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Mathematical model of wall shear stress-dependent vasomotor response based on physiological mechanisms

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ABSTRACT

Flow-mediated dilation (FMD) is the most commonly used noninvasive method for the assessment of vascular endothelial function; this assessment uses the magnitude of vasodilation according to reactive hyperemia. The physiological mechanism of vasodilation has been well studied; it was recently hypothesized that endothelial function can reversibly be estimated by computational analysis. This leads to more reliable information about cardiovascular risk factors. In this study, we first developed a mathematical model of vasodilation involving both intra- and inter-cellular pathways, which is constructed by integrating small-scale models based on known physiological mechanisms. We evaluated the proposed model with respect to several aspects: reproducibility of the FMD response; analysis of the relationship between FMD and endothelial function; and analysis of underlying mechanisms of low flow-mediated constriction. We confirmed that the simulated results corresponded well with those observed physiologically. Therefore, the results of the present study show that the proposed model has sufficient capability to quantitatively analyze FMD.

1. Introduction

Cardiovascular and circulatory system diseases are major causes of death worldwide [1]. At the early onset of atherosclerosis, the bioavailability of atheroprotective agents, such as nitric oxide (NO), decreases in the vascular wall [2]. The above-mentioned physiological behavior is also closely related to many cardiovascular and circulatory system diseases besides atherosclerosis [3]. Therefore, using such physiological information, we can expect to realize the early diagnosis of cardiovascular diseases.

Flow-mediated dilation (FMD) refers to vasodilation in response to changes in shear stress during reactive hyperemia. FMD analysis is commonly considered as an effective method for the noninvasive evaluation of the vascular endothelial function [4,5]. This method commonly involves the measurement of a longitudinal section of the brachial artery using an ultrasonic reflect scope. After the measurement of the baseline vascular diameter, a cuff is placed on the forearm, and inflated to produce ischemia. The cuff is deflated after 5 min, and vasodilation is caused by an increase in the wall shear stress during reactive hyperemia.

The magnitude of the FMD is used as an FMD index, and the maximum diameter after cuff deflation is normalized by the resting diameter. The FMD index is used as a surrogate marker for endothelial function, which corresponds to endothelial NO production [6]. A large amount of the related literature suggests that the value of this index is related to cardiovascular risk factors, such as smoking, hypercholesterolemia, hypertension, and diabetes.

When this measurement is applied, in addition to the FMD response, a low flow-mediated constriction (L-FMC) response is observed in some individuals, which represents vasoconstriction at the low flow state during cuff inflation [7–10]. Previous studies suggest that L-FMC is caused by the following factors: (1) the release of endothelin-1; (2) the inhibition of the release of cyclooxygenase-dependent products; and (3) the release of the endothelium-derived hyperpolarizing factor [7,8,11,12]. This suggests that the L-FMC response exhibits more complicated physiological mechanisms than the FMD response [7].

Thus, both FMD and L-FMC responses provide useful information for the determination of endothelial function. Recently, a novel evaluation method using the magnitude of both FMD and L-FMC was proposed [8], and a similar association with cardiovascular system diseases was suggested [7–9]. Thus, L-FMC is also a surrogate marker of endothelial function. However, because the vasomotor response with this method is influenced by many factors, the efficiency of this marker in representing detailed endothelial function is unclear [7].

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In contrast, the physiological mechanism of vasodilation has been well studied, and it is thought that the endothelial function can be estimated reversibly. In this study, we developed a multi-scale mathematical model of vasodilation with intra- and inter-cellular pathways. We also used blood flow velocity data obtained from the FMD measurement as an input to the proposed model and evaluated the results of the model.

2. Wall shear stress-dependent vasomotor response model

We modeled the vasodilation mechanism in this study. Four separate models were integrated to represent the FMD response. Fig. 1 shows the models and a schematic of their integration. In the following sections, we explain the models and there interrelationship.

2.1. NO concentration model

First, the wall shear stress stimulates the endothelial cell, and endogenous NO is synthesized. In this study, the NO production and transport was expressed as illustrated in Fig. 1. The NO concentration ([NO]) was computed according to the following differential equation:

$$\frac{d[\mathrm{NO}]}{dt} = R_{NO}(\tau) - \alpha_D[\mathrm{NO}] \tag{1}$$

where τ is the wall shear stress, $R_{\mathrm{NO}}(\tau)$ is the endogenous NO production rate according to the wall shear stress, and α_D is the NO diffusion rate parameter.

The magnitude of the relationship between the endothelial NO synthase (eNOS) concentration and the wall shear stress was assumed to be sigmoidal [4], and this assumption is supported by several investigations [4,5]. Under this assumption, the distribution of NO within a flow chamber seeded with endothelial cells has been investigated numerically [17,18]. The endothelial NO production rate (R_{NO}) is described by the following sigmoid function:

$$R_{\mathrm{NO}}(\tau) = \frac{R_{\mathrm{NO,\,max}}}{1+\exp[-P_1\tau+P_2]} + R_{\mathrm{NO,\,min}} \tag{2}$$

where $R_{\mathrm{NO,max}}$ represents the maximum NO production rate; P_1 and P_2 are coefficients that determine the shape of the function; and $R_{\mathrm{NO,min}}$ corresponds to the minimum value of R_{NO}, which equals the limit of R_{NO} as τ approaches to negative infinity.

