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Theoretical study on the effects of pressure-induced remodeling on geometry and mechanical non-homogeneity of conduit arteries

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Abstract

A structure-based mathematical model for the remodeling of arteries in response to sustained hypertension is proposed. The model is based on the concepts of volumetric growth and constitutive modeling of the arterial tissue within the framework of the constrained mixture theory. The major novel result of this study is that remodeling is associated with a local change in the mass fractions of the wall constituents that ultimately leads to mechanical non-homogeneity of the arterial wall. In the new homeostatic state that develops after a sustained increase in arterial pressure, the mass fraction of elastin decreases from the intimal side to the adventitial side of arteries, while the collagen fraction manifests an opposite trend. The results obtained are supported by some experimental observations reported in the literature.

Keywords

Vasomotor response; Stress-mediated volumetric growth; Mixture theory; Finite elasticity

1 Introduction

Quantifying the remodeling response of healthy matured arteries to sustained changes in blood pressure is important to understand normal arterial function and to reveal potential mechanisms associated with vascular disorders. Remodeling manifests as a change in the arterial geometry and mechanical properties; these factors govern the size of the arterial lumen and thereby the amount of blood conveyed and the structural stiffness of the vessel. Results from in vivo experiments reveal that remodeling to a sustained increase in arterial pressure, under normal blood flow, leads to maintenance of the deformed inner diameter and increase in the wall thickness such that the wall shear stress and mean circumferential stress are restored to baseline values (cf. Fung and Liu 1989; Liu and Fung 1989). Thus,

remodeling results in the preservation of the local mechanical environment of the endothelial and smooth muscle cells despite the changes in the global load conditions of the artery. It is well accepted that disturbance in the local mechanical environment (caused by the altered loading) triggers a series of cellular processes, such as proliferation, hyperplasia, cell death (apoptosis or necrosis), hypertrophy, and cell migration, and also elicits imbalance between extracellular matrix synthesis and degradation. The mechanobiological response involves signaling pathways, the precise nature and control of which are not entirely known. Long-term remodeling proceeds through changes in the mechanical properties, which have been interpreted as a mechanical adaptation that tends to restore the normal arterial function under sustained hypertension (cf. Matsumoto and Hayashi 1996).

While experimental studies reveal important descriptive information about remodeling, mathematical models offer a useful tool for testing plausible mechanisms of remodeling, designing experiments, and interpreting experimental data. There are several groups of models in the literature, which address different aspects of arterial remodeling caused by sustained hypertension. Briefly, the models based on the global growth approach consider the time variation of the zero-stress dimensions of an artery to be driven by the deviation of circumferential wall stress from homeostatic values (cf. Rachev et al. 1996, 1998; Fridez et al. 2001; Tsamis and Stergiopoulos 2007). Recently, using a global growth approach, a structure-based mathematical model for remodeling in response to sustained hypertension was proposed. The model accounts for the causal link between the stress-induced variation in the total arterial mass and the time course of the mass fractions of the basic structural constituents of the vascular tissue (Tsamis et al. 2009). The models adopting the volumetric growth approach consider the vessel as a collection of infinitesimal growing elements, which change their mass because of a local stress or strain deviation from certain preferred baseline values (Taber and Eggers 1996; Taber 1998a,b; Alford et al. 2008). Finally, some models utilize the theory of constrained mixtures, consider remodeling of the individual structural constituents, and track the amount and mechanical state in which individual constituents are produced and removed (Humphrey and Rajagopal 2002; Gleason et al. 2004; Gleason and Humphrey 2004, 2005a,b). A common characteristic of all these models is that the arterial tissue was considered mechanically homogeneous across the vessel wall before, during, and after remodeling. The only exception is the model proposed in Alford et al. (2008), which accounts for the variation of mechanical properties across the wall, but they remain unchanged during remodeling. The common assumption adopted in the previous studies was that remodeling does not cause a radial variation in arterial composition. However, a detailed analysis of the outcomes of the remodeling process suggests an opposite conclusion. It is well documented that the mass of an artery increases during pressure-induced remodeling because of smooth muscle cell hypertrophy and enhanced synthesis of collagen fibers, while the mass of elastin remains virtually unchanged. An increase in pressure causes a deviation of wall stress across the thickness from the values under normotensive conditions. Accepting that remodeling is a local process associated with the local stress distribution, it is reasonable to assume that remodeling might cause a variable distribution of the major structural constituents across the arterial thickness. Therefore, in addition to geometrical and mechanical adaptations, it is realistic to expect that the development of mechanical non-homogeneity of the arterial wall may also occur with remodeling.

There have been very few experimental studies on the radial distribution of the basic structural constituents across the arterial wall (Feldman and Glagov 1971; Hasan and Greenwald 1995). Similarly, only a few mathematical models incorporate mechanical non-homogeneity of the arterial wall by assuming increasing stiffness of the media from the intimal side toward the adventitial side (Taber and Humphrey 2001) or by prescribing variation of the fractions of the elastin and collagen across the wall thickness (Alford et al.

2008). These models, however, have not addressed the casual link between arterial non-homogeneity and the remodeling process. In this study, we built a predictive model of arterial remodeling in response to sustained hypertension that includes the effects of remodeling on mechanical non-homogeneity of the arterial tissue.

2 Theoretical framework

We hypothesize that remodeling causes local changes in the mass fractions of the wall constituents that ultimately lead to mechanical non-homogeneity of the arterial wall. To test this hypothesis, a mathematical model is proposed. The model includes the concepts of volumetric growth (cf. Rodriguez et al. 1994; Taber 1998b), with constitutive modeling of the arterial tissue within the framework of the constrained mixture theory (cf. Brankov et al. 1975, Humphrey and Rajagopal 2002).

2.1 Volumetric growth

An artery is considered to be a thick-walled cylindrical tube, which is in the state of axisymmetric strain and stress under physiological loads. The vascular tissue is modeled as a constrained mixture of smooth muscle cells and extracellular matrix comprised of elastin, collagen, and water. The mass and structure of the tissue can be altered via cell hypotrophy, misbalance between cell mitosis and apoptosis, and misbalance between extracellular degradation and synthesis. These processes are locally controlled by the local stresses in the arterial media, which in turn depend on the vessel geometry, mechanical properties, applied load, and contractile response (tone) of the vascular smooth muscle cells.

