A Mathematical Model of Maladaptive Inward Eutrophic Remodeling of Muscular Arteries in Hypertension

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We propose a relatively simple two-dimensional mathematical model for maladaptive inward remodeling of resistive arteries in hypertension in terms of vascular solid mechanics. The main premises are: (i) maladaptive inward remodeling manifests as a reduced increase in the arterial mass compared to the case of adaptive remodeling under equivalent hypertensive pressures and (ii) the pressure-induced circumferential stress in the arterial wall is restored to its basal target value as happens in the case of adaptive remodeling. The rationale for these assumptions is the experimental findings that elevated tone in association with sustained hypertensive pressure down-regulate the normal differentiation of vascular smooth muscle cells from contractile to synthetic phenotype and the data for the calculated hoop stress before and after completion of remodeling. Results from illustrative simulations show that as the hypertensive pressure increases, remodeling causes a nonmonotonic variation of arterial mass, a decrease in inner arterial diameter, and an increase in wall thickness. These findings and the model prediction that inward eutrophic remodeling is preceded by inward hypertrophic remodeling are supported by published observations. Limitations and perspectives for refining the mathematical model are discussed. [DOI: 10.1115/1.4055109]

Keywords: vascular solid mechanics, vascular smooth muscle and endothelial cells response, phenotype switching, endothelial dysfunction

1 Introduction

Hypertension is one of the most prevalent life-threatening diseases in the civilized world. Understanding mechanisms of occurrence and modes of hypertension are important for both its prevention and treatment. A key cause for the development of hypertension is the pathological structural and functional changes in arteries. The basic function of arterial vessels is to convey blood to organs and tissues according to transient metabolic demands. Large arteries, located close to the heart, serve also as an elastic reservoir that transforms the highly pulsatile heart output into a flow of moderate fluctuations. Muscular arteries, particularly the smaller ones and arterioles located distally from the heart with relaxed lumen diameter of 100–400 μm, finely tune local blood supply to organs and determine the peripheral resistance that governs the magnitude of the arterial pressure. These functions are realized by the maintenance of appropriate vascular lumen diameter and mechanical response to applied loads. Lumen diameter depends on the size of the vessel in the state of no-load, mechanical properties of arterial tissue, the magnitude of arterial pressure, vessel longitudinal stretch due to tethering to surrounding tissues, and the level of arterial constriction due to the portion of vascular smooth muscle cells (VSMCs) in the media that manifest a contractile phenotype. The latter, called generally the muscular tone, is governed by the inherent contractile capability of VSMCs, the stimulation to contract due to neurological signals [1], blood-borne vasoconstrictor substances [2], myogenic stimulus due to the pressure-induced wall stress [3], and also by opposing factors that induce relaxation, mainly the vasodilator compound nitrite oxide (NO) produced by endothelial cells (ECs) at the intima [4]. Another part of the VSMCs manifests a synthetic phenotype by producing load-bearing tissue constituents such as elastin and collagen to ensure the vessel's integrity and adequate mechanical performance. By maintenance of a preferable balance between contractile and synthetic phenotype, VSMCs establish cellular level homeostasis, keeping a dynamic ratio between cell apoptosis and mitosis, synthesis and degradation of load-bearing extracellular proteins, and preservation of basal muscular tone.

Vascular cells are mechanosensitive. ECs sense the flow-induced shear stress at the endothelium while the VSMCs sense the circumferential stress in the media caused by the arterial pressure. Under normotensive pressure, flow, and basal muscular tone, matured healthy vessels manifest a mechanical response that ensures a preferable mechanical environment for ECs and VSMCs in terms of certain basal target values of corresponding stress. If a healthy vessel is subject to a sustained increase in pressure and/or flow, stresses are altered and the local cellular homeostasis is disturbed. Altered stresses trigger a series of cellular and subcellular processes, termed remodeling, that ultimately lead to a new homeostatic state, which on the organ level is characterized by a change in geometrical dimensions and some cases a change in the wall tissue composition and structural organization. The change in geometry, called often remodeling-induced growth, might be evaluated in two ways. First, by comparing the geometrical parameters of an artery in the zero-stress configuration before remodeling and after it is complete, which describes the true growth. Second, by comparing the arterial dimensions in the analogous deformed states, which describes the apparent growth because geometry is modulated by the deformation due to altered pressure and the VSMCs tone [5]. Often in the medical literature, the geometrical outcomes of remodeling are termed as inward or outward to reflect the directional change in the lumen diameter, and also as hypertrophic, eutrophic, or hypotrophic to indicate an increase, retention, or decrease of the arterial wall area [6].

An important particular case of arterial remodeling is hypertension-induced adaptive remodeling, in which the flow-induced shear stress and pressure-induced medial stress are restored to their baseline values. A comprehensive review of

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findings from different experimental modes that cause hypertension-induced adaptive remodeling is given in Ref. [7]. On the other hand, there were proposed several successful theoretical approaches to describe and predict the evolution or outcomes of remodeling by building appropriate mechanics-based mathematical models (e.g., Refs. [8–12]). Quantification of the remodeling response of healthy matured arteries to sustained changes in blood pressure is important to understand the normal arterial function and to reveal potential mechanisms involved in vascular disorders such as hypertension. Apart from these investigations, a lot of studies are devoted to arterial pathophysiology. It is well established that there are cases in which remodeling of arteries has gone wrong, termed as maladaptive, resulting in a new homeostatic state that at the cellular level is not identical to the homeostasis manifested under normotensive conditions. In the particular case of essential hypertension there exists substantial evidence that muscular arteries and arterioles change their geometry in a manner to reduce the lumen diameter with virtually no change in the wall cross-sectional area (CSA) [13–20]. In line with definitions introduced in Ref. [6], this response is termed maladaptive inward eutrophic remodeling. As stated in several papers [13–17], this type of maladaptive response is closely associated with (or "maybe caused by") augmentation of the VSMCs tone that causes a chronic constriction of muscular arteries and arterioles and with an increase in arterial pressure. Surprisingly, to our knowledge, there are no published mathematical models devoted to inward eutrophic remodeling. In this paper, we propose a simple mathematical model that promotes analysis of some experimental findings and model predictions from the point of view of the vascular solid mechanics.

2 Theoretical Framework

First, we briefly describe the continuum mechanics-based strain and stress quantification in the wall of a pressurized and longitudinally stretched artery. Later, using a global growth approach [5,8], we formulate and solve inverse boundary value problems to identify the change in geometrical dimensions in the cases of adaptive and maladaptive inward remodeling of arteries in hypertension.

