An integrated model of arteriole tissue dynamics accounting for passive and active stresses

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Abstract

Previous models of intravascular functionality have been restricted to the investigation of biochemical and electrochemical procedures in the smooth muscle cells of an arteriole[1].Typically, they have ignored the impact of hemodynamics, the presence of glycocalyx and the endothelium layer, the mechanical-induced signaling responsible for the development of active stresses in smooth muscle cells, the shear-induced signaling responsible for the production of NO in endothelial cells as well as all relative biochemical pathways. In this work, we have developed a multicellular - multicomponent model that incorporates all these features in a fully coupled manner. Specifically, it accounts for the effect of ionic balances (e.g., Ca^{2+}, K^{+}) and the NO/cGMP pathway on the regulation of vascular-muscle-cells relaxation. To this end, we introduce a detailed description of NO activation of soluble guanylate cyclase (sGC), cGMP production and degradation, activated ion channels and myosin contractile system. The dynamics in a smooth muscle cell is modeled by a system of differential equations that accounts for intracellular ionic signaling; especially, the calcium ion which is found to has a significant impact on arteriole wall dynamics [2]. In endothelial cells, three key mechanotransducers are activated, leading in NO production. Namely, these are the mechanosensing ion channels, integrins, and G-protein-coupled receptors [3]. The mechanosensing ion channels are activated by a shear-induced signal coming from the hemodynamics in the lumen. This is a two-phase blood flow model, composed of an RBC rich core region, a dynamic cell-free layer (CFL) rich in plasmatic proteins, and a porous medium of about 500 nm of thickness which corresponds to the glycocalyx layer. All these sub-models are properly coupled in order to, configure an integrated model to incorporate the arteriole wall dynamics from the synergy of passive and active stresses. The extended model predicts the tissue fluctuations accurately under the alteration of hemodynamics or electrochemical signals. Although these deformations are insensible in normal conditions, it is found that the model is able to predict the impact of abnormal hemodynamic conditions on the structural dynamics of arteriole wall appreciably. These predictions are close enough to experimental data, substituting an increase in muscle tone and a decrease in diameter. An integrated parametric analysis will consequently reveal the complex behavior and interdependencies of all hemorheological, electrochemical and biomechanical properties.

Introduction

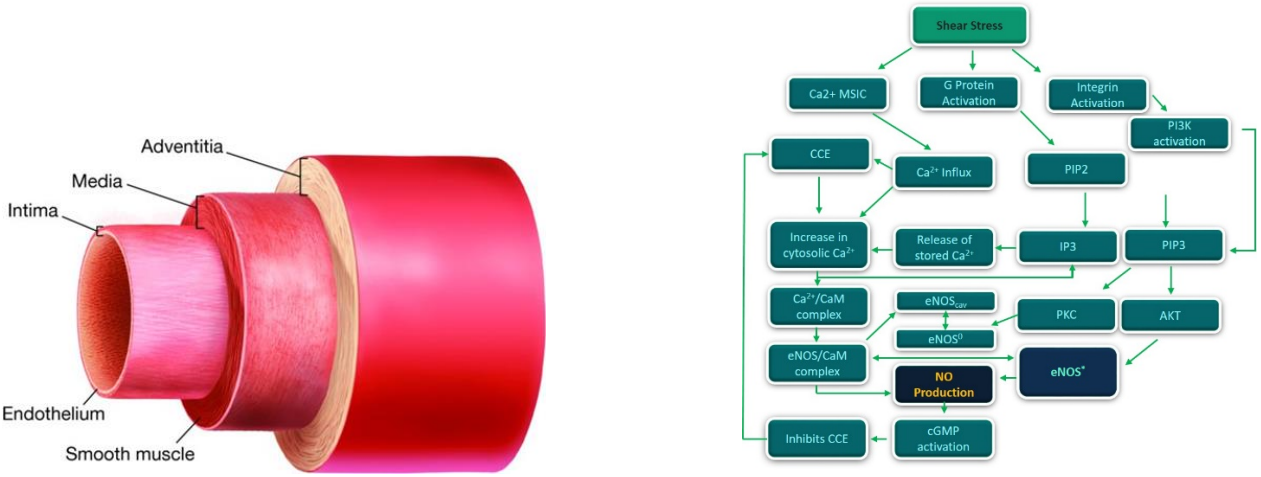
The contribution of nitric oxide (NO) to myogenic response and vasodilation effects is at the forefront of scientific research in the endeavor of deeply understanding the mechanisms of autoregulation and mechanotransduction control in the vasculature. To this end, we present an augmented model, in order to couple the hemodynamics with solid mechanics of vessel walls combined with the wall shear stress-induced NO production and the complex biochemical path of eNOS release in endothelial cells. Particularly, a time-dependent fully coupled model is derived from the fusion of three sub-models, namely a blood flow model for the RBC distribution, a convection-diffusion model for the NO/O2 transport, and a biochemical model for the synthase of eNOS. Arteriole wall can be treated as an elastic material able to deform under changes in dynamics of intravascular functionality. This function is mainly contributing with the ability of vascular beds to maintain a relatively constant blood flow over a large range of arterial pressures, known as autoregulation [3]. Arteriole is composed by three primary layers namely intima, media and the outermost adventitia, each of them performing distinct functions and structure (Figure 1a). The