2.1.1 Kinematics—Consistent with the previous studies (cf. Chuong and Fung 1986), the zero-stress configuration of an artery is the opened-up configuration that is taken by an unloaded arterial segment after a radial cut; the vascular smooth muscle is maximally relaxed. The zero-stress configuration β_0 represents a cylinder of length L_0 , sectorial cross-section of opening angle Φ_0 (as defined in Chuong and Fung 1986), and radii of curvature of the inner and outer arc length R_i and R_o , respectively (Fig. 1). It is assumed that in the configuration β_0 , each basic structural constituent of the arterial tissue, i.e. the elastin, collagen and, smooth muscle cells, is in the natural (stress-free) state. At time $t = 0$, the artery is subjected to internal pressure, axial extension to in situ deformed length, and the vascular smooth muscle is stimulated to develop the baseline constrictive response (basal tone). Considering the solid structural constituents as elastic continua, the artery instantaneously takes the deformed configuration $\beta(0)$, which represents a cylinder of length ℓ_o , circular cross-section of inner radius $r_i(0)$, and outer radius $r_o(0)$ (Fig. 1). If the magnitude of the applied pressure is equal to its baseline (normotensive) value P_0 , the stresses and strains in $\beta(0)$ have their baseline values. The vessel conveys blood at a flow rate Q_0 , such that the shear stress at the luminal surface is at the baseline value. The configuration $\beta(0)$ is in a biological equilibrium (homeostatic state), characterized by a balance between cell mitosis and cell apoptosis and between synthesis and degradation of the extracellular matrix. At time $t = 0^+$, let the arterial pressure increase in a step-wise manner to $P = k_P P_0$, where $k_P > 1$ and remain constant for $t \geq 0^+$; the flow rate Q_0 is kept unchanged. The vessel undergoes an instantaneous elastic deformation from $\beta(0)$ to $\beta(0^+)$. Both the stress in the arterial wall and the flow-induced shear stress at the lumen undergo changes, and the local mechanical environment of the smooth muscle cells and endothelial cells alters. The deviation of stresses from their baseline values initiates remodeling of the arterial wall, which manifests as a change in the geometrical dimensions and a change in the arterial structure over time. At time t , the artery takes the current configuration $\beta(t)$ that represents a cylinder of length ℓ and circular cross-section of inner radius $r_i(t)$ and outer radius $r_o(t)$ (Fig. 1). The process of remodeling continues until a new homeostatic state is

achieved, the configuration $\beta_h(t_h)$, in which the wall stress, flow-induced shear stress and smooth muscle contractility reach biological equilibrium.

Mapping of β_0 into $\beta(t)$ is described by the relations

$$r=r(R,t) \quad \theta=\chi\Theta \quad z=\lambda Z \quad (1)$$

where (R, Θ, Z) and (r, θ, z) are the cylindrical coordinates of a point in β_0 and $\beta(t)$, respectively; $\chi = \pi/(\pi - \Phi_0)$ and $\lambda = \ell/L_0$. The configuration $\beta(t)$ is a result of two simultaneous processes: (a) a change in the natural (i.e., stress-free) configuration of any infinitesimal element caused by mechanobiologically mediated processes termed as growth (indicated by subscript g); and (b) a finite elastic axisymmetric deformation, which preserves the integrity of the vessel and is caused by the applied internal pressure, longitudinal extension to in vivo length ℓ , and by the constriction caused by the contractile activity of the vascular smooth muscle (indicated by subscript e). Following Rodriguez et al. (1994), the mapping from β_0 to $\beta(t)$ can be decomposed into a mapping from configuration β_0 to the locally stress-free configuration $\beta_g(t)$ due to the process of growth in which the zero-stress configurations of two neighboring rings do not match each other, followed by a mapping from $\beta_g(t)$ to the current configuration $\beta(t)$, which restores the integrity of the vessel wall. Thus, the total deformation gradient tensor $[\mathbf{F}] = \text{diag} [\lambda_r, \lambda_\theta, \lambda_z]$ associated with mapping $\beta_0 \rightarrow \beta(t)$ given by Eq. 1 can be decomposed into $[\mathbf{F}_g] = \text{diag} [\lambda_{gr}, \lambda_{g\theta}, \lambda_{gz}]$ and $[\mathbf{F}_e] = \text{diag} [\lambda_{er}, \lambda_{e\theta}, \lambda_{ez}]$, where $\lambda_r, \lambda_\theta, \lambda_z$ are the total stretch ratios in the radial, circumferential, and axial direction. Thus,

$$\lambda_r = \frac{\partial r(R,t)}{\partial R} = \lambda_{gr} \lambda_{er}, \quad \lambda_\theta = \frac{\chi r}{R} = \lambda_{g\theta} \lambda_{e\theta}, \quad \text{and} \quad \lambda_z = \lambda_{gz} \lambda_{ez} = \lambda \quad (2)$$

In general, growth results in an increase or decrease in the mass and therefore $J_g(R, t) = \det[\mathbf{F}_g] = \lambda_{gr} \lambda_{g\theta} \lambda_{gz} \neq 1$. Assuming material incompressibility $\det(\mathbf{F}_e) = 1$, i.e. $\lambda_{er} \lambda_{e\theta} \lambda_{ez} = 1$, which leads to an ordinary differential equation for $r(R, t)$ that has solution

$$r(R,t) = \sqrt{\frac{2}{\lambda\chi} \int_{r_i}^R J_g R dR + r_i^2} \quad (3)$$

where $r_i(t)$ is the deformed inner radius.

2.1.2 Constitutive equations for arterial tissue—Considering the tissue as a constrained mixture, the constitutive equations for the arterial tissue represent sums of the individual constitutive equations for elastin, collagen, and smooth muscle cells weighted by their individual mass fraction (cf. Gleason and Humphrey 2004). Elastin is modeled as an isotropic elastic solid. In a normal healthy mature artery, the elastin turnover is negligible after birth, and it is assumed that its zero-stress configuration does not change during remodeling (cf. Humphrey 2001). Therefore, the total stretch experienced by elastin at moment t is a result of both the elastic stretching and the tissue growth stretch according to Eq. 2. Collagen is considered as a system of circumferentially oriented nonlinear elastic fibers that continually turn over. It is assumed that the growth of the tissue is determined by the growth of the collagen. The contribution of the passive (non-contracted) smooth muscle

to the total stress is neglected. However, if stimulated, the smooth muscle cells, which are oriented predominately in the circumferential direction, develop an active circumferential stress. Making use of the rule-of-mixture

$$\begin{aligned}\sigma_{rr} &= \varphi_{el} \lambda_r \frac{\partial W_{el}}{\partial \lambda_r} + \varphi_{col} \lambda_{er} \frac{\partial W_{col}}{\partial \lambda_{er}} - p, \\ \sigma_{\theta\theta} &= \varphi_{el} \lambda_\theta \frac{\partial W_{el}}{\partial \lambda_\theta} + \varphi_{col} \lambda_{e\theta} \frac{\partial W_{col}}{\partial \lambda_{e\theta}} + \varphi_{sm} \sigma_{sma} - p, \\ \sigma_{zz} &= \varphi_{el} \lambda_z \frac{\partial W_{el}}{\partial \lambda_z} + \varphi_{col} \lambda_{ez} \frac{\partial W_{col}}{\partial \lambda_{ez}} - p.\end{aligned}\quad (4)$$