2.1 Two-Dimensional Arterial Model. Continuum mechanics-based analysis of arterial response to loads can be found in many publications (e.g., Refs. [5,21]). An artery is modeled as a circular cylindrical membrane made of an elastic orthotropic and incompressible material. Under internal arterial pressure, longitudinal stretch, and contraction of the VSMCs, the vessel undergoes a finite axisymmetric deformation from the undeformed (stress-free) state at no load and relaxed VSMCs. The deformed state is described by the deformation of the midwall arterial surface in terms of the right Cauchy–Green strain tensor $\boldsymbol{C} = \text{diag}\{\lambda_1^2, \lambda_2^2\}$ and the change in wall thickness, where the principal stretches in the axial (1) and circumferential (2) direction, and deformed wall thickness are

$$\lambda_1 = \frac{l}{L} \quad \lambda_2 = \frac{r_i + h/2}{R_i + H/2} \quad h = \frac{H}{\lambda_1 \lambda_2} \tag{1}$$

$\{L, R_i, H\}$ and $\{l, r_i, h\}$ are the length, inner radius, and wall thickness of the arterial segment before and after deformation, respectively. Following Ref. [22] the stress field in the arterial wall is described as a sum of passive Cauchy stress tensor due to elastic deformation, $[\boldsymbol{\sigma}^{\text{pas}}] = \text{diag}\{\sigma_1^{\text{pas}}, \sigma_2^{\text{pas}}\}$, uniformly distributed across the deformed wall thickness, and an active circumferential stress σ_2^{act}, which is generated by the stimulated circumferentially oriented VSMCs.

Given the strain energy function (SEF) $W(\boldsymbol{C})$ that describes the passive mechanical properties of arterial tissue and adopting the general form for σ_2^{act} as proposed in Ref. [22], the total stresses in the arterial wall are

$$\sigma_1 = \lambda_1 \frac{\partial W}{\partial \lambda_1}, \quad \sigma_2 = \lambda_2 \frac{\partial W}{\partial \lambda_2} + S F(\lambda_2) \tag{2}$$

The magnitude of the active circumferential stress depends on the intensity of muscular stimulation according to agonist dose-response relationship and on the actual deformation of the VSMCs, both accounted for in terms of continuum mechanics quantities, disregarding modeling of the contractile act in the framework of biophysics. The parameter S, called often the activation parameter, reflects the level of contractile activity of the VSMCs and is a measure of the ability of the muscular cells to contract and generate active stress. It is equal to the maximal value of the active circumferential stress that VSMCs are able to generate for given intensity of muscular stimulation. Depending on the level of stimulation, S varies from 0, which corresponds to relaxed VSMCs, to $S_{\max}$, which is the absolute maximal value of the active circumferential stress that muscle cells can generate. $F(\lambda_2)$ is a normalized function that varies over the interval [0, 1] and describes the influence of the deformed configuration on the active stress according to the length-active stress relationship. Often $F(\lambda_2)$ was identified as parabolic functions of λ_2. The operating points lay over the ascending part of the corresponding graphs before reaching maximum [22]. Both the stimulus intensity-specific values of S and function $F(\lambda_2)$ are determined from data of biaxial mechanical experiments of inflation of a tubular arterial segment at a different longitudinal stretch under monotonically increasing values of stimulation until reaching a repeatable response.

Finally, for Poiseuille flow the shear stress at the endothelium is $\tau = 4\mu Q/\pi r_i^3$, where Q is the volumetric flow rate and μ is the dynamic blood viscosity.

The equation of equilibrium in the radial direction that follows from a free-body diagram of a vessel inflated by an internal pressure is $\sigma_2 = \text{Pr}_i/h$, often called Laplace's law, which after making use of Eq. (1) takes the form

$$\lambda_2 \frac{\partial W}{\partial \lambda_2} + S F(\lambda_2) = P \frac{\left[\lambda_1 \lambda_2^2 \left(R_i + \frac{H}{2}\right) - \frac{H}{2}\right]}{H} \tag{3}$$

Given the SEF $W(\boldsymbol{C})$, initial dimensions R_i and H, axial stretch λ_1, activation parameter S, and function $F(\lambda_2)$, Eq. (3) allows us to calculate the only unknown parameter, the stretch λ_2, that governs the deformed and stress state of the vessel inflated by the pressure P.

In the particular case when an artery is inflated by the normotensive pressure P^N and is extended to in situ axial stretch $\lambda_1 = \lambda$, Eqs. (1)–(3) yield the strain and stress values termed the basal and hereafter are denoted by the subscript (b).

2.2 Adaptive Remodeling in Hypertension. We use the global growth approach proposed in Refs. [5] and [12], which allows us to calculate directly the outcomes of remodeling after its completion. In general, to obtain changes in arterial geometry, structure, and muscular tone when remodeling is complete, this approach entails the formulation and solution of a system of two sets of algebraic and/or transcendental equations. Firstly, the equations that follow from the continuum solid mechanics, and second phenomenological equations that describe the conditions imposed on outcomes of the remodeling process based on experimental observations or heuristic assumptions. The formulated system of equations exhibits a unique solution. This means that the geometrical configuration reached after completion of the remodeling process does not depend on the manner and rate by which it evolves over time before reaching the steady-state [5,12]. We consider the particular case of remodeling due to sustained hypertensive pressure P^H, keeping the basal values of the axial stretch and flow. We assume that remodeling does not alter the composition of the arterial tissue and therefore the mass fractions of the basic

structural constitutes remain unchanged. This implies that after completion of the remodeling process, the passive mechanical properties remain unchanged and the magnitude of the maximal active stress developed by the VSMCs is due solely to the change in the activation parameter S in the second of Eq. (2). As will be shown in Secs. 2.3–2.5, the passive mechanical properties and the magnitude of active stress do not affect directly the hypertension-induced apparent growth evaluated in terms of the deformed dimensions of the remodeled artery. However, they influence the zero-stress dimensions and the ratio between the passive and active stress when hypertensive pressure increases. In fact, the pioneer and most of subsequent mathematical models devoted to adaptive arterial remodeling in hypertension adopt as a reasonable premise the preservation of tissue composition [8–10].

Remodeling is adaptive when it restores at the cellular level the arterial homeostasis as it exists in the normotensive artery, i.e.,

$$r_{i(a)} = r_{i(b)}\,, \quad h_{(a)} = h_{(b)}\frac{P^H}{P^N} \tag{4}$$

where all values referring to the state of completed adaptive remodeling are hereafter denoted by subscript (a). The first equation in system (4) follows from the expression for flow-induced shear stress at the inner arterial surface and the requirement for its restoration to the basal value, i.e., $\tau_{(a)} = \tau_{(b)}$. The second equation in system (4) results from the requirement for restoration (normalization) of medial circumferential stress, namely, $\sigma_{2(a)} = \sigma_{2(b)}$, using Laplace's law for the normotensive and hypertensive artery with account for the first equation.

Obviously the remodeling-induced apparent growth, evaluated in terms of deformed dimensions $r_{i(a)}$ and $h_{(a)}$, does not depend on the mechanical properties of the wall material nor the active stress developed by the VSMCs provided the basal dimensions are known when the vessel is subject to the normotensive pressure.

It follows from system (4) that the deformed CSA is:

$$a_{(a)} = 2\pi\left(r_{i(b)} + \frac{h_{(b)}}{2}\frac{P^H}{P^N}\right)h_{(b)}\frac{P^H}{P^N} \tag{5}$$

Because $h_{(a)} > h_{(b)}$, according to the definition given in Ref. [6], adaptive remodeling is an outward hypertrophic growth. Obviously, the first equation of system (4) can be replaced by

$$2\pi\left(r_{i(a)} + h_{(a)}/2\right)h_{(a)} - a_{(a)} = 0 \tag{6}$$

Considering $a_{(a)}$ as a known input parameter.

