussed the symmetry recovery of the hematocrit profile (Carr, 1989; Carr and Xiao, 1995; Pries et al., 1989). The hematocrit profile downstream of a bifurcation was found to have different symmetry recovery rates depending on the flow rate ratio between daughter vessels and the upstream hematocrit profile. Furthermore, longer inter-bifurcation distances generally produced greater symmetry recovery for the hematocrit profile due to more prolonged lateral migration of RBCs. Experimental studies performed by Pries et al. (1989) estimated that the critical vessel length for a recovery of the hematocrit profile symmetry downstream of an arteriolar bifurcation with internal diameters (D) < 40 μm was about 10D distance away from the bifurcation. Numerical simulations performed with RBC dispersion models by Carr and Xiao (1995) likewise estimated the critical vessel length and suggested that based on the inter-bifurcation segment lengths reported in literature, hematocrit asymmetry was prevalent in small arteriole bifurcations. Both studies (Carr and Xiao, 1995; Pries et al., 1989) have shown the direct influence of the hematocrit profile development downstream of a bifurcation on the RBC partitioning in the subsequent bifurcation, but not the influence of flow asymmetries on other important physiological processes such as vasoregulation and gas diffusion. In general, the role of microrheology in these two processes has been understood through

* Corresponding author at: Department of Biomedical Engineering, National University of Singapore, 9 Engineering Drive 1, Block EA #03-12, Singapore 117575, Singapore.
*E-mail address:* bieks@nus.edu.sg (S. Kim).

http://dx.doi.org/10.1016/j.mvr.2016.03.003
0026-2862/

mechanistic concepts of the CFL acting as a gas diffusion barrier (Lamkin-Kennard et al., 2004) and the wall shear stress (WSS) as one of the modulating agents for vessel diameter (Davis et al., 2001). It remains to be investigated however, the extent of similarity between hematocrit profile symmetry recovery and the CFL symmetry, and their relation to WSS patterns downstream of the bifurcations.

The CFL development length as a result of entrance effects was reported to be 8D–15D for vessels with 20–24 μm D in a numerical study by Oulaid and Zhang (2014) and 25D for vessel D ranging 10–100 μm in a separate numerical study by Katanov et al. (2015). However, neither of these numerical studies employed bifurcations as the source of the CFL disturbance nor discussed the effects of the CFL asymmetry on the vessel WSS. Microphotographs of rat cremaster arteriolar bifurcations shown in Fig. 1 and similar images in previous studies (Pries et al., 1989; Secomb et al., 2007) suggest that the positional asymmetry of RBCs in daughter arterioles directly downstream of the bifurcation is a common occurrence and that bifurcations may significantly contribute to the CFL disturbance in arteriolar networks. This is further supported by *in vivo* findings of persistent CFL asymmetry in daughter arteriole segments 2D–6D away from bifurcation sites for rat cremaster arteriolar networks (Ng et al., 2015; Ong and Kim, 2013). Despite the regularity of the bifurcation-induced CFL asymmetry, inter-bifurcation distances that extend beyond the limited focal window of microscopy techniques prevents experimental measurements of the CFL asymmetry over the entire daughter arteriole. Thus, physiological implications of the CFL and WSS symmetry recovery lengths in relation to anatomical inter-bifurcation distances have been difficult to study using experimental methods. In order to circumvent the experimental difficulty and address the existing knowledge gap from theoretical models on the CFL and WSS development in bifurcation flows, we investigated the recovery of CFL and WSS symmetries downstream of a bifurcation found in transverse arteriole networks using a numerically constructed microbifurcation model. By quantifying the spatial developments of the CFL and WSS along the daughter arterioles resulting from a bifurcation, we were able to demonstrate their respective recovery rates under different flow rates.

## 2. Methods

### 2.1. Numerical simulation

Detailed information on the two-dimensional simulation methods utilized in this study can be found in the Supplementary Information section A. In brief, simulation of the RBC transport was achieved with the Lattice Boltzmann Method (LBM) fluid flow model (Guo et al., 2002), our recently developed large deformation discrete RBC model (Ye et al., 2014), and the Immersed Boundary Method (IBM) for the fluid–structure interaction (Peskin, 1977).