where $W_{el}(\lambda_r, \lambda_\theta, \lambda_z)$ and $W_{col}(\lambda_{e\theta})$ are the strain energy density functions for the elastin and collagen, respectively, $p(r, t)$ is an unknown function that must be determined from the equations of equilibrium and boundary conditions, $\sigma_{sma}(r, t)$ is the active stress generated by smooth muscle cells, and φ_j , $j = el, col, sm, w$ are the corresponding mass fractions for each constituent; the subscript w stands for water. The function $p(r, t)$ is due to mechanical incompressibility of the elastin and collagen and also contains the contribution of the water fraction to the Cauchy stress. Because all constituents have virtually the same mass density, the mass fractions can be calculated by using infinitesimal volume elements as follows

$$\begin{aligned}\varphi_j &= \frac{dv_j}{dv} \quad j = el, col, sm, w, \quad \text{and} \\ \varphi_{el} + \varphi_{col} + \varphi_{sm} + \varphi_w &= 1,\end{aligned}\quad (5)$$

where dv_j is the differential volume of a specific component, and dv is the total differential volume. Each constituent is considered incompressible, and therefore the fractions can be calculated using the differential elements either in configuration $\beta(t)$ or in configuration $\beta_g(t)$.

The active circumferential stress developed by the vascular smooth muscle depends on the intensity of stimulation according to the dose-response relationship, and on the current deformed configuration according to the length-active tension relationship (cf. Dobrin 1973). At constant length (the so-called isometric contraction), the magnitude of the active stress depends on the intensity of stimulation via concentration of the free calcium ions (Ca^{++}) in the muscular cells. Following Rachev and Hayashi (1999), the active circumferential stress is proposed in the following form

$$\sigma_{sma}(r, t) = S(t) \lambda_{e\theta} N(\lambda_{e\theta}), \quad \text{where } \max [N(\lambda_{e\theta})] = 1. \quad (6)$$

$N(\lambda_{e\theta})$ is a normalized function, which accounts for the length-active tension relationship and $S(t)$ is the activation parameter, proportional to intercellular calcium concentration. It is assumed that the activation parameter does not vary across the thickness; thus, $S(t)$ represents the maximum Lagrangian stress that might be developed by the smooth muscle cells at time t for a given intensity of the stimulation if the tissue level stretch ratio yields the optimal stretch ratio for which $N(\lambda_{e\theta}) = 1$.

2.1.3 Equilibrium—Given axisymmetry of the growth and deformation processes, the equations of equilibrium require that

$$\frac{\partial \sigma_{rr}}{\partial r} + \frac{\sigma_{rr} - \sigma_{\theta\theta}}{r} = 0, \quad \text{and} \quad \sigma_{r\theta} = \sigma_{\theta z} = \sigma_{zr} = 0. \quad (7)$$

Accounting for the boundary conditions $\sigma_{rr}(r_i) = -P$ and $\sigma_{rr}(r_o) = 0$, where P is the luminal pressure, the equilibrium yields that

$$P = \int_{r_i}^r (\sigma_{rr} - \sigma_{\theta\theta}) \frac{dr}{r} + \varphi_{el} \lambda_r \frac{\partial W_{el}}{\partial \lambda_r} + \varphi_{col} \lambda_{er} \frac{\partial W_{col}}{\partial \lambda_{er}} + P, \quad (8)$$

and

$$P = \int_{r_i}^{r_o} (\sigma_{\theta\theta} - \sigma_{rr}) \frac{dr}{r} \quad \text{and} \quad f = 2\pi \int_{r_i}^{r_o} \sigma_{zz} r dr, \quad (9)$$

where f is the axial force required to realize the prescribed deformation.

Given the configuration $\beta(t)$, two specific deformed states are of interest: the traction-free configuration $\beta_{tf}(t)$ and the opened-up configuration $\beta_{co}(t)$, (Fig. 1). Following Rachev (1997) the traction-free configuration $\beta_{tf}(t)$ is determined from the condition of incompressibility and the equations $P = 0$ and $f = 0$. The inner and outer radii of curvature, the opening angle of the cross-section, and the length of the artery in the opened-up configuration $\beta_{co}(t)$ are determined from the condition of incompressibility and the equations $P = 0$, $f = 0$, and $M = \int_{r_i}^{r_o} \sigma_{\theta\theta} r dr = 0$. The advantage of these configurations is that they are experimentally measurable and therefore can be used for verification of the model by comparing theoretical predictions to experimentally recorded data.

Finally, it is of interest to monitor the evolution of the passive structural stiffness of the artery as remodeling progresses. At time t , the stiffness is estimated in terms of the pressure-outer radius relationships over the pressure range of interest. Again, the overall mechanical response of the artery can be measured and used to test the predictive capability of the model.

2.2 Growth laws

A substantial part of modeling the remodeling process is the postulation of the growth laws that relate the local growth stretch ratios λ_{gi} and parameters that describe locally the stress and/or strain state of the tissue. Several local mechanical parameters, including all three components of total stress, the components of the partial stress for individual constitutions, the flow-induced shear stress at the luminal surface, and the parameters characterizing the contractile state of the smooth muscle cells simultaneously change when pressure varies. In this study, we postulate the growth laws in a form close to one proposed in (Taber and Eggers 1996; Taber 1998a,b; Rachev et al. 1998) as follows

$$\frac{\partial \lambda_{gr}}{\partial t} = \frac{1}{T_r} \left(\frac{\sigma_{\theta} - \sigma_{\theta\theta}}{\sigma_{\theta\theta}} \right), \quad \frac{\partial \lambda_{g\theta}}{\partial t} = \frac{1}{T_\theta} \left(\frac{\sigma_{\theta} - \sigma_{\theta\theta}}{\sigma_{\theta\theta}} \right), \quad \frac{\partial \lambda_{gz}}{\partial t} = 0, \quad (10)$$

where T_r and T_θ are time constants. Because the key mediators in the remodeling process are smooth muscle cells, which are predominately oriented circumferentially, both the radial and circumferential growth are assumed to be driven by the deviation of the current circumferential stress from its base-line value $\sigma_{\theta 0}$ considered as a “target value”.