To calculate the initial dimensions of the remodeled artery $R_{i(a)}$ and $H_{(a)}$, and deformation parameter $\lambda_{2(a)}$, system (4) must be rewritten in terms of these variables using Eq. (1), and adding the constitutive equation for restored circumferential stress $\sigma_{2(a)}$ as follows:

$$\begin{aligned}
\lambda_{2(a)}\left(R_{i(a)} + \frac{H_{(a)}}{2}\right) - \frac{H_{(a)}}{2\lambda\lambda_{2(a)}} - r_{i(b)} &= 0\\
\frac{H_{(a)}}{\lambda\lambda_{2(a)}} - h_{(b)}\frac{P^H}{P^N} &= 0\\
\lambda_{2(a)}\frac{\partial W}{\partial\lambda_{2(a)}} + S_{(b)}F\left(\lambda_{2(a)}\right) - \sigma_{2(b)} &= 0
\end{aligned} \tag{7}$$

It is worth noting that accepting parameter S as a measure of contractile state of the VSMCs, the restoration of basal homeostasis at the cellular level implies that $S_{(a)} = S_{(b)}$ as it was established experimentally in Ref. [23]. However, the active circumferential stress alters because $F\left(\lambda_{2(a)}\right) \neq F\left(\lambda_{2(b)}\right)$.

2.3 Maladaptive Inward Remodeling in Hypertension. Based on reported experimental observations, the outcomes of maladaptive inward remodeling do not meet two conditions that are present in the case of adaptive remodeling - the restoration of deformed inner radius and the restoration of basal tone. A substantial number of studies provide strong evidence that observed maladaptive inward hypertrophic remodeling is accompanied by a sustained elevation of the arterial pressure and the VSMCs tone [16,24]. In line with these findings, we built a mathematical model introducing two main premises: (i) maladaptive inward remodeling manifests as a reduced increase in the arterial mass compared to the case of adaptive remodeling under equivalent hypertensive pressures and (ii) the pressure-induced circumferential stress in the arterial wall is restored to its basal target value as happens in the case of adaptive remodeling. The rationale for these assumptions is the experimental findings that elevated tone in association with sustained hypertensive pressure down-regulate the normal differentiation of vascular smooth muscle cells from contractile to synthetic phenotype [25,26] and the data for the calculated hoop stress before and after completion of remodeling [27–29].

Given hypertension pressure P^H and in situ axial stretch $\lambda_{1(ma)} = \lambda$, to calculate the geometrical parameters that describe apparent growth due to maladaptive inward remodeling, i.e., $r_{i(ma)}$ and $h_{(ma)}$, we formulate and solve the following system of governing equations:

$$\begin{aligned}
&\frac{P^H r_{i(ma)}}{h_{(ma)}} - \sigma_{2(b)} = 0\\
&S_{(ma)} = \begin{cases} S_{(b)} + \left(S_{(\max)} - S_{(b)}\right)\dfrac{P^H - P^N}{P^{cr} - P^N} & \text{if } P^H \le P^{cr} \\ S_{(\max)} & \text{if } P^H > P^{cr} \end{cases}\\
&2\pi\left(r_{i(ma)} + \frac{h_{(ma)}}{2}\right)h_{(ma)} - a_{(b)}\\
&\quad + \left(\frac{S_{(\max)} - S_{(ma)}}{S_{(\max)} - S_{(b)}}\right)\left(a_{(b)} - a_{(a)}\right) = 0
\end{aligned} \tag{8}$$

where the subscript (ma) refers to maladaptive remodeled artery and P^H serves as a running input parameter.

The first equation in system (8) follows from the imposed requirement that the total circumferential stress in the remodeled artery, calculated from Laplace's law, is equal to the baseline circumferential stress. The second equation in system (8) gives the relationship between hypertensive pressure P^H and the corresponding value of activation parameter S. It is reasonable to assume that since under normotensive pressure P^N the artery exhibits basal muscular tone $S_{(b)}$, the augmentation of tone is monotonic as hypertensive pressure P^H increases. It takes a maximal value $S_{(\max)}$ for pressures equal to or higher than a certain critical value P^{cr}. Because of the lack of appropriate experimental data we selected a linear relationship to describe the association between hypertensive pressure and muscular tone, in which P^H serves as a running control parameter (Fig. 1(*a*)).

The third equation in system (8) is the key relationship of the proposed mathematical model. It defines the relationship between the CSA $a_{(ma)}$ of the deformed maladaptive artery (the first term in LHS) and the VSMCs activation parameter $S_{(ma)}$, both referring to a hypertensive pressure P^H. In agreement with the basic premises of this study, the existence of abnormal VSMCs tone modulates the remodeling response that would have happened in adaptive remodeling under elevated pressure P^H. It is assumed that the higher the tone $S_{(ma)}$ corresponding to the pressure P^H (according to the second equation in system (8)), the bigger the deviation of the value of the CSA of the maladapted artery $a_{(ma)}$ from the CSA $a_{(a)}$ of the artery provided it would have manifested adaptive remodeling under P^H. We postulate a hypertensive pressure-specific inverse linear relationship between $a_{(ma)}$ and $S_{(ma)}$ over the interval $[a_{(b)},\ a_{(a)}]$ when the tone varies over the interval $[S_{(b)},\ S_{(\max)}]$, as illustrated in Fig. 1(*b*). Provided the tone

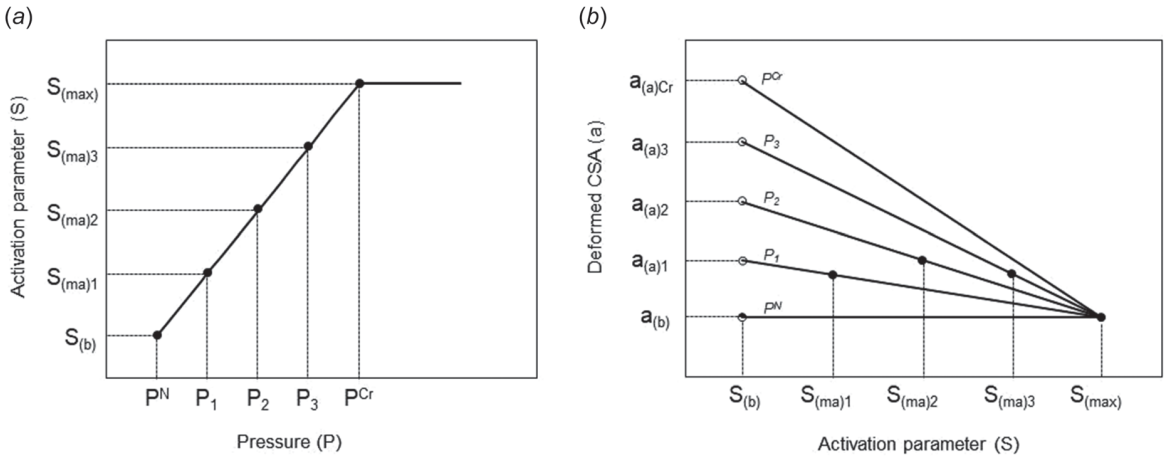

Fig. 1 Illustration of postulated analytical expressions for relationships between model parameters in system (8). (*a*) Points marked by solid circles (●) indicate activation parameter values in maladaptive remodeling due to elevated pressure. (*b*) Points marked by open circles (○) indicate arterial CSA resulting from adaptive remodeling to elevated pressure and basal VSMCs tone; points marked by solid circles (●) indicate arterial CSA resulting from maladaptive remodeling to elevated pressure and correspondingly increased VSMCs tone.

takes the maximal value $S_{(\max)}$ (when the hypertensive pressure is equal to or bigger than P^{cr}) the corresponding CSA of the maladapted remodeled artery is equal to the area $a_{(b)}$ of the normotensive vessel. Hence according to the definition given in Ref. [6], remodeling manifests as maladaptive eutrophic.