mechano-elastic properties of arteriole wall are performed by smooth muscle cells (SMCs) located in the second tissue layer in conjunction with other significant electrochemical operations in other layers which eventually affect the contractility of arteriole, called vasomotion. Moreover, endothelium, a cellular mono-layer lining the inner surface of intima plays a crucial role in regulation of blood flow through the activation and bioavailability of the main vascular regulator of nitric oxide (NO)[6]. The activation of contractile mechanism is firstly driven by the signal transduction pathway of phosphorylation of the actin–myosin motors which leads to increase of intracellular Ca^{+2}. Although, intracellular calcium concentrations in normal states provide modest fluctuations in vascular tone, abnormal hemodynamic conditions significantly reflect to intravascular activity which eventually affect the contractility of vascular wall. Alterations in Ca^{+2}concentration can accretion from Ca^{+2} influx through voltage-dependent sarcolemmal Ca^{+2} channels, and/or a release of Ca^{+2} from internal Ca^{+2} stores [e.g., from the sarcoplasmic reticulum (SR)]. In the cytosol, free Ca^{+2} binds to a special Ca^{+2} binding protein called calmodulin (CM), and the calcium-calmodulin complex (CaCM) activates myosin light chain kinase (MLCK), an enzyme that facilitates the phosphorylation. All these factors can be represented by an integrated model for the description of biochemical reactions which eventually gives accurately predictions for calcium and NO bioavailability in vasculature.

Methodology

The methodology of multiscale modelling consists by coupling of primary vascular models namely the smooth-muscle contractile apparatus with the mechanoelastic properties of the arteriole wall in conjunction with blood flow in the lumen. These models's compartments are represented by distinct functions and are coupled with proper mathematical relationships based on experimental observations. This multicomponent approach is separated into four sub-models: a continuous blood flow model accounting for the prediction of cell-free layer (CFL) interface location, a cellular model for NO/O2 production/diffusion, an integrated mathematical description for NO/cGMP pathway in smooth muscle cells and a structural model accounting for the fluctuations of arterial walls. The accurate prediction of wall shear stress (WSS) on the endothelium surface, which is the signal for NO production, is based on a two-phase moving interface model with the rich-in-RBCs core represented by a viscoplastic constitutive model, a dynamically adjustable cell-free layer (CFL) thickness, and a porous medium of about 500 nm of thickness which represents the glycocalyx layer. We use experimental data to accurately predict the thickness of the CFL in order to verify the empirical observations from *Pries et al* for both In Vitro and In Vivo cases. We further consider the existence of three additional adjoining connective layers corresponding to endothelium, vascular wall and smooth muscle tissue which are assumed to be elastic and to exhibit both active and passive response to blood flow. From the structural point of view, the medial tissue is considered as a hyper-elastic fibre-reinforced material, with the fibres aligned along the circumferential direction [5]. Various representations of the arterial tissue have been previously proposed, including models of transverse fibre distribution at a diagonal angle. These approaches were specifically proposed to accurately represent the adventitia layer of the vessel wall. As we are primarily focusing on the media layer, in this study, we have followed the work proposed [5] where the media layer fibres are aligned only in the circumferential direction. The models accounts for the both passive and active stresses completing the autoregulation description of intravascular response. The active component depends directly on the cross-bridge attached while the passive component is represented by an anisotropic hyperelastic material. Each layer is described by different elastic properties due to different fibre orientation or absence of fibres. In order to define the activation path of NO into the endothelial cells, we introduce a time-dependent biochemical model incorporating three major synthase mechanisms including mechanosensing ion channels, integrins, and G protein-coupled receptor. The whole biochemical model is represented by an integrated model as illustrated in