2.3 Evolution equation for the contractile state of vascular smooth muscle

There are a great deal of experimental observations indicating that an increase in pressure is followed by rapid smooth muscle contraction, which constricts the artery. The acute vasomotor response tends to restore the strain distribution in the arterial wall and the magnitude of flow-induced shear at the lumen to their baseline levels. In the long term, a persistent increase in pressure induces geometrical and structural remodeling of the artery, and it has been speculated that remodeling tends to revert the contractile state of the smooth muscle cells toward the baseline level (Rachev 2000; Fridez et al. 2001). Similarly, in this study the evolution of the contractile state of the vascular smooth muscle is monitored through an evolution equation of the activation parameter S . It is postulated that

$$\frac{dS}{dt} = \frac{S_0}{T_{s1}} \left(\frac{r_i^3 - r_{i0}^3}{r_i^3} \right) + \frac{S_0}{T_{s2}} \left(\frac{\langle \sigma_\theta \rangle - \langle \sigma_{\theta 0} \rangle}{\langle \sigma_{\theta 0} \rangle} \right) - \frac{1}{T_{s3}} (S - S_0), \quad (11)$$

where $r_i = r_i(t)$ and $r_{i0} = r_i(0)$ are the inner radii in configurations $\beta(t)$ and $\beta(0)$, respectively; $\langle \sigma_\theta \rangle$ and $\langle \sigma_{\theta 0} \rangle$ are the corresponding current and initial average circumferential stresses; and T_{s1} , T_{s2} , and T_{s3} are time constants. Equation 11 is a generalization (by introducing the effects of the wall stress) of the evolution equation proposed in Rachev (2000), which was derived from the processes that control the concentration of calcium ions within the smooth muscle cells. The first two terms on the right hand side account for the effects of flow-induced shear stress and the medial tensile stress on the activation parameter S . The third term takes account of the inherent ability of the smooth muscle cells to restore their tone when it is perturbed from its baseline value (basal tone). Details about the derivation of Eq. 11 can be found in Rachev (2000).

According to Eq. 11, an increase in pressure initiates a gradual increase in the activation parameter S due to the abrupt increase in the inner radius and the circumferential stress. As remodeling proceeds, the first two terms in Eq. 11 diminish and the contribution of the third term changes the evolution trend of the activation parameter S toward the baseline value S_0 .

2.4 Evolution of the mass fractions

For illustrative purposes, it is assumed that the vascular tissue is initially mechanically homogeneous. The volume fractions in configuration β_0 (and in $\beta(0)$ and $\beta(0^+)$) are denoted by ϕ_{j0} ($j = el, col, sm, w$) and do not vary across the thickness. As the artery remodels, the volume of each differential element of the mixture alters locally due to the local growth. In general, each structural constituent changes its differential volume at a different rate. We define individual growth parameters $\alpha_j(r, t) = dv_j(r, t)/dv_{j0}$, where $dv_j(r, t)$ and dv_{j0} are the differential volume of constituent j of the same differential element in configuration $\beta(t)$ and $\beta(0^+)$, respectively. As shown in Sect. 2.1.1, the volume of a differential element of the mixture in configurations $\beta(t)$ and $\beta(0^+)$ is related by the equation $dv(r, t) = J_g(r(R), t) dv_0$. With account of Eq. 5, it follows that

$$\varphi_j(r, t) = \frac{\alpha_j(r, t)}{J_g(r, t)} \varphi_{j0}. \quad (12)$$

Because the fractions $\varphi_j(r, t)$ must satisfy the second equation in Eq. 5, it is possible to prescribe only three independent evolution equations for parameters $\alpha_j(r, t)$. They can be specified from general biological considerations, from direct experimental observations of the structural changes during remodeling, or can be postulated *a priori* and later justified or rejected from observable model predictions. Unfortunately, there are no available experimental data for the time course of mass of the basic structural constituents of the vascular tissue during remodeling. To complete the governing equations of the model, we introduce a set of equations for parameters $\alpha_j(r, t)$ from some general considerations. Accounting for the notion that the amount and distribution of elastin in a healthy non-aged arterial tissue remain unchanged after birth (cf. Greenwald 2007), we accept that (at least for a relatively moderate time period) $\alpha_e = 1$ during the entire period of pressure-induced remodeling. Although elastin degradation may occur over long periods of remodeling, we neglect such loss of functional elastin in the simulations herein. Additionally, we adopt the assumption that at any moment the increased volume of the smooth muscle cells is proportional to the increased volume of the collagen i.e. $dv_{sm}(r, t) = \kappa dv_{col}(r, t)$, where κ is a coefficient of proportionality. This is the simplest relationship that does not contradict the experimental observation that both the mass of smooth muscle cells (due to smooth muscle hypertrophy and increased mitosis) and mass of collagen (due to upregulated synthesis) increase during hypertension. Finally, it seems reasonable to assume that the amount of water varies in a manner to keep the mass fraction $\varphi_w(r, t)$ as it exists in configuration β_0 . Recalling the volume fraction definition, the first equation in Eq. 5, and using the second equation in Eq. 5 and 12, the following relations hold true

$$\begin{aligned} \varphi_{el}(r, t) &= \frac{\varphi_{el0}}{J_g(r, t)}, & \varphi_{sm}(r, t) &= \kappa \varphi_{col}(r, t), \\ \varphi_w(r, t) &= \varphi_{w0}, \\ \varphi_{col}(r, t) &= \frac{1}{1+\kappa} \left(1 - \varphi_{w0} - \frac{\varphi_{el0}}{J_g(r, t)} \right). \end{aligned} \quad (13)$$

2.5 Initial value problem

Modeling the pressure-induced remodeling process requires formulating and solving an initial value problem for the system of derived governing equations. The following model parameters and functions are prescribed: (i) the artery dimensions in the zero-stress state β_0 , i.e. the inner radius of curvature R_i , the outer radius of curvature R_o , the opening angle Φ_o , and the longitudinal stretch ratio in situ λ ; (ii) the normotensive pressure P_0 and the pressure augmentation parameter k_p ; (iii) the strain energy density functions for elastin and collagen W_{el} , W_{col} , the baseline value of the smooth muscle activation parameter S_0 and the function $N(\lambda_\theta)$; (iv) the initial mass fractions φ_{j0} of each constituent; and (v) the time constants T_r , $T_\theta T_{S1}$, T_{S2} , and T_{S3} . After solving Eqs. 1–9 for $P = P_0$, $S = S_0$ and $\lambda_{gr} = \lambda_{g\theta} = \lambda_{gz} = 1$, the strain and stress state in the deformed configuration $\beta(0)$ is obtained. The corresponding circumferential stress distribution $\sigma_{\theta 0}(r)$, the average stress $\langle \sigma_{\theta 0} \rangle$, and the deformed inner radius r_{i0} are taken as baseline values for evolution Eqs. 10 and 11. Similarly, after solving Eqs. 1–9 for $P = k_p P_0$, $S = S_0$ and $\lambda_{gr} = \lambda_{g\theta} = \lambda_{gz} = 1$, the inner radius $r_i(0^+)$, and the distribution of the circumferential stress $\sigma_\theta(r, 0^+)$ in the deformed configuration $\beta(0^+)$ are calculated. The process of pressure-induced remodeling is described by the functions $r_i(t)$, $\varphi_j(r, t)$, $\lambda_{gr}(r, t)$, $\lambda_{g\theta}(r, t)$, and $S(t)$, which must be determined. They are solutions of the Eqs. 1–13 for the $t \in [0^+, t]$ at the initial conditions $r_i(0^+)$, $\varphi_j(r, 0^+) = \varphi_{j0}$, $\lambda_{gr}(0^+) = \lambda_{g\theta}(0^+)$

$= 1$, and $S(0^+) = S_0$. The governing equations are coupled and must be solved simultaneously.