Similar to the case of adaptive remodeling, given the values of $\sigma_{2(b)}$, $a_{(b)}$, and $S_{(b)}$, to find the solutions of the system (8) it is not necessary to have information for the analytical form of the SEF of the arterial tissue.

Finally, as done in Sec. 2.2, to calculate the true growth, the first and the third equations in system (8) are rewritten in terms of the initial arterial dimensions and circumferential stretch $\lambda_{2(ma)}$, and the expression for restoration of the circumferential stress $\sigma_{2(ma)}$ is given as a sum of passive and active stress. The set of governing equations becomes

$$
\begin{aligned}
&P^H \frac{\left[\lambda\lambda_{2(ma)}^2\left(R_{i(ma)}+\frac{H_{(ma)}}{2}\right)-\frac{H_{(ma)}}{2}\right]}{H_{(ma)}}-\sigma_{2(b)}=0\\
&S_{(ma)}=\begin{cases} S_{(b)}+\left(S_{(\max)}-S_{(b)}\right)\dfrac{P^H-P^N}{P^{cr}-P^N} & \text{if } P^H\le P^{cr}\\ S_{(\max)} & \text{if } P^H>P^{cr}\end{cases}\\
&2\pi\left[\lambda_{2(ma)}\left(R_{i(ma)}+\frac{H_{(ma)}}{2}\right)-\frac{H_{(ma)}}{2\lambda\lambda_{2(ma)}}\right]\frac{H_{(ma)}}{2\lambda\lambda_{2(ma)}}\\
&\quad -a_{(b)}+\left(\frac{S_{(\max)}-S_{(ma)}}{S_{(\max)}-S_{(b)}}\right)\left(a_{(b)}-a_{(a)}\right)=0\\
&\lambda_{2(ma)}\frac{\partial W}{\partial\lambda_{2(ma)}}+S_{(ma)}F\left(\lambda_{2(ma)}\right)-\sigma_{2(b)}=0
\end{aligned}
\tag{9}
$$

Solutions of systems (8) and (9) for the set of increasing arterial pressures from the normotensive value P^N to the critical hypertensive pressure P^{cr} yield the evolution of the remodeling outcomes from adaptive to maladaptive eutrophic.

2.4 Maladaptive Inward Eutrophic Remodeling in Hypertension. Focusing on the maladaptive eutrophic remodeling it is of interest to specify the system of governing equations that allow evaluating how the magnitude of the critical pressure P^{cr} modulates the geometrical outputs. The deformed arterial dimensions are calculated from the system of two equations that describe the normalization of circumferential stress and preservation of the basal CSA as follows:

$$
\begin{aligned}
&P^{cr}\frac{r_{i(eu)}}{h_{(eu)}}-\sigma_{2(b)}=0\\
&2\pi\left(r_{i(eu)}+\frac{h_{(eu)}}{2}\right)h_{(eu)}-a_{(b)}=0
\end{aligned}
\tag{10}
$$

where the subscript *(eu)* denotes eutrophic remodeling.

To calculate undeformed dimensions and circumferential stretch, system (10) is modified as was done in Secs. 2.2 and 2.3, namely,

$$
\begin{aligned}
&P^{cr}\frac{\left[\lambda\lambda_{2(eu)}^2\left(R_{i(eu)}+\frac{H_{(eu)}}{2}\right)-\frac{H_{(eu)}}{2}\right]}{H_{(eu)}}-\sigma_{2(b)}=0\\
&2\pi\left(R_{i(eu)}+\frac{H_{(eu)}}{2}\right)\frac{H_{(eu)}}{\lambda}-a_{(b)}=0\\
&\lambda_{2(eu)}\frac{\partial W}{\partial\lambda_{2(eu)}}+S_{(\max)}F\left(\lambda_{2(eu)}\right)-\sigma_{2(b)}=0
\end{aligned}
\tag{11}
$$

Finally, the pressure-induced changes in arterial dimensions caused by a hypertensive pressure when an artery has already developed inward eutrophic remodeling, i.e., for $P^H > P^{cr}$, are obtained by solving again the systems (10) and (11) replacing P^{cr} with P^H.

2.5 Fictitious Adaptive Remodeling in Hypertension. Maladaptive remodeling considered in Secs. 2.3 and 2.4 is modeled by accounting for the effects of altered arterial CSA and the change in the muscular tone. To evaluate solely the individual contribution of the VSMCs tone, we consider a fictitious scenario in which an artery restores both shear and medial stress but not the tone. The deformed inner radius and deformed thickness are equal to the dimensions in the case of adaptive remodeling calculated from system (4). The only difference is in dimensions in the state of zero-stress that have to be obtained from system (7) replacing in the last equation the input parameter $S_{(b)}$ with $S_{(ma)}$, calculated from the second equation in system (9).

3 Illustrative Simulations

To illustrate the descriptive and predictive power of the proposed model, we utilize a published constitutive model of

muscular basilar artery of male New Zealand white rabbits that accounts for both the passive and active mechanical properties [30]. The authors quantified the passive properties of arterial tissue with a four-fiber family structure-motivated SEF

$$W = \frac{c}{2}(I_1 - 3) + \sum_{k=1.4} \frac{c_1^k}{4c_2^k} \left\{ \exp\left[c_2^k \left((\lambda^k)^2 - 1 \right)^2 \right] - 1 \right\} \quad (12)$$

I_1 is the first invariant of the right Cauchy–Green strain tensor; c is a material constant that accounts for the contribution of the elastin-dominated matrix; c_1^k and c_2^k are material parameters associated with the k^{th} collagen fiber family, where $k = 1, 2$ denotes fibers oriented in the axial and circumferential direction and $k = 3, 4$ - helically oriented symmetric fibers with equivalent mechanical properties ($c_1^3 = c_1^4$ and $c_2^3 = c_2^4$). The tissue stretch in the direction of a fiber family is