Figure 1b. The dynamically shear-induced NO diffusion both into the vessel lumen and to the surrounding tissue is described through a versatile diffusion-reaction model that accounts even for the NO scavenging from the RBCs haemoglobin. All these hemodynamical and biochemical features are totally connected under an imposed pressure gradient adequately representing the cardiovascular pulse.



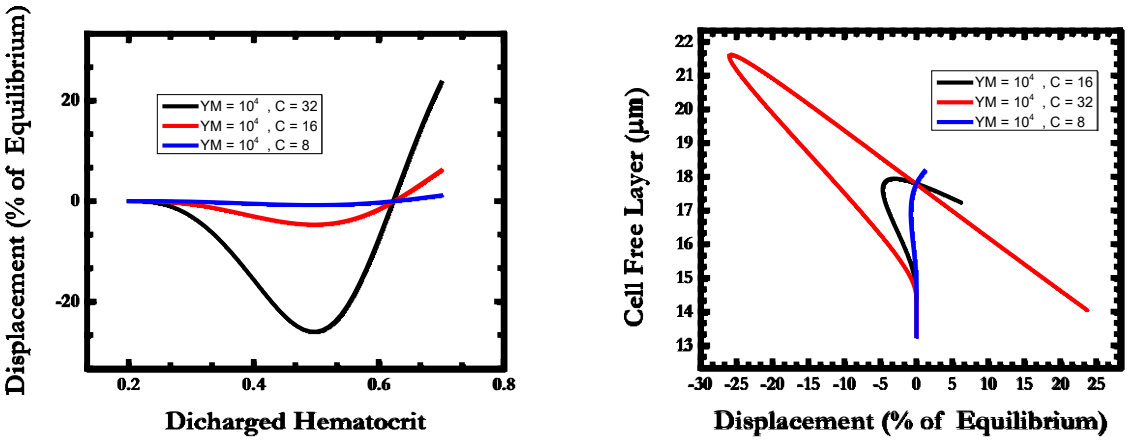
(a) (b)