Note that Eq. 10 are partial differential equations for the growth stretch ratios λ_{gr} and $\lambda_{g\theta}$. Because the Cauchy circumferential stress is defined per unit area in the current deformed and grown configuration, the range of radial coordinates over which σ_θ is defined varies as the vessel remodels and is different from the range of radial coordinates over which the stress $\sigma_{\theta 0}$ is defined. Each partial differential Eq. 10 is replaced by a set of ordinary differential equations for the growth stretch ratios that refer to sufficient numbers of points across the thickness. The points are chosen to have same normalized radial coordinate in the zero-stress configuration β_0 .

3 Illustrative example

To illustrate the proposed analysis of pressure-induced remodeling, data for a rabbit thoracic aorta were used (Chuong and Fung 1986). In the zero-stress configuration, the aortic cross-section has a form of a circular sector of inner radius $R_i = 3.92$ mm, thickness $H = 0.60$ mm, and opening angle $\Phi = 108.6^\circ$ (Fig. 1). The initial mass fractions are taken $\varphi_{el0} = 0.06$, $\varphi_{col0} = 0.16$, $\varphi_{sm0} = 0.08$, and $\varphi_{w0} = 0.7$ (Fischer and Llauro 1966). The elastin is modeled as a neo-Hookean solid (cf. Gleason and Humphrey 2005a,b), and the collagen fibers of exponentially increasing stiffness are oriented in the circumferential direction (Kim et al. 2009).

$$\begin{aligned} W_{el} &= c_{el} (\lambda_r^2 + \lambda_\theta^2 + \lambda_z^2 - 3), \\ W_{col} &= c_{1col} \left(\exp(c_{2col} E_{e\theta}^2) - 1 \right), \end{aligned} \quad (14)$$

where $E_{e\theta} = 0.5 (\lambda_{e\theta}^2 - 1)$. Following Rachev and Hayashi (1999), the active stress generated by the stimulated smooth muscle is

$$\sigma_{sma} = S \lambda_{e\theta} \left(1 - \left(\frac{\lambda_m - \lambda_{e\theta}}{\lambda_m - \lambda_0} \right)^2 \right), \quad (15)$$

where $\lambda_m = 2.2$ and $\lambda_0 = 0.8$.

The normotensive pressure was chosen to be $P = 13.33$ kPa (100 mmHg), the in vivo longitudinal stretch ratio is $\lambda = 1.691$ (Chuong and Fung 1986), and $k_p = 1.5$, so that the hypertensive pressure is $P = 20.00$ kPa (150 mmHg). To identify the material constants in Eq. 14 and the initial value S_0 of the activation function in Eq. 15, the mechanical response that follows from the proposed structure-based constitutive model was enforced to match the mechanical response described by the phenomenological strain energy function given in Chuong and Fung (1986) and $S = 50$ kPa. The values $c_{el} = 10$ kPa, $c_{col1} = 118$ kPa, $c_{col2} = 1.1$, $S_0 = 625$ kPa, together with the parameters already specified, yield a mismatch less than 2% for the deformed dimensions and circumferential strain and stress distribution, calculated over pressure range 80–180 mmHg. Finally, the constants $T_r = 10$ days, $T_\theta = 100$ days, $T_{S1} = 1/1500$ days, $T_{S2} = 1/500$ days, $T_{S3} = 1/1000$ days were chosen to yield a time course of geometrical changes that agree with experimental observations. It is well known that the fast vasomotor response to increased pressure develops within minutes to hours (cf. Dobrin 1983); almost 80% of wall thickening is complete at the end of the first week after

an increase in pressure (Liu and Fung 1989); and the circumferential growth, which is the major mechanism during flow-induced remodeling, proceeds slower than wall thickening caused by the sustained increase in pressure (Langille 1993).

Given all model parameters and functions, the initial value problem formulated in the previous subsection was numerically solved using the commercial software (MATLAB, Release 2009a from MathWorks Inc., USA). The wall thickness was divided into ten intervals, and a sufficiently small explicit time step was chosen such that the solution is virtually insensitive to any further decrease in the time step. The results showed that solution of the initial value problem satisfies the requirements for uniqueness and stability. Moreover, the numerical simulations showed that small variations of a single input parameter, or combinations of parameters, cause small changes in the output results, proving the necessary requirement for robustness of the model. To estimate the effects of remodeling-induced non-homogeneity, the model predictions were compared to the results of a homogenous model in which the fractions of the structural constituents remain unchanged.

The results obtained can be sorted over several groups. The first group comprises model predictions that are predetermined by the selection of the growth laws (Eq. 10) and the evolution of the smooth muscle tone (Eq. 11). After an abrupt increase in circumferential stress at the moment of the step-wise change in pressure, the stress gradually decreased (Fig. 2a, b) to restore the stress distribution as it exists under normotensive pressure (Fig. 3). The ionic state of the vascular smooth muscle, modeled by the activation parameter $S(t)$, is a continuous function of time (Fig. 4a, b). Due to an abrupt change in flow-induced shear (via altered deformed inner radius) and due to the myogenic response (via altered average circumferential stress), $S(t)$ non-monotonically varies over time and finally attains a value near its initial baseline value S_0 .

The second group of results includes model predictions of trends, which are not obvious but are experimentally observable. After an increase in radius and decrease in thickness due to the elastic deformation, a rapid decrease in deformed diameter and rapid increase in thickness occur as a result of the vasomotor response (Figs. 5, 6). As remodeling proceeds, the deformed radius and thickness continue to vary monotonically due to stress-induced remodeling. The deformed inner radius attains a stationary value close to the baseline values under normal pressure, while the deformed thickness increases to restore the stress distribution, as it exists in the normotensive vessel. In contrast, the opening angle changes non-monotonically over time (Fig. 7). The dynamics of the deformed geometry explain the time course of the circumferential stress. Although for the specified set of time constants the vasomotor response is not sufficient to restore the deformed configuration to the baseline configuration, the rapid increase in the activation parameter causes a rapid decrease in the circumferential stress (Fig. 2a). Further decrease in stress is due to remodeling that manifests predominately as an increase in the wall thickness.