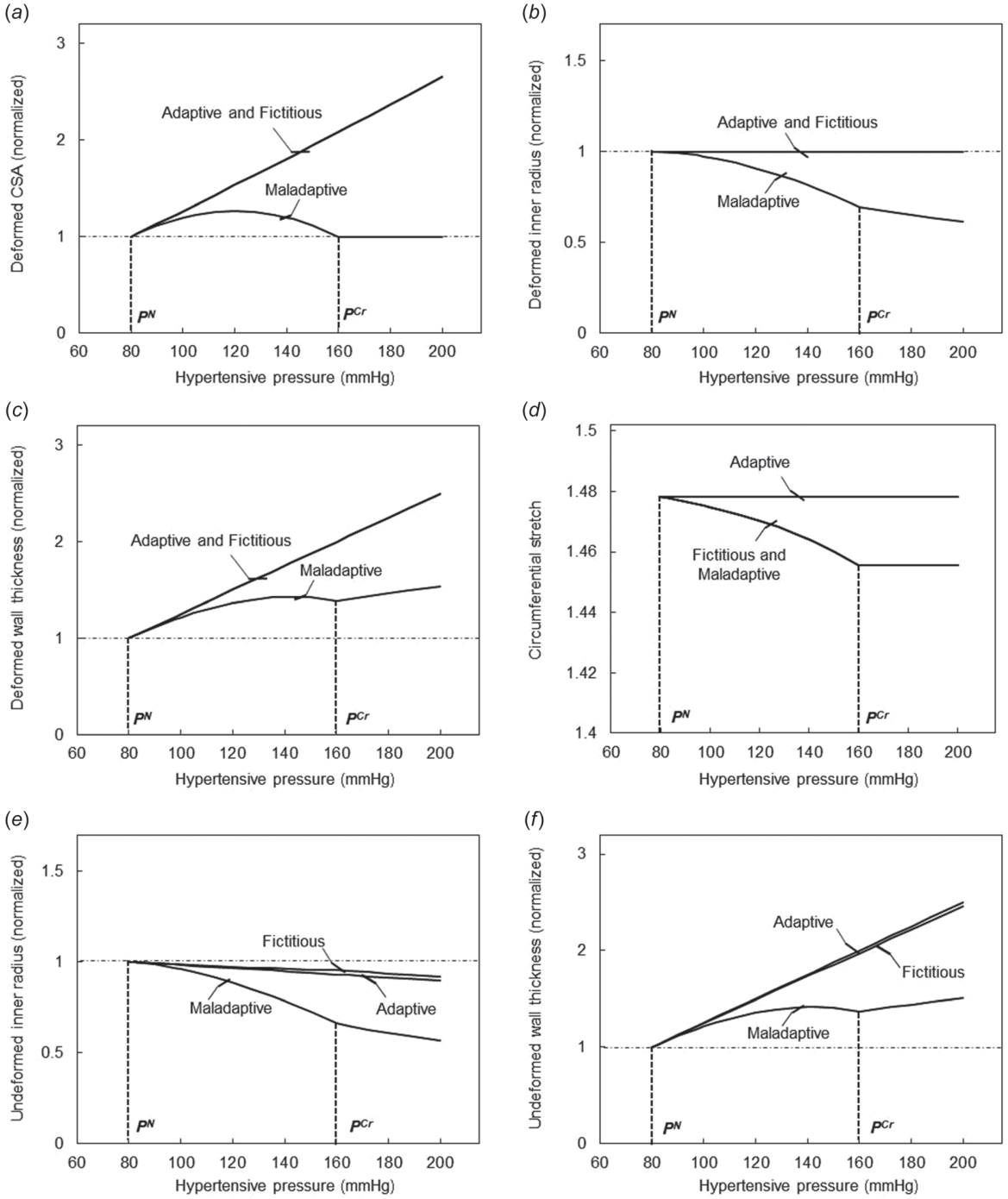

Fig. 2 Outcomes of pressure-induced remodeling. (*a*) Normalized deformed arterial CSA, (*b*) normalized deformed inner radius, (*c*) normalized deformed wall thickness, (*d*) circumferential stretch, (*e*) normalized undeformed inner radius, and (*f*) normalized undeformed wall thickness. Depicted fictitious and maladaptive arteries were assigned a critical pressure of 160 mmHg; normalization was done with respect to the baseline values for arterial pressure of 80 mmHg. Note that CSA remains unchanged in the maladaptive case for hypertensive pressures higher than the critical pressure of 160 mmHg.

$$\lambda^k = \sqrt{\lambda_2^2 \sin^2\alpha^k + \lambda_1^2 \cos^2\alpha^k} \tag{13}$$

where α^k is the angle between the k^{th} fiber direction and the axial direction.

Following the accepted trend in the description of the active mechanical response, the authors considered the active circumferential stress to be additive to the passive stress and to depend on the degree of VSMCs contractility and the tissue stretch. To comply with the analytical description of the active circumferential stress given by the second of Eq. (2) we modified the original expression given in Ref. [30] as follows:

$$\sigma_2^{\text{act}} = Se^{-b\left[\frac{\lambda_M - \lambda_2}{\lambda_M}\right]^2} \tag{14}$$

where S is the activation parameter that reflects the degree of VSMCs contractility, b is a dimensionless parameter, and λ_M is the circumferential stretch at which the active stress exhibits maximal value.

We adopted from Ref. [30] the mean values for geometrical parameters of 12 basilar arteries as follows: inner radius $R_i = 0.282$ mm and wall thickness $H = 0.064$ mm The passive and active mechanical response-related model parameters are assigned in accordance with a specific representative vessel (basilar artery specimen number 5), namely, $c = 6.63 \times 10^{-1}$ kPa; $c_1^1 = 12.71$ kPa; $c_2^1 = 3.47$; $c_1^2 = 4.35 \times 10^{-9}$ kPa; $c_2^2 = 15.16$; $c_1^3 = c_1^4 = 11.11$ kPa; $c_2^3 = c_2^4 = 1.19$; $\alpha^1 = 0$ deg; $\alpha^2 = 90$ deg; $\alpha^3 = 55.95$ deg; $\alpha^4 = -55.95$ deg; $b = 6.09$; $\lambda_M = 2.31$.

Baseline loading conditions are assigned based on reported basilar artery mean values as follows: normotensive pressure $P^N = 80$ mmHg, in situ axial stretch $\lambda = 1.15$, baseline tone $S_{(b)} = 51.91$ kPa. The vessel undergoes a finite elastic deformation with circumferential stretch $\lambda_{2(b)} = 1.48$ and in the deformed state the dimensions are $r_{i(b)} = 0.446$ mm, $h_{(b)} = 0.038$ mm, and CSA $a_{(b)} = 0.110$ mm^2. The corresponding total basal circumferential stress is $\sigma_{2(b)} = 125.9$ kPa.

The maximal tone $S_{(\max)}$ and the critical pressure P^{cr} are specific parameters of the proposed mathematical model. We adopted from Ref. [30] $S_{(\max)} = 127.01$ kPa, which was experimentally identified under very high stimulation though there is not explicit evidence that the contractile response has reached a plateau. As for the critical pressure, which in concert with maximal muscular tone causes inward eutrophic remodeling, it is reasonable to assume that its value is muscular artery type- and patient-specific. Because of the lack of such data, to obtain illustrative predictive results we assigned $P^{cr} = 160$ mmHg, except in the case when it varies in order to evaluate its effects on arterial geometry upon completion of inward eutrophic remodeling. The experimental identification of the critical pressure requires simultaneous recording of the arterial pressure and morphological data that track changes in arterial CSA over time of maladaptive remodeling. In line with the premises of the proposed model, the critical pressure is the smallest value of pressure at which the CSA of maladaptive vessel becomes equal to the baseline CSA.

