Microvascular Research 113 (2017) 40–49

Contents lists available at ScienceDirect

Microvascular Research

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

# Modeling of pulsatile flow-dependent nitric oxide regulation in a realistic microvascular network

Ruofan Wang [a], Qing Pan [b], Wolfgang M. Kuebler [c,e], John K.-J. Li [d], Axel R. Pries [e], Gangmin Ning [a,*]

[a] Department of Biomedical Engineering, MOE Key Laboratory of Biomedical Engineering, Zhejiang University, 38 Zheda Road, Hangzhou 310027, China
[b] College of Information Engineering, Zhejiang University of Technology, 288 Liuhe Road, Hangzhou 310023, China
[c] Keenan Research Centre for Biomedical Science of St. Michael's, University of Toronto, 30 Bond Street, Toronto M5B 1W8, Canada
[d] Cardiovascular Research, Department of Biomedical Engineering, Rutgers University, 599 Taylor Road, Piscataway, NJ 08854, USA
[e] Department of Physiology and Center for Cardiovascular Research, Charité Universitätsmedizin in Berlin, Charitéplatz 1, 10117 Berlin, Germany

ARTICLE INFO

*Article history:*
Received 14 December 2016
Revised 14 April 2017
Accepted 2 May 2017
Available online 03 May 2017

*Keywords:*
Pulsatile flow
Microvascular network
Nitric oxide
Shear stress
Vascular regulation

ABSTRACT

Hemodynamic pulsatility has been reported to regulate microcirculatory function. To quantitatively assess the impact of flow pulsatility on the microvasculature, a mathematical model was first developed to simulate the regulation of NO production by pulsatile flow in the microcirculation. Shear stress and pressure pulsatility were selected as regulators of endothelial NO production and NO-dependent vessel dilation as feedback to control microvascular hemodynamics. The model was then applied to a real microvascular network of the rat mesentery consisting of 546 microvessels. As compared to steady flow conditions, pulsatile flow increased the average NO concentration in arterioles from 256.8 ± 93.1 nM to 274.8 ± 101.1 nM ($P < 0.001$), with a corresponding increase in vessel dilation by approximately 7% from 27.5 ± 10.6% to 29.4 ± 11.4% ($P < 0.001$). In contrast, NO concentration and vessel size showed a far lesser increase (about 1.7%) in venules under pulsatile flow as compared to steady flow conditions. Network perfusion and flow heterogeneity were improved under pulsatile flow conditions, and vasodilation within the network was more sensitive to heart rate changes than pulse pressure amplitude. The proposed model simulates the role of flow pulsatility in the regulation of a complex microvascular network in terms of NO concentration and hemodynamics under varied physiological conditions.



## 1. Introduction

The pulsatility of systemic blood flow, which can be observed in the vast majority of the vasculature from large conduit arteries to small resistance microcirculatory vessels (Gaehtgens, 1970; He and Ku, 1996; Mahler et al., 1979; Seki, 1994), is a physiological characteristic of perfusion and has drawn increasing attention with respect to its effects on microcirculatory function. Pulsatile blood flow has been reported to cause vascular dilation (Pinaud et al., 2006), which consequently benefits tissue perfusion (Baba et al., 2003; Baba et al., 2004; Kim et al., 2005; Konishi et al., 1997). Moreover, dysfunctions of the microcirculation, such as microcirculatory shunting (Mavroudis, 1978), inflammation during and after cardiopulmonary bypass (CPB) (Orime et al., 1999), and multi-organ failure after cardiogenic shock (Orime et al., 1996), could be improved or prevented under pulsatile but not non-pulsatile blood flow conditions, indicating the essential role of pulsatility for microvascular homeostasis and normal microcirculatory function.

Regulation of endothelial nitric oxide (NO) production has been proposed as a potential pathway by which pulsatility may affect microvascular function. Noris et al. (1995) reported increased NO release under pulsatile as compared to non-pulsatile flow in cultured human umbilical vein endothelial cells (HUVECs). Similar results were found in a variety of experiments using different cultured endothelial cells (ECs) (Juffer et al., 2014; Li et al., 2003; Li et al., 2005; Walshe et al., 2005). In *in vivo* experiments in dogs (Nakano et al., 2001; Nakano et al., 2000) and rats (Inamori et al., 2013; Uryash et al., 2009), pulsatile flow significantly increased the concentration of the NO metabolites nitrite/nitrate in plasma. These observations support the conclusion that pulsatile flow may promote NO release. The subsequent increase in NO concentration is generally considered to evoke a relevant increase in vessel diameter by relaxing vascular smooth muscle cells (VSMCs) and thus, to result in blood flow and pressure redistribution in the microvascular network.

Mathematical models are helpful to adequately understand the mechanisms of NO regulation by pulsatility in the microcirculation (Buerk et al., 2011). The majority of mathematical models of NO regulation are based on flow chamber or single vessel experiments and focus on the specific molecular pathways of NO regulation and vascular wall remodeling by use of large numbers of differential equations (Chen et

* Corresponding author at: Department of Biomedical Engineering, Zhejiang University, 38 Zheda Road, 310027 Hangzhou, China.
*E-mail address:* gmning@zju.edu.cn (G. Ning).