One of the major results of this study is the evolution of the mass fractions of elastin and collagen with time and location across the deformed wall thickness (Figs. 8, 9, 10). During the initial period of remodeling (about 2 days after a step elevation in pressure), the decrease in elastin fraction and increase in collagen fraction are greater in the inner region of the arterial wall (Figs. 8a, 9a). After 2 days, the decrease in elastin fraction and increase in collagen fraction are greater in the outer region of the arterial wall (Figs. 8b, 9b). Thus, remodeling causes a mechanical non-homogeneity of the arterial wall, which is characterized by a positive gradient of collagen fraction and negative gradient of the elastin fraction from the inner to the outer surface (Figs. 10a, b). Assuming proportionality, the time course and distribution of smooth muscle fraction follows those of the collagen.

The evolution of the structural stiffness of the artery is illustrated by the pressure–outer radius relation (Fig. 11). As remodeling proceeds, the structural stiffness of the artery varies as a net effect of geometrical changes, restoration of the basal contractile activity and changes in the amount and spatial distribution of the basic structural components. Over physiological ranges of pressures, the remodeled hypertensive vessel deforms less than the normotensive one. When compared at corresponding operating pressures, the hypertensive vessel is still less compliant, but remodeling reduces this effect. Due to the step increase in pressure from 100 to 150 mmHg, the Peterson modulus $E_p = r_o \Delta P / \Delta r_o$ increases by 210% at the onset of remodeling but is 148% higher at day 50.

The third group of results is not experimentally testable but can promote understanding the mechanisms of remodeling within the framework of the proposed model. Both the growth and elastic stretch ratios gradually increase as remodeling progresses (not shown). As the vessel remodels, the volume of the artery locally increases, which is illustrated by the time course and spatial distribution of the Jacobian $J_q(r, t)$, which is a measure of the relative change in the differential volume at given point (Fig. 12a,b).

To account for the effects of remodeling-induced non-homogeneity, the initial value problem is solved when $J_q(r, t)$ is set equal to 1 in Eq. 13. This simulates the case when all mass fractions remain unchanged, i.e. the growth is a result of a proportional local increase in the mass of the basic constituents (homogenous model). The results obtained are illustrated in Figs. 4, 5, 6, and 7 by dashed lines.

4 Discussion

The model proposed in this study is based on the notion that remodeling is a locally controlled stress-mediated process that includes an acute vasomotor response and a chronic increase in mass. The results from the illustrative example allow one to compare the model predictions with results of previous studies and to offer plausible explanations for some of the experimental findings reported in the literature.

4.1 Results of previous studies that support the proposed model

The monotonic increase in wall thickness, (Fig. 6), that virtually restores the baseline values of the circumferential stress is supported by the experimental observations reported in the literature (Liu and Fung 1989; Fung and Liu 1989; Matsumoto and Hayashi 1996) and by the predictions of most existing models of remodeling in response to sustained hypertension (cf. Rachev et al. 1996, 1998; Gleason and Humphrey 2004; Alford et al. 2008). Remodeling restores the deformed inner radius to a value, which is close to the value under normotensive pressure, (Fig. 5), which is in agreement with experimental observations (Liu and Fung 1989; Fung and Liu 1989; Matsumoto and Hayashi 1996) and predictions of mathematical models proposed (Rachev et al. 1996, 1998; Gleason and Humphrey 2004; Alford et al. 2008).

The time course of the geometrical parameters depends on the parameters that govern the dynamics of the vasomotor response and volumetric growth. The results obtained in this study show that at the beginning, a rapid increase in the activation parameter occurs, and the vessel constricts prior to the effects of stress-induced remodeling. Depending on how fast the activation parameter elevates, which is governed by the values of time constants T_{S1} and T_{S2} in Eq. 11, the vasomotor response might bring the inner radius and wall thickness to values, respectively, smaller and larger than the corresponding baseline value under normotensive pressure. According to the model, further changes in the deformed inner radius and thickness are net results of two competing processes. First, the vessel dilation caused by the decrease in activation parameter S phenomenologically modeled by the third

term in Eq. 11; second, the deformed radius and thickness increase due to volumetric growth according to the growth laws Eq. 10. Having accepted that the tissue grows faster in the radial than in the circumferential direction, the net effect of the vasomotor and remodeling processes is a monotonic increase in wall thickness. However, the deformed inner radius might show a non-monotonic time course. We do not know of experimental data that confirm or reject this scenario and can guide the specification of time constants in Eqs. 10 and 11.

The non-homogeneous growth causes a development of local residual elastic strains that are needed to keep the continuity of the arterial wall (not shown). In part, the residual stresses are released by a radial cut on the unloaded ring segment. The model predicts that when the smooth muscle is fully relaxed (i.e. $S = 0$), the opening angle varies non-monotonically over time (Fig. 7). Initially, the opening angle slightly increases due to a faster increase in the inner arc length compared to the outer arc length because of the higher deviation of the pressure-induced stress from the baseline value at the inner portion of the vessel. As remodeling progresses, the opening angle decreases because the new mass is added predominately in the outer part of the vessel wall, and at day 50 the opening angle attains a negative value. The predicted time course is qualitatively in agreement with experimental observations for a thoracic aorta distal to a local ligation of the vessel that causes sustained hypertension (Fung and Liu 1989; Liu and Fung 1989). In contrary, Matsumoto and Hayashi (1996) observed an increase in the opening angle of hypertensive rat aorta compared to the normotensive one. However, Matsumoto and Hayashi found higher thickening in the inner layers of the aorta, which according our model results in an increase in collagen fraction and thereby an increase in the circumferential stress in locations near the inner wall. The increase in opening angle is the only response that can reduce (via its effect on strains) the high circumferential stress in the inner part of wall thickness. Therefore, the results in Matsumoto and Hayashi (1996) do not contradict our basic hypothesis that remodeling produces a mechanical non-homogeneity of the vessel wall.