The commercially available numerical solver MAPLE 12 (Maplesoft^{TM}, Waterloo, ON, Canada) was used to solve the governing equations referring to normotensive load conditions at basal VSMCs tone and in each of the remodeling scenarios. The governing systems of equations are given in Secs. 2.2, 2.3, and 2.5 were solved by keeping the basal value of the axial stretch and varying the hypertensive arterial pressure within the interval from 80 to 200 mmHg. The results obtained are illustrated in Fig. 2. Solving the governing system of equations given in Sec. 2.4 yields results that show how the arterial geometry resulting from an inward eutrophic remodeling is modulated by the magnitude of critical pressure (Fig. 3) and how arterial geometry remodels when the hypertensive pressure is higher than the critical pressure (Fig. 2 portions of curves for $P^H > P^{cr}$ and Fig. 4). Finally, numerical results were processed to illustrate the arterial response before and after completion of pressure-induced adaptive and maladaptive remodeling (Fig. 5).

4 Discussion

We propose a relatively simple two-dimensional mathematical model of maladaptive inward arterial remodeling that combines equations of mechanics with phenomenological equations that describe the remodeling-induced change in arterial mass, augmentation of the VSMCs tone, and the value of hypertensive pressure. Results from illustrative simulations allow to test the proposed hypotheses and to evaluate the descriptive and predictive power of the model. The analysis is performed in two aspects. First, we discuss how and why arterial dimensions change due to increasing hypertensive pressure when adaptive, maladaptive inward, and inward eutrophic remodeling is completed. Second, we discuss how the arterial geometry changes as a result of hypertensive

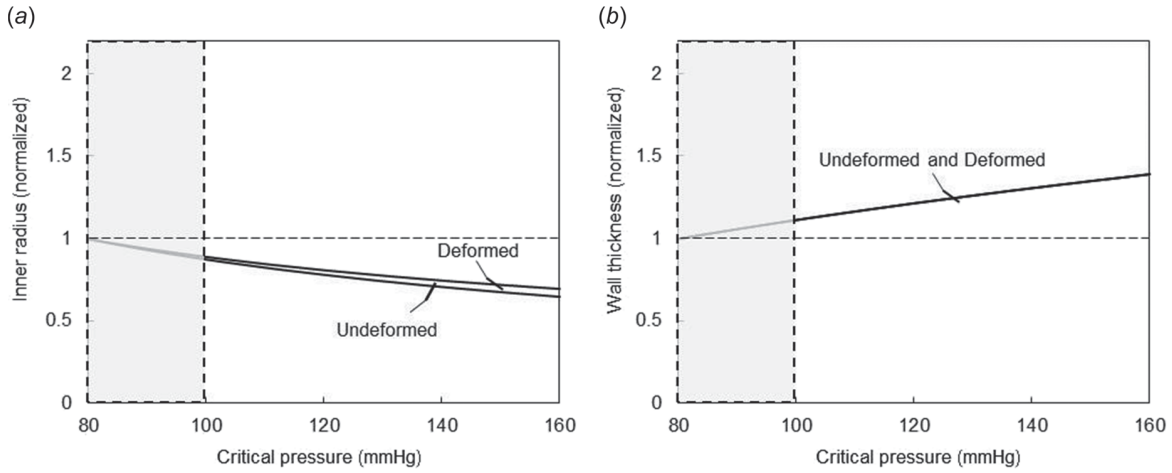

Fig. 3 Effects of critical pressure on arterial geometry upon completion of inward eutrophic remodeling. (*a*) normalized inner radius and (*b*) normalized wall thickness. Curves refer to remodeling outputs when the hypertensive pressure is equal to the critical pressure. The shaded regions indicate physiologically implausible remodeling response calculated for hypothetical critical pressure below 100 mmHg. Normalization was done with respect to the values for critical pressure of 80 mmHg.

pressure for an artery after completion of inward eutrophic remodeling.

4.1 Descriptive and Predictive Results. It is typical for biological events that they do not develop in a stepwise manner and therefore cannot be modeled in the framework of catastrophe theory [31]. Rather a continuous evolution of a steady-state is observed when one or more governing parameters vary. The normotensive artery and the hypertensive artery after completion of inward eutrophic remodeling have equal CSA. Therefore it is reasonable to assume ad hoc that the CSA of the maladaptive remodeled artery evolves in a nonmonotonic manner as the arterial pressure increases. However, no clues exist about the type of relationship in which this happens.

We introduce subsets "hypertrophic remodeling+" and "hypertrophic remodeling–" to label the directional changes in the arterial mass when hypertensive pressure increases. Adaptive and fictitious adaptive remodeling belong to the subgroup of "hypertrophic remodeling+" (Fig. 2(*a*)). According to introduced assumptions, remodeling-induced growth is a result of the altered synthetic activity of the VSMCs toward the restoration of the basal level of the circumferential wall stress. Hypertensive pressure, via produced high medial stress, is the governing factor for augmentation of the synthetic activity of the VSMCs, which leads to a monotonic increase in arterial CSA in the case of adaptive and fictitious adaptive remodeling (Fig. 2(*a*)). The remodeling response is identical because the deformed inner radius keeps its baseline value and CSA varies as a result of wall thickening, which is driven solely by the total circumferential stress irrespective of the relative contribution from the passive and active stress components. The results obtained for maladaptive remodeling, predict, however, that the apparent growth manifests as a nonmonotonic variation of CSA with increasing hypertensive pressure (Fig. 2(*a*)). For P^H lower than P^{cr}, remodeling is hypertrophic but the CSA is smaller than the CSA for the case of adaptive remodeling compared at identical pressures. This result follows from the last equation in system (8), which implies that the pressure-associated increase of muscular tone downregulates the mass production. For pressure ranges (P^N, P^I) and (P^I, P^{cr}), the growth is due to "hypertrophic remodeling+" and "hypertrophic remodeling–," respectively, and the inversion point is at pressure $P^I = (P^N + P^{cr})/2$ (Fig. 2(*a*)). Critical pressure P^{cr} corresponds to the extreme case of inward eutrophic remodeling when the deformed CSA is equal to the area of the normotensive vessel, which remains the same for pressures higher than P^{cr}. Similar is the mode illustrating the variation of normalized undeformed CSA (results not shown), because due to material incompressibility the deformed and undeformed areas differ only by a factor equal to the inverse value of the axial stretch.

If a high hypertensive pressure causes inward eutrophic remodeling, the model predicts that under smaller hypertensive pressure the vessel experienced maladaptive hypertrophic remodeling (Fig. 2(*a*)). This conclusion is supported by published data from medical observations. For instance, in Ref. [6] the author wrote that in hypertension "it is possible, for example, that the vessel could first experience inward hypertrophic remodeling which could then move to inward eutrophic remodeling." Similar conclusions based on experimental findings are given also in Refs. [13] and [32].

