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Mathematical model of hypertension-induced arterial remodeling: A chemo-mechanical approach

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ABSTRACT

The development of chronic hypertension is a poorly described process involving many chemical and structural changes to the artery. Typically, mathematical models of this disease focus primarily on the mechanical aspects such as arterial geometry, elasticity, and tissue content, or alternatively on the chemical drivers of vasoactivity such as nitric oxide and reactive oxygen species. This paper presents a model that considers the powerful interaction between mechanical and biochemical drivers of hypertension and arterial remodeling. Based on biological processes thought to be involved in the development of hypertension, we have built a system of algebraic, differential, and integral equations. Endothelial dysfunction, which is known to limit vasodilation, is explicitly considered in the model and plays a vital role in the development of chronic hypertension. Numerical solutions to the system are consistent with available experimental data for normal and spontaneously-hypertensive rats.

1. Introduction and background

In the development of chronic hypertension, we see changes in the structure of the arterial wall, including thickening, stiffening, and narrowing. This remodeling is a reaction to wall stress and strain; these changes come about through an intricate process initiated by biochemical signaling. To complicate matters further, the levels of these biochemicals become unbalanced during hypertension. Thus, understanding arterial remodeling requires examining mechanical and biochemical mechanisms simultaneously. Published mathematical models of hypertension-induced arterial remodeling tend to separate the biochemically-induced vasoactivity from the tissue-level hemodynamics and histomorphometrics. In the introduction, we will review work that has been done developing biochemical models of arterial remodeling, address existing models on the mechanics of arterial remodeling, and mention the few models that begin to combine these two perspectives.

Nitric oxide (NO), functioning as a primary vasodilator, is an important signaling molecule in arterial homeostasis, and so it is included in most cellular level mathematical models. Sriram et al. present a detailed model of NO production signaled by shear stress on the endothelium [1]. Similarly, Yang et al. model the signal transduction of NO by various G-proteins, which then interact with the vascular smooth muscle cells in order to signal vasodilation [2]. Layton and Edwards model the interaction of NO and superoxide during vasoactivity of arterioles [3]. However, measuring the transient biochemical cellular concentration in vivo or ex vivo is challenging. Thus, a lack of experimental data for important signaling molecules makes modeling the biochemical aspects of chronic hypertension difficult.

By comparison, data on hemodynamic and histomorphometric variables is easier to collect. Many models use this data to study the effects of flow and pressure on the structural properties of arteries [4–7]. These models propose detailed mathematical descriptions of the relationships between stresses, strains, and elasticity in the artery wall. Finite element methods have been used to solve equations that model residual stresses due to collagen and fibronectin levels [8,9]. Elastic modulus-wall stress curves have been fitted to experimental data [10,11], and extensive work by Fung and others has lead to equations modeling an artery's opening angle (a measure of residual stress) for

Abbreviations: A, Remodeled inner area; App, Apoptosis; Ang, Ang-II, Angiotesin-II; b_j^N, b_j^H, Normotensive (N) and hypertensive (H) material constants; BP, Mean arterial pressure; c^N, c^H, Noromotensive (N) and hypertensive (H) material constants; Cl, Normalized collagen deposition; F_X, External forcing term for state variable X; GF, Growth Factors (TGF-β); Gth, Cell Growth; NO, Nitric Oxide; PN, Peroxinitrate ($ONOO^-$); Q, Blood Flow Rate; r_e, r_{ep}, R_e, External artery radius (active-deformed, passive-deformed, reference state); r_i, r_{ip}, R_i, Lumen radius (active-deformed, passive-deformed, reference state); $\bar{r}$, $\bar{r}_p$, $\bar{R}$, Mean radius (active-deformed, passive-deformed, reference state); ROS, Reactive Oxygen Species; t_h, Time history; TGF-β, Transforming Growth Factor beta; Vcn, Vasoconstriction; W, Strain energy density function; WA, Wall Area; η, Blood viscosity; ζ, Proportion increase in flow rate; τ, Shear stress; λ_r, λ_θ, λ_z, Radial, circumferential, axial Green's strains; σ_θ, $\sigma_{\theta p}$, $\sigma_{\theta a}$, Cauchy circumferential stress (total, passive, active)

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times after experimental induction of hypertension in rats [12,13]. Sáez, Humphrey, and others model macrostructural arterial wall adaptation to high blood pressure, stress, and strain through microstructural mechanics of tissues in the human carotid artery [14–18]. They consider the interaction of stress, mass density, cellular turnover rates, extracellular matrix, collagen, and fibronectin at individual locations within the artery wall. While these models include subcellular factors – transforming growth factor-β (TGF-β), tissue inhibitors of metalloproteinases (TIMPs), and matrix metalloproteinases (MMPs) – they focus on the structural changes in the artery and do not address active vasoconstriction and dilation through biochemical means. For a more detailed review of mathematical models of vascular mechanics, see [19] and the references therein.

The many models listed above focus on a refined way of describing the geometric and/or constituent changes in the artery itself but do not incorporate the body's first response to high blood pressure – vasoactivity. Rachev and Hayashi incorporate passive and active stress in [20], but treat vasoactivity as a parameter rather than a quantity that varies over time. Furthermore, the major molecules in vasoactivity, reactive oxygen species (ROS) and nitric oxide (NO), are also important in collagen deposition, cell growth, and apoptosis, all of which influence the geometry of the artery wall and thus the stresses experienced therein (see Appendix A.2.2) [21–23]. Hayenga et al. address this interplay by coupling a continuum based biomechanical model, which is well-suited for structural variables, with a discrete stochastic agent based model, which is well-suited for cellular-level models [24]. Due to differences in state variable scales, they verify the coupled model by ensuring congruency across scales, leading to a model that better aligns with experimental data. While this model does provide cellular and tissue level information, it lacks the advantages of a single model. It may prove more difficult to analyze the two models while prioritizing the consistency in their overlapping variables.