Though the time variation of the activation parameter $S(t)$ (Fig. 4) cannot be directly monitored, the consequences of its dynamics are experimentally recordable. The fast increase in the activation parameter during the vasomotor response produces a rapid vessel constriction; this result is in agreement with experimental observations (Bayliss 1902; Johnson 1980; Sipkema et al. 1997; Fridez et al. 2003). As a result, the flow-induced shear on the endothelium and the mean circumferential stress diminish; however, the stimuli on the smooth muscle cells that induce vasoconstriction may only be partially abolished. The activation parameter continues to increase during the initial period of remodeling, and slowly decreases as remodeling progresses due to the intrinsic cellular mechanisms that lead to a restoration of the ionic state of the smooth muscle cells. Thus, during a relatively long period, the vessel might be constricted more than a normotensive vessel (if both are compared at equivalent pressure). Such a result is a net effect of the increased activation factor, increased smooth muscle mass, increased structural stiffness of the vessel due to wall thickening and collagen amount augmentation, and the effects of the actual circumferential strain via active tension–circumferential stretch relationship. This conclusion can be supported by the results of (Fridez et al. 2001), who have shown that up to 52 days after the onset of hypertension in Wistar rats (caused by a ligation of the abdominal aorta), the functional contraction ratio, which is a normalized measure of the vessel constriction with respect to the state of passive deformation, is higher in the hypertensive vessel undergoing remodeling than the normotensive control.

In this study, we have chosen to track the evolution of the activation parameter instead of active stress because S is directly related to the ionic state of the smooth muscle cells via intercellular concentration of free calcium ions and is a single value function of time. In

contrary, the active stress, the magnitude of which is modulated by the actual circumferential stretch ratio, is a multi-value function that takes the same values at many combinations of activation parameter and circumferential strains. Although remodeling virtually restores the baseline value of the activation parameter, because of the altered overall structural stiffness of the vessel, the model predicts that the contractile response of a normotensive and hypertensive vessel to identical stimulation under same pressure might be different; this result is consistent with experimental observations (Cox 1979; Hayashi and Sugimoto 2007).

4.2 Novel theoretical results versus available experimental findings

The major novel result in this study is the gradual change in the amount and spatial distribution of the basic structural constituents of the arterial wall. Having accepted that a blood vessel changes its mass locally and the amount of elastin remains constant, the decrease in elastin fraction and increase in collagen and smooth muscle fractions over time are obvious consequences. As for the evolution of the fractions spatial distribution, it results from the different rate at which the tissue locally increases its mass. Immediately after a pressure jump and during the early period of remodeling, the stress deviation from the target stress is higher at inner locations of the wall compared to outer locations. Therefore, locations near the inner wall grow faster than locations near the outer wall and the corresponding decrease in elastin fraction and increase in collagen fraction is more pronounced (Figs. 8a, 9a). However, remodeling leads to a faster restoration of the circumferential stress in the inner part of the vessel compared to the outer part, where remodeling and associated changes in mass fractions proceed at a slower rate but for a longer period (Figs. 8b, 9b). As a result, in the new homeostatic state, the elastin fraction manifests a decreasing trend, while the collagen fraction manifests an increasing trend from the inner toward the outer surface (Fig. 10). Ultimately, the initially homogenous aortic wall becomes structurally and mechanically non-homogenous.

There are few experimental data reporting non-homogeneity of the arterial wall. Direct histological studies on human aortas have shown that the amount of elastin decreases while that of collagen increases from the intimal side to the adventitial side in young individuals, while a opposite tendency manifests with aging (Feldman and Glagov 1971). An increase in the collagen/elastin ratio from the intima toward the adventitia has been reported in the bovine aorta (Hasan and Greenwald 1995). Indirectly, the distribution of collagen can be evaluated via the levels of expression and activation of MMP-2 and MMP-9, which are involved in collagen turnover. Higher expression and activation of MMP-2 and MMP-9 correlates with higher collagen content and was documented in porcine arteries studied in organ culture (Chesler et al. 1999; Xu et al. 2000). It was found that induced hypertension initiates rapid gene expression for collagen type I predominantly in the outer media and adventitia of rabbit aortas.

Without addressing to the spatial distribution of structural constituents, some studies report non-homogeneity in wall thickening induced by increase in pressure. Fridez et al. (2003) observed that induced hypertension of rat common carotid arteries causes fast thickening of the innermost lamellar units of the media during the early period of remodeling, which later slowed down, while the outermost lamellar units continued to thicken; after 56 days, the outermost lamellar units became thicker than the inner lamellar units. Interpreted in terms of structural components that are involved in arterial remodeling, this finding suggests an increased collagen synthesis and higher collagen fraction at the outer part of the artery compared to the inner part. These experimental findings support the model predictions in our study. Opposite to these results, Matsumoto and Hayashi (1996) observed a higher thickening of the innermost layer in the adaptation of rat aortas to Goldblatt hypertension at 8 weeks. The difference between results of Matsumoto and Hayashi (1996) with those of

Fridez et al. (2003) may be due to the type of induced hypertension, location along the vascular tree, or host animal.

Experimentally observed arterial non-homogeneity may also be associated with a decrease in the amount of elastin at the intimal side with age, which might be associated with degradation due to fatigue or elevated protease expression at the localization of higher circumferential stress. Based on the results obtained in this study, we speculate that the origin of stiffening of the wall toward the adventitia is a result of a stress-induced volumetric growth during biological growth and maturation. It is well documented that blood vessels change their size, structure, and composition not only under the influence of genetic factors but also due to variable epigenetic factors, such as arterial pressure and blood flow rate. Therefore, the proposed model suggests that the observed non-homogeneity of healthy matured vessels might be caused by the gradual change in the mechanical environment after birth. In the illustrative example of this study, we considered a healthy matured aorta as mechanically homogeneous and attributed the non-homogeneity to the remodeling response to a sustained high pressure. Most likely, the hypertension does not initiate but rather alter already existing structural and mechanical non-homogeneity. However, lack of reliable experimental data that can be used for identifying model parameters does not allow performing such type of simulations.

The net effect of structural reorganization of elastin and collagen ultimately leads to a gradual stiffening of the vascular tissue from the intimal toward adventitial side. Indirect support to these model predictions are the results in Taber and Humphrey (2001) and Alford et al. (2008). Taber and Humphrey have postulated material heterogeneity via gradual increase in the leading material constant in a phenomenological strain energy function, which yields results that are in agreement with experimental findings. Similarly, considering the vessel as a two-layered tube that has a higher collagen fraction and lower elastin fraction in the adventitia, compared to the corresponding fractions in the media, a model proposed in Alford et al. (2008) predicted results that are supported by experimental observation.

The results from the illustrative example do not show significant differences in the time course of the geometrical dimensions and total mass increase when they are calculated from the homogeneous model. It might be speculated that the mechanical non-homogeneity that results from adaptive remodeling to hypertension is rather a consequence than an objective of the remodeling process.

4.3 Limitations

The limitations of this study are associated with the introduced simplifying assumptions. The analytical form of the growth laws (10) and the evolution equation (11) were heuristically chosen to account for certain already established mechanisms and outputs of the acute vasomotor response and successive remodeling process that are caused by a stepwise increase in pressure. Due to a lack of detailed data for the time course of remodeling of a rabbit thoracic aorta, the time constants referring to the illustrative example are specified to yield predominantly qualitative information.