http://dx.doi.org/10.1016/j.mvr.2017.05.001
0026-2862/

al., 2007; Fadel et al., 2009; Koo et al., 2013; Yamazaki and Kamiyama, 2014; Yamazaki et al., 2013). These complicated models, however, are not applicable to microvascular network simulations due to limited computational efficiency. Cornelissen et al. (2002) proposed an artificial network model of the coronary artery tree with a nonlinear function for the relationship between NO and shear stress to better represent the NO-dependent flow dilation mechanism. This model consists of 10 resistance compartments with each compartment having a different number of identical vessels in parallel. Diameter heterogeneity was neglected in this model, but is important in real microvascular networks (Pries et al., 2009; Pries and Secomb, 2009). In addition, both the single vessel model and the artificial network model lack pulsatile shear stress characteristics. Lanzarone et al. (2009) considered the pulsatile flow effect and proposed an endothelial control model integrated with a lumped-parameter model of the systemic arterial circulation. The NO concentration and diameter change in peripheral networks were compared between pulsatile and steady perfusion, revealing increased NO production and widespread vasodilation under pulsatile perfusion. However, the peripheral networks were simplified as a single arteriole with a uniform diameter of 20 μm and the corresponding parameters were defined in a relatively narrow range. This simplification greatly reduced the usefulness of the model in the application to complex microvascular network. To our knowledge, there has not been any established mathematical model so far allowing for the study of NO regulation under pulsatile flow conditions in realistic microvascular networks.

The adequate function of the microcirculation relies on its angioarchitecture (Pries and Secomb, 2008). Thus, an accurate model should be based on a realistic network structure. In the present study, we aimed to develop a new mathematical model supported by experimental data for the study of pulsatile flow-mediated NO regulation in a microvascular network. The proposed model system is comprised of a pulsatile flow mediated endothelial NO regulation model, and a dynamic hemodynamic model. The model is supported by morphological and topological data for a real microcirculatory network, and allows for the analysis of the impact of flow pulsatility on NO regulation in a microvascular network and its consequential functional changes.

## 2. Methods

The schematic of the entire model including the sub-models of endothelial NO regulation and the hemodynamics of the microcirculatory network is illustrated in Fig. 1. Shear stress and pressure pulsatility values were calculated from blood flow and pressure in the hemodynamic model and serve as inputs for the endothelial NO regulation model. The outputs of the endothelial NO regulation model are vascular diameters which feedback to the hemodynamic model.

### 2.1. Hemodynamic model

In order to investigate the pulsatile flow properties in a microvascular network, a zero-dimensional (0D) Bond Graph model was employed to simulate the hemodynamic features. The Bond Graph model is a widely used technique in system dynamic modeling (Borutzky, 2010). The arbitrary $i$th vessel segment in a network Bond Graph model can be represented by flow resistance $R_i$, inertia of blood flow mass or inductance $I_i$ and vessel compliance or capacitance $C_i$ based on the Windkessel theory, as shown in Fig. 2.

The governing equations of the $i$th vessel segment are given as:

$$\frac{dV_i}{dt} = Q_{i-1} - Q_i \tag{1}$$

$$\frac{d\lambda_i}{dt} = P_i - P_{i+1} - R_i \cdot Q_i \tag{2}$$

$$Q_i = \lambda_i / I_i \tag{3}$$

$$P_i = V_i / C_i \tag{4}$$

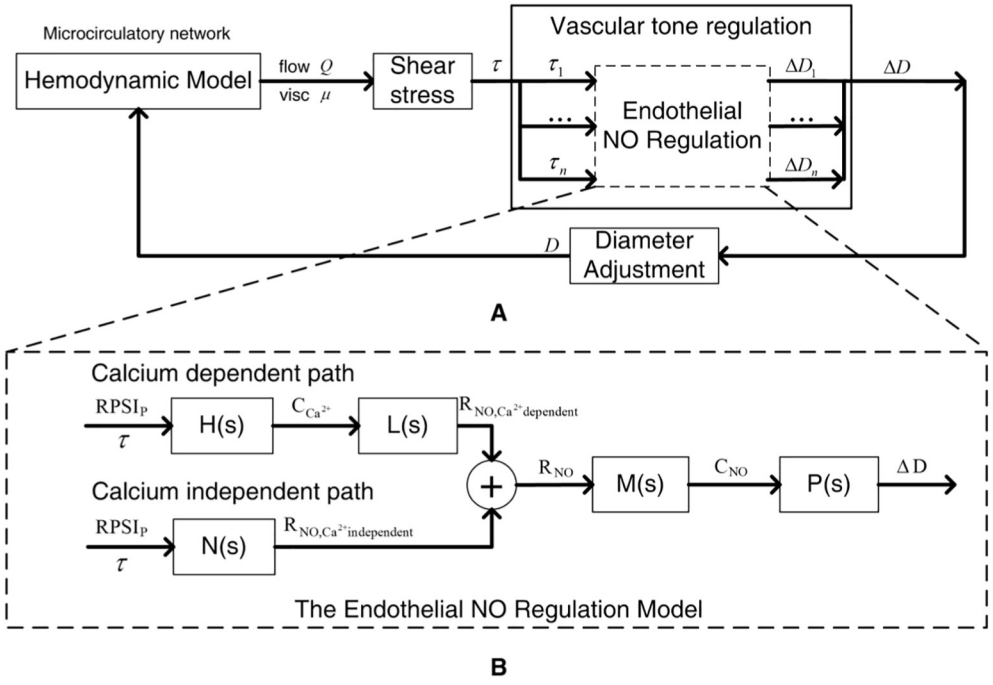


**Fig. 1.** Schematic diagram of the whole model. (A) Flow diagram of model simulation process: The hemodynamic model generates the flow values of each vessel segment as output and the shear stress is calculated as the input for the endothelial NO regulation model. The consequential diameter increase is the output of the endothelial NO regulation model and feedbacks to the hemodynamic model to change the flow distribution. The model is allowed to converge until the diameters do not change any more. (B) Block diagram of the endothelial NO regulation model. Transfer functions represent the reactions between the variables of shear stress (dyn/cm$^2$), RPSI$_P$ (s$^{-1}$), calcium concentration (nM), NO production rate (nM/s), NO concentration (nM), and vessel dilation.