2.2. Vascular smooth muscle electrophysiology model

The synthesized NO rapidly diffuses into the neighboring vascular smooth muscle (VSM), where it activates soluble guanylate cyclase (sGC). This activation acts on the conversion of guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP). As a second messenger, cGMP activates a family of cGMP-dependent protein kinases. This activation causes the following effects on the vascular smooth muscle cell: (1) decrease in intracellular Ca^{2+} concentration and (2) Ca^{2+} desensitization of the actin–myosin contractile system. Both effects yield vasodilation [13–16].

Kapela et al. developed an electrophysiological model of the vascular smooth muscle cell [21] that can simulate the molecular dynamics of ions, such as Ca^{2+}, Na^+, K^+, and Cl^-. Therefore, Model 2 is an important factor in the simulation of the FMD response. In particular, the molecular dynamics of Ca^{2+} is most important for the vasomotor response [20].

In this study, this model can be used to compute the dynamic state of the intracellular Ca^{2+} concentration ($[Ca^{2+}]$), from the dynamic states of both the NO concentration and the total wall stress. A detailed description of Model 2 is provided in the supplementary materials of a previous study [19]. To understand how the molecular dynamics of ions are expressed in this model, we present only the part of the model that constitutes the main path for the FMD response.

The NO concentration calculated using Model 1 was used as the input to the vascular smooth muscle electrophysiology model. The resulting analysis yielded evidence of NO diffusion in blood vessels

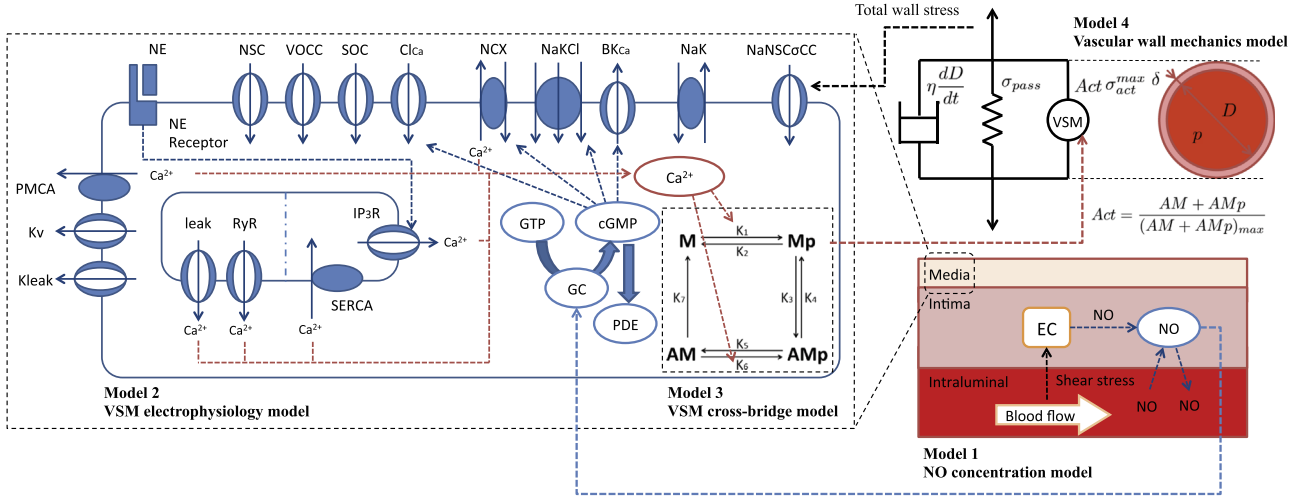

Fig. 1. Integrated multiscale model of the FMD response showing the following four models: Model 1: NO concentration model; Model 2: VSM electrophysiology model with vessel stress-controlled channels [19]; Model 3: four-state VSM cross-bridge model [23,24]; and Model 4: one-dimensional vessel wall mechanics model [25,26]. Model 1 simulates the NO production and transport on the endothelial cell (EC). As the mathematical model of plasma membrane electrophysiology, Model 2 shows intra- and inter-cellular ion behavior of the VSM cell by some materials: voltage-operated calcium channels (VOCC); large conductance Ca^{2+}-activated K^+ channel (BKCa); voltage-dependent K^+ channel (Kv); unspecified K^+ leak channel (Kleak); nonselective cation channel (NSC); store-operated nonselective cation channel (SOC); Ca^{2+}-activated Cl^- channel (ClCa); plasma membrane Ca^{2+}-ATPase pump (PMCA); plasma membrane Na^+/Ca^{2+} exchanger (NCX); Na^+/K^+ pump (NaK); $Na^+/K^+/Cl^-$ cotransporter (NaKCl); IP3 receptor on sarcoplasmic reticulum (IP3R); sarcoplasmic reticulum calcium pump (SERCA); sarcoplasmic reticulum four-state ryanodine receptor (RyR); NSC with stress-controlled Na^+ conductance (NaNSCσCC); norepinephrine(NE) receptor. Model 3 shows myosin binding and phosphorylation as the four states: free nonphosphorylated (M), free phosphorylated (Mp), attached phosphorylated (AMp), and attached dephosphorylated (AM). Model 4 shows the vasomotor response according to the change in the activation, which is calculated by Model 3.