### 2.2. Bifurcation model and flow analysis

The bifurcation flow in a transverse arteriole was represented in a computational domain consisting of a 170-μm long parent branch (PB) of 15-μm inner diameter (D), a 160-μm long main daughter branch (MB) of 15-μm D and a 120-μm long side daughter branch (SB) of 10-μm D (see Fig. 2a). In previous experiments performed on rat cremaster muscles, Frame and Sarelius (1993) reported the inter-bifurcation distances to be within ranges of 67–905, 48–714, 48–714 and 188–2144 μm for the 1st, 2nd, 3rd and 4th stages, respectively in transverse arterioles with feed vessel D of 8.5–23.2 μm. A recent study by Ong et al. (2012) reported similar inter-bifurcation distances of 172–663 μm for small vessels with D of 12.5–104 μm. For the sake of computational economy, our model was limited to the region of interest around the 1st stage bifurcation and vessel lengths were representative of the inter-bifurcation distances seen in small arteriole branches.

Three sets of simulations were performed in three flow conditions to achieve PB pseudoshear rates (PSR) of 60 (low flow), 170 (moderate flow) and 470 $s^{-1}$ (high flow) while maintaining a similar feed hematocrit ($H_{PB}$) of about 55% (in the two-dimensional plane) and an approximate MB-to-PB flow fraction ($Q_{MB}$:$Q_{PB}$) of 0.82. The two lower PSRs were chosen to represent the flow conditions found in reduced flow and physiological normal flow as reported in a previous experimental study by Ong and Kim (2013) while the highest PSR represents the higher range of physiological flow reported by Popel and Johnson (2005). The non-equal flow portioning of blood at the bifurcation was chosen to study the flow recovery behavior in daughter arterioles with distinctly different hematocrits. MB was primarily set up to be the RBC-rich daughter while the SB was a plasma-skimming vessel with single-file RBC flow. The PSR and flow rate ratios were achieved by maintaining pressures presented in Table 1. To maintain a constant tube hematocrit of 55% in the parent vessel ($H_{PB}$) and a continuous flow of RBCs at the bifurcation, two regions of RBC simulation were employed in the bifurcation model. As shown in Fig. 2b, a periodic zone in the bifurcation model was assigned at the PB inlet to repeat the RBCs in a periodic fashion within the 60-μm long domain. In this method, parent cells identified by the cell numbers 1 to 10 generated RBC clones (numbered 11 to 72) of themselves every time they passed the periodic boundaries. Clone cells that exited the region of interest (ROI) domain through the outlets of the MB and the SB were removed from the simulation and their cell indices were recycled. The repetition of this cloning and removal process enabled a stable feed hematocrit and continuous RBC flow to be achieved in the ROI domain.

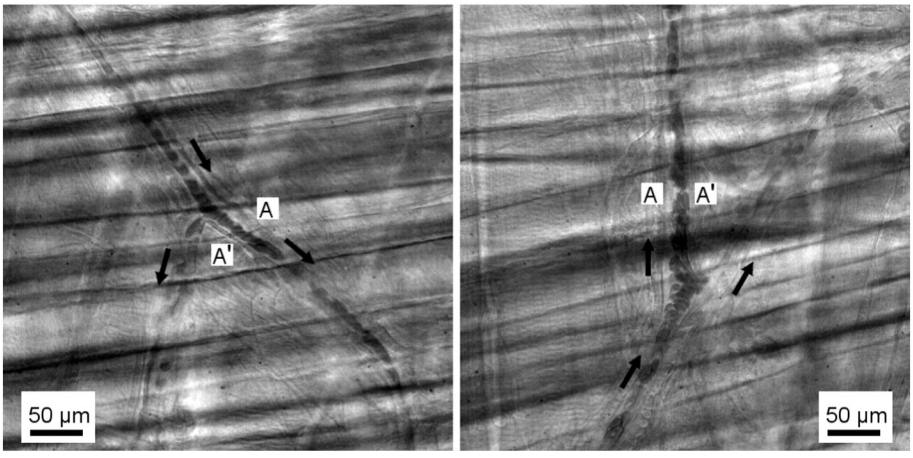


**Fig. 1.** Microphotographs of arteriolar bifurcations in a rat cremaster muscle; arrows indicate the flow direction. Positional asymmetry of RBCs in the daughter vessels can be seen by the differences in plasma layer thickness between vessel walls A′ and A.