A motivated choice of growth laws and evolution of the muscular tone remain an open issue. Like most objective laws, the selection of these equations can be done either based on a set of simple experiments or by comparing the consequences from postulated growth laws and experimental observations. *A priori* postulation of the growth and evolution laws has several aspects: identification of the arguments of the equations, choice of their analytical form, and specifications of the time constants included in the equations. In general, following the “principle of equipresence”, the growth laws can relate the growth stretch ratios or their time derivatives to the deviations from certain preferable values of *all local* parameters that

undergo changes when the load on the artery is altered. Usually, the preferable values (often termed as “target values”) are those that exist in the physiological state under normal loads and ensure the baseline homeostatic state. When the flow rate and pulse pressure remain unchanged, a step-wise increase in the mean arterial pressure causes an increase in the circumferential wall stress and strain, increase in the axial wall stress, decrease in the pulsatile circumferential wall strain, and decrease in the flow-induced wall shear stress at the endothelium. Moreover, in response to the altered shear stress and circumferential stress, the contractile state of the vascular smooth muscle alters, which elicits an acute vasomotor response that additionally affects the value of the strains and stresses in the vessel. An open question remains as to which parameters mediate remodeling and (serving as “driving stimuli”) should be selected as arguments in the growth laws. To date, the mean circumferential stress, by itself or in combination with the flow-induced shear stress, are the most often used arguments in the growth laws that have been proposed in the literature (Taber and Eggers 1996; Taber 1998a,b; Rachev et al. 1998). As for selection of the analytical form of the growth laws, most authors proposed a first-order kinetics (Taber and Eggers 1996; Taber 1998a,b; Rachev et al. 1998) and additive contribution in the case of more than one argument (Alford et al. 2008). Finally, the important issue is the specification of the time constants in the equations that determine the dynamics of the remodeling process. A novel paradigm for performing *ex vivo* experiments on arteries that is based on recording the remodeling inputs caused by a controlled change in a single local mechanical parameter, such as the medial strain, stress, or flow-induced shear stress, might provide useful insights for experimentally motivated selection of growth laws (Rachev et al. 2009).

A constant ratio between amount of collagen and smooth muscle during entered process of remodeling, as it was assumed in this study, requires experimental verification. For illustrative purposes, a relatively simple constitutive model of collagen fibers was chosen neglecting their gradual recruitment and contribution in bearing the axial load. The proposed model does not incorporate changes in mechanical properties that occur in the long term after onset of pressure elevation as reported in Matsumoto and Hayashi (1996) and was proposed by some theoretical models (Rachev et al. 1998; Tsamis et al. 2009). It was assumed in this study that the mechanical non-homogeneity originates solely from the variation of the mass fractions of the structural components but not on the spatial changes in their mechanical properties. It is possible that contribution of the collagen fibers in load bearing may vary locally as it was assumed in Kim et al. (2009) or remodeling affects globally the mechanical properties of collagen as assumed in Tsamis et al. (2009). A refined model can test the speculation that more collagen closer to the outer surface of media may prevent the vessel from over inflation, as does the adventitia.

All data that are used for the parameter identification and for testing the model predictions must come from one type of artery of one animal species. Unfortunately, as in most published theoretical papers devoted to remodeling, the data used for the illustrative example do not meet this requirement. Moreover, to the best of our knowledge, data for the time and spatial evolution of mass fractions of the basal structural constituents during process of pressure-induced remodeling are not available.

Though a generalization of the governing equation to include hypertension-induced growth in longitudinal direction is straightforward, it leads to certain difficulties. Additional model parameters must be specified without strong experimental support. Moreover, it would be reasonable to replace the oversimplified constitutive model of the collagen with a model that accounts for the helical configuration of collagen fibers and their contribution in the load bearing in the longitudinal direction. Finally, the vessel is considered as a one-layered thick wall tube with no account for the individual contribution of the media and adventitia in load bearing and remodeling. Most of the limitations can be incorporated in further generalization

of the model. Obviously, this can refine the model predictions but will not change the major result of this study regarding the existence of remodeling-induced mechanical non-homogeneity.

4.4 Conclusion

This study proposes a structure-based model of arterial remodeling to a sustained increase in arterial pressure. The model is based on the volumetric growth approach and accounts for some specifics in remodeling of the basic structural constituents of vascular tissue. The major novel result is that remodeling can induce structural alterations that lead to mechanical non-homogeneity across the wall thickness. There is a pressing need for more experimental data for spatial variation of arterial wall structure and composition to test the model prediction and refinement of the model. Experimental studies motivated and interpreted by relevant models together with reliable theoretical predictions can provide insights to the modes and mechanisms of arterial remodeling and promote better understanding of vascular mechanics and mechanically mediated remodeling.

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Fig. 1.
Schematic of the vessel's configurations before and during pressure-induced remodeling

Fig. 2. Time course of the circumferential stress at three locations in the deformed thickness: **a** during acute vasomotor response; **b** during entire period of remodeling. The stress is normalized by its baseline value under pressure of 100 mmHg

Fig. 3. Distribution of the circumferential stress across the thickness at different times. The stress is normalized by its baseline value under pressure of 100 mmHg

Fig. 4. Time course of the activation parameter **a** during the initial period of remodeling; **b** during the entire period of remodeling. The parameter is normalized by its baseline value under pressure of 100 mmHg. The *dashed line* refers to the homogenous model

Fig. 5. Time course of the deformed inner radius. The radius is normalized by its baseline value under pressure of 100 mmHg. The dashed line refers to the homogenous model

Fig. 6. Time course of the deformed wall thickness. The thickness is normalized by its baseline value under pressure of 100 mmHg. The *dashed line* refers to the homogenous model

Fig. 7.
Time course of the normalized opening angle. The angle is normalized by its value before onset of remodeling

Fig. 8. Time course of elastin mass fraction at three locations in the deformed thickness: **a** during initial period of remodeling; **b** during entire period of remodeling. The mass fraction is normalized by its baseline value

Fig. 9.

Time course of collagen mass fraction at three locations in the deformed thickness: **a** during initial period of remodeling; **b** during entire period of remodeling. The mass fraction is normalized by its baseline value

Fig. 10. Distribution of mass fractions across the thickness at different times: **a** elastin fraction; **b** collagen fraction. The mass fractions are normalized by their baseline values

Fig. 11.
Pressure-deformed outer diameter relationship at different times

Fig. 12. Time course of Jacobean J_g at three locations in the deformed thickness: **a** during initial period of remodeling; **b** during entire period of remodeling