It is well known that chemical factors (ROS, NO, angiotensin-II (Ang), transforming growth factor β (GF)); biological processes (cell growth (Gth), apoptosis (App), vasoactivity (Vcn)); and microstructural properties (cross-sectional wall area (WA), lumen radius (r_i), stiffness (Cl), shear and circumferential stresses (τ and σ_θ)) modulate mechanical properties of the arterial wall [25]. Up until this point, a single model connecting these specific biochemical, biological, and structural properties has yet to be developed, and so we propose a mathematical model that incorporates the dynamic interaction between these three types of factors. We include passive mechanical variables (stiffness, thickness, and internal radius) and active mechanical processes (vasoconstriction and vasodilation). Here we think of the passive variables as those that remain after the artery has been excised from the body (but may still be pressurized), whereas the impact of active variables depends on the concentrations of biochemicals only present in vivo.

By considering only some contributors to elasticity (ignoring, for example, the alignment of collagen fibers), assuming a uniform (rather than multilayer) artery wall composition, and using only ordinary (instead of partial) differential and integral equations, our system of equations simplifies the model of the mechanics. Also note, that instead of specifying a prescribed blood pressure (profile), we define mean arterial pressure according to the Law of Laplace as a function of the artery radius (among other things) and model changes in the radius as triggered by vasoactivity and outward remodeling rather than blood pressure itself. We recognize there are many models that provide a more refined mathematical description of certain complex dynamics; however, we have chosen to make many simplifying assumptions in order to combine the vasoactive and structural remodeling aspects into one model. By combining the two, we can study the important role of endothelial dysfunction and its influence on both NO production and the histomorphometric properties of the artery. These simplifications are a first step toward simultaneously considering these two major types of influences on hypertension while providing a model that is easier to analyze and modify. Despite these simplifications, we find that our model produces numerical results that are well in line with published results for a rat model of hypertension [26–28].

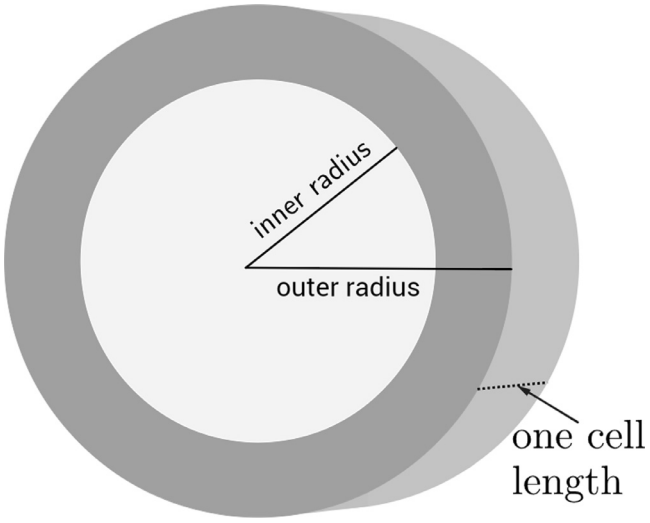

Fig. 1. The model describes a one-cell long cross-sectional slice of the carotid artery. The slice is radially symmetric in its undeformed (reference) state, loaded state, and vasoactive state. The inner radius lengths are denoted by R_i, r_{ip}, and r_i for the respective states and the outer radius lengths are denoted by R_e, r_{ep} and r_e respectively. The area of the cross-section perpendicular to the longitudinal axis (shaded dark grey) at time t is denoted WA(t).

2. The model

Our model describes a one-cell-long cross-sectional slice of the carotid artery of a rat, as shown in Fig. 1, over time t measured in days. Due to the cylindrical nature of the carotid, the results found in this thin slice may be extrapolated to longer artery lengths. The relative ease of carotid measurements has facilitated a substantial amount of published experimental data for the rat carotid [29]. By choosing the carotid, we hope that the results of our model can be easily tested. As such, we use initial conditions and parameters that, whenever possible, correspond to the carotid artery of a normotensive rat. Values for initial conditions and all model parameters are listed in the appendix. Parameter values are chosen such that at initial conditions the model is in equilibrium. Change in state variable values is driven by a prescribed flow profile of the type shown in Fig. 4.

We separate the state variables in our model into three categories – signaling molecules (Section 2.1), biological processes (Section 2.2), and mechanical variables (Section 2.3). A compartment diagram of the model can be found in Fig. 2.

2.1. Signaling molecules

While there are many signaling molecules involved in arterial remodeling, we focus on four: reactive oxygen species (ROS), transforming growth factor beta (TGF-β or GF), angiotensin II (Ang-II or, for brevity, Ang in this model), and nitric oxide (NO). These molecules are chosen for their well-known pervasive effects in arterial remodeling [21,25,30–33]. All signaling molecules are modeled in a similar fashion. A term for each signaling molecule appears in its respective differential equation with a negative sign to indicate its inactivation from the active molecule population as it signals a process. We assume that once an individual molecule binds to a receptor this molecule leaves the active molecule population either by degradation or inactivation. The same term appears with a positive sign in the differential equation corresponding to the state variable that is being signaled. Because certain signals may be amplified and the units of measurements for state variables are different, this positive term is