Effects of remodeling on geometry and circumferential stretch are shown in Figs. 2(*b*)–2(*e*). In contrast to the cases of adaptive and fictitious adaptive remodeling, the deformed inner radius in maladaptive remodeling does not keep its basal value but decreases monotonically with pressure (Fig. 2(*b*)). This means that provided the blood flow remains unchanged, according to the Poiseuille formula the flow-induced shear stress at the endothelium increases. In healthy arteries, elevated shear stress, which might happen due to an increase in flow, causes an increase in endothelium-derived relaxing factor, mainly NO. The diminished VSMCs tone provokes an acute arterial vasodilation which tends to restore the basal shear [5]. On the contrary, in the case of maladaptation, the increased shear caused by the reduced lumen is associated with elevation of tone, accounted for in the model by the imposed proportionality between the activation parameter and hypertensive pressure (second equation in system (8)). One plausible cause for the persistent existence of high VSMCs tone is a common arterial pathology termed as endothelial dysfunction [33]. Endothelial cells are not capable to oppose, by producing NO, the factors that cause VSMCs constriction, and the tone is kept persistently elevated. Moreover, it is assumed that ECs might contribute to the augmentation of tone by production of the so-called endothelium-derived constricting factors [34]. Presence of endothelial dysfunction was reported in (e.g., Refs. [35,36]) as an important determinant for the development of maladaptive inward vascular remodeling. Therefore coexistence of high pressure, elevated tone, and reduced lumen which was observed in the case of endothelial dysfunction supports the predictive model result for narrowing the arterial lumen under hypertensive pressure and proportionally increased muscular tone. For instance, in Ref. [36] the authors wrote: "endothelial dysfunction may participate to the increased vascular tone in hypertension" and "resistance arteries undergo vascular remodeling (reduced lumen with increased media width)."

Results from the illustrative simulations show that due to maladaptive remodeling the deformed wall thickness increases with pressure in a nonmonotonic manner (Fig. 2(*c*)). It seems that it is a variation of the wall thickness that is affected by the nonmonotonic variation of CSA, while the variation of inner radius persistently decreases. The difference in modes of change in geometrical parameters is due to the fact that each of them is included differently in the analytical expression for deformed CSA (LHS of the third equation in system (8)). Provided the CSA is expressed in terms of inner and outer radii, which makes their contribution analytically similar, the outer deformed radius monotonically decreases with hypertensive pressure (result not shown).

The trends of the normalized undeformed dimensions of the remodeled artery when the hypertensive pressure increases are very similar to those for deformed inner radius and thickness (Figs. 2(*e*) and 2(*f*)). As follows from the corresponding systems of governing equations given in Secs. 2.2–2.5, the difference between curves is due to the effects of the circumferential stretch λ_2 needed to transform the undeformed configuration of the remodeled artery into a deformed configuration. Three inequalities hold true: the thermodynamic restriction that $\partial W/\partial\lambda_2 > 0$ at constant λ_1, by definition $\partial F/\partial\lambda_2 > 0$ over the operating range, and from the postulated relation given by the second equation in system (8) that $dS/dP^H \geq 0$. Simultaneous satisfaction of these conditions and the postulated assumption that circumferential wall stress is restored in all remodeling scenarios, impose that stretch λ_2 cannot be an increasing function of hypertensive pressure, i.e., $\partial\lambda_2/\partial P^H \leq 0$. The circumferential stretch is constant in the case of adaptive and developed eutrophic remodeling in which the activation parameter S does not vary with the hypertensive pressure and takes value $S_{(b)}$ or $S_{(\max)}$, respectively. Decreasing λ_2 with increasing hypertensive pressure in the case of fictitious adaptive or maladapted remodeling, in which S increases accordingly, is illustrated in Fig. 2(*d*). Because of the specifics of the input data adapted from Ref. [30] this effect is insignificant (less than 1.5%) over considered pressure range.

The predictive model results in Fig. 2 follow from the premise that the new mass and its spatial distribution, needed to normalize the circumferential stress under hypertensive pressure, is governed by the pressure-associated chronic elevation of the VSMCs tone. This happens via several pathways. A comparison of the results obtained for the undeformed dimensions of the vessel in the cases of adaptive and fictitious adaptive remodeling (Figs. 2(*e*) and 2(*f*)) shows that the individual contribution of the increased tone to the total circumferential stress by augmentation of the active stress is

not a predominate factor. The most important effect of the elevated tone is due to the restriction that it imposes on the mass of the maladapted artery. The major novelty of the model is the introduced hypothesis that the elevated tone determines a hypertensive pressure-specific mass, which represents a fraction of the mass produced by the VSMCs in the case of adaptive remodeling as governed by third equations in systems (8) and (9). The hypertensive pressure defines the hypothetical upper bound of the mass, while the elevated muscular tone modulates remodeling and determines the actual mass (Fig. 1(*b*)). These two factors compete with one another. As a net result, the model predicts that at low hypertensive pressures, maladaptive remodeling manifests as "hypertrophic remodeling+," and turns into "hypertrophic remodeling–," over high-pressure domain (Fig. 2(*a*)).

So far the discussion focused on the results that follow from the proposed mathematical model but did not address the biological events that initiate the development of maladaptive remodeling. In this regard, some well-established biological findings can serve as a rationale for the hypothesized scenario of the remodeling response and facilitate interpretation of the obtained descriptive and predictive results. Under normotensive conditions, most of medial VSMCs display a contractile phenotype, while the remaining part is involved in keeping the balance between synthesis and degradation of extracellular mass. In hypertension, a subset of VSMCs manifests phenotype switching to differentiate from contractile into a synthetic phenotype [25]. This process is considered to be the leading mechanism in arterial remodeling [26,27] and is directed to keep the local homeostasis. On the other hand, there is substantial evidence that the persistent vasoconstriction of VSMCs suppresses their normal phenotype switching that would have ensured adequate mass synthesis needed for normalization of both the flow-induced shear stress at the endothelium and pressure-induced medial circumferential stress. It appears that restoration of the target stress sensed by the VSMCs takes priority over keeping baseline shear stress at the endothelium. When the remodeling process is completed, the mass is rearranged in a manner that the artery becomes a vessel with smaller lumen and thicker wall, such that only the circumferential stress is normalized. Therefore, the configuration of the arterial cross section shows that the pressure-induced arterial growth manifests as maladaptive inward remodeling, which in the extreme case becomes eutrophic [24,28,29].