Figure 1. *a) tissue structure, b)biochemical pathway of eNOS*

Conclusions

We have taken an integrative modeling approach to the characterization of the electrical, chemical, and mechanical behavior of the intravascular functionality. The model developed takes into account membrane activation by either electrical current pulses or mechanical stretch, and regulates calcium, contractile kinetics, force generation and muscle mechanics. An extensive parametric analysis portrays the dynamically related hemodynamics and biochemical quantities in a complex manner which originates from the highly nonlinear biphasic transient behavior of eNOS activation and NO production. The radial diffusion model is certainly adequate for elucidating the role of each compartment in the microvessel and its surrounding tissue with regards to NO/O2 exchange. Vascular wall elasticity was found to present an appreciable implication to WSS variation leading to a new configuration of NO activation and hence a modification to the diffusion and scavenging rates inside the lumen. The WSS is then activate the biochemical processes take place into the endothelial and smooth muscle cells controlling the vascular tone. The alteration of discharged haematocrit affects appreciably the fluctuations of arteriole walls from the base state of equilibrium for different elastic properties of each layer separately. For greater RBCs concentrations the force acted on vascular wall are greater imposing a bigger active stress to arteriole tissue which exhibits an increase in inner radius. For abnormal statements where the Young modulus is appreciably high, the prediction of arteriole systolic behaviour is quite high due to the enforced regulation form passive stresses to maintain the blood flow in regular statements. At cellular level our model subsystem testing of the integrated model shows: (1) the electrochemical model (membrane–fluid compartment model) not only provides very good fits voltage clamp data, but also to the induced calcium transients as well; and (2) the chemomechanical model (myosin phosphorylation/force development/cell mechanics model) provides close fits to experimental curves obtained from single smooth muscle cells. The complete integrated cell model was tested by predicting the cell response to both voltage pulse stimulation and strain pulses applied to the cell membrane with the muscle held under isometric conditions. The component isometric and isotonic phases of this response, mimic closely what is presently known of smooth muscle mechanics. This model can also predict

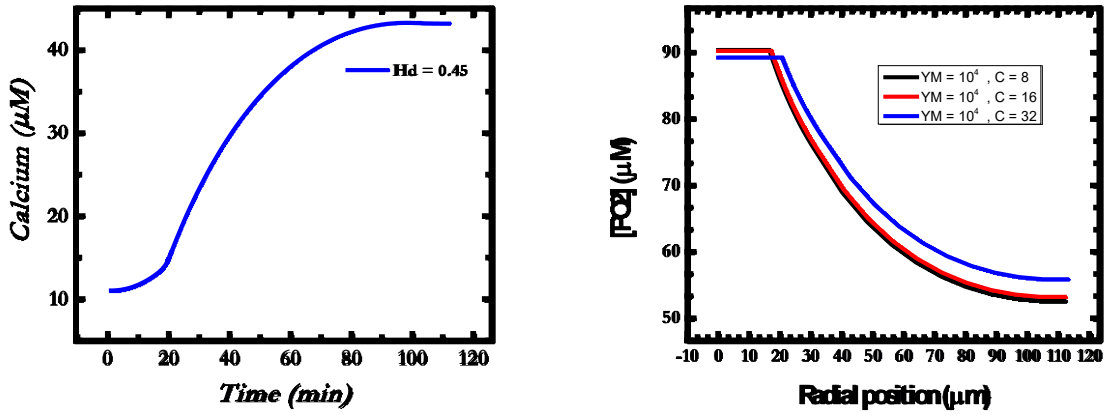
contractile events that are difficult to measure, including: (1) the transition occurring between phosphorylated cross-bridges and the latch-bridge state during the response , (2) the internal length adjustments of mechanical elements within the smooth muscle cell, and (3) the integrated responses of several different functional components. Our hemodynamical predictions are in excellent agreement with experimental observations and thus our model is able to predict an accurate WSS prediction which is the major signal for the biochemical processes of intraluminal pressure and calcium activation.



(a) (b)

Figure 2. *a) the impact of discharged hematocrit to inner radius fluctuations for different elastic properties, b) the CFL layer prediction in systolic statement for different elastic properties.*

The calcium transient is important, since it represents the input of the contractile mechanism. Figure 3, shows that leading edge of this calcium transient is due mainly the ionic calcium pumps but also to the SR release current. Decay in the calcium transient is mainly due to the rapid decline in ICa,L coupled with the increase in sarcolemmal and SR uptake pump currents. This novel combination of individual models which essentially incorporates all the major mechanisms of autoregulation, proves particularly advantageous compared to the existing incomplete models.



(a) (b)

Figure 3. *a) Transient calcium concentration for a normal dischared hematocrit, b) O_2 concentration distribution into the endothelium cells.*

Acknowledgments
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