A specific characteristic of the proposed mathematical model is the dual role that hypertensive pressure plays. Recall that to investigate experimentally the adaptive remodeling in hypertension the authors used different methods to generate a sustained increase in arterial pressure [7]. Accordingly, mathematical models study adaptive remodeling of an artery caused by a stepwise increase in arterial pressure considering it as a known input parameter [8–12]. In contrast, the proposed model includes the hypertensive pressure P^H not solely as a load on the artery but also as a model state parameter that is inter-related to another state parameter, i.e., the activation parameter S (the second equation in systems (8)). From a biological point of view, the magnitude of arterial pressure that inflates an artery is determined by the resistance to the blood flow created by the resistive vessels located distally. It is reasonable to assume that in the case of maladaptive inward remodeling, which develops under increased tone, the reduction of lumen diameter due to increased constriction upregulates the vascular resistance and thereby affects the magnitude of the systemic arterial pressure. Therefore, based on mechanical speculations, the equation that postulates proportionality between the tone and arterial pressure accounts for a long-distance cause-response effect. The second equation in system (8) does not belong to equations of continuum mechanics, which is a local field theory. It is typical for cybernetics, where such type relations are often quantified from experimental data using regression analysis. Due to lack of appropriate information, we selected the simplest linear relations (Fig. 1(*a*)). Some numerical simulations were performed using several types of sigmoidal relationships between the hypertensive pressure and muscular tone, which gave qualitatively similar results (not shown).

Results obtained in Fig. 3 show that inward eutrophic remodeling may develop at different hypertensive pressure (termed as critical pressure) when the associated VSMCs tone takes a maximum value. The geometrical outcomes of eutrophic remodeling may occur in cross-sectional configurations with different inner radius/wall thickness ratio. The model predicts that the higher the hypertensive pressure at which eutrophic remodeling develops the smaller are both the deformed and undeformed arterial radius and the thicker is the arterial wall. Whether inward hypertrophic remodeling may evolve into eutrophic depends on the magnitude of the chronic increase in the VSMCs tone, but how mass is distributed to specify arterial cross section in a way to normalize the circumferential wall stress is governed by the magnitude of hypertensive pressure. Like many biological events, it seems that inward eutrophic remodeling is patient-specific.

Not surprisingly, the model predicts that once an artery has developed a configuration corresponding to inward eutrophic remodeling, a further increase in arterial pressure keeps the CSA constant and solely redistributes the available mass in a manner that the inner radius continues to decrease while the wall thickness increases (Figs. 2 and 4). It follows from Fig. 2(*d*) that not only the total circumferential stress but also its passive and active components do not change. Similar to adaptive remodeling, geometrical outcomes do not depend on remodeling history. It is

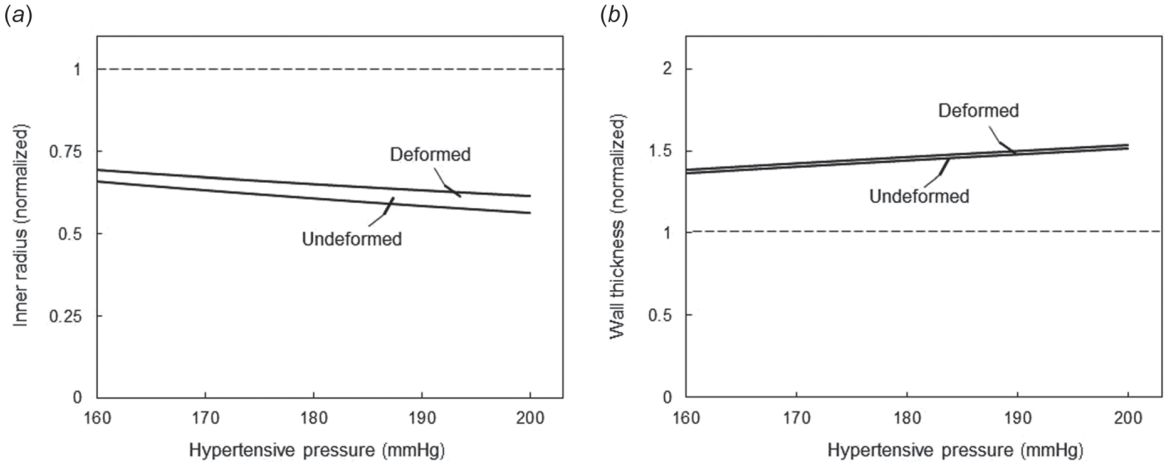

Fig. 4 Outcomes of maladaptive inward remodeling after development of the eutrophic response. (*a*) Inner radius and (*b*) wall thickness. Normalization was done with respect to the baseline values for pressure of 80 mmHg.

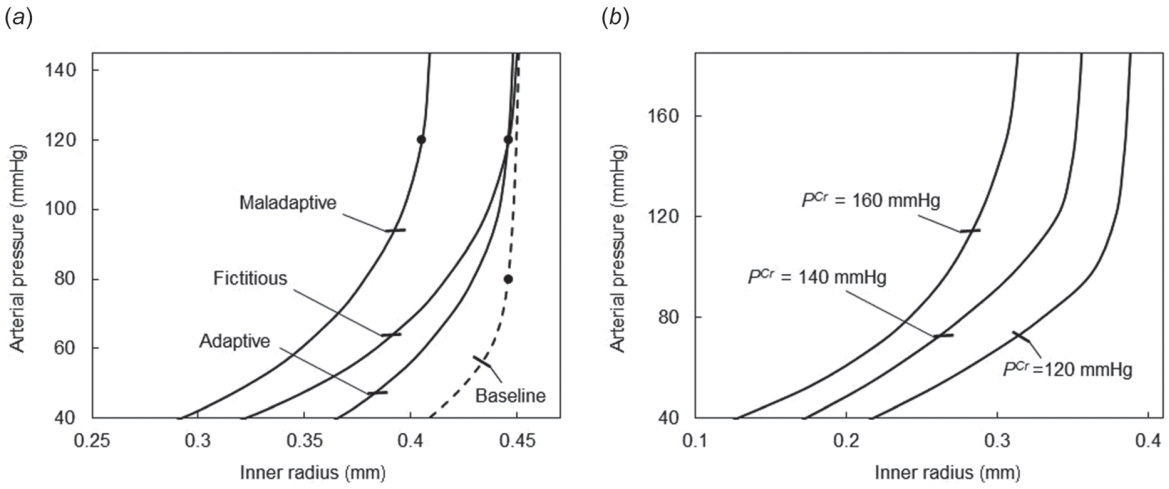

Fig. 5 Arterial response before and upon completion of pressure-induced adaptive and maladaptive remodeling. (*a*) The pressure-radius response of the baseline and remodeled arteries due to hypertensive pressure of 120 mmHg; in the cases of fictitious and maladaptive remodeling, the assigned critical pressure is 160 mmHg; solid circles (●) denote deformed states under arterial pressure of 120 mmHg for remodeled arteries and 80 mmHg for the normotensive artery. (*b*) The pressure-radius response of arteries upon completion of maladaptive inward eutrophic remodeling under different critical pressures.

reasonable to speculate that narrowing of the lumen due to inward eutrophic remodeling occurs also in resistance vessels located distally, augments the vascular resistance, and proceeds as positive feedback that might cause further elevation of arterial pressure. Therefore, maladaptive remodeling might promote not only the development of hypertension but also its progression.

Arterial response evaluated in terms of pressure-inner radius relationship is strongly affected by the arterial geometry. As the vessel remodels under hypertensive pressure the inner radius/thickness ratio decreases and the artery displays a progressive decrease in deformability (Fig. 5). This effect is relatively moderate in the cases of adaptive and fictitious adaptive remodeling compared to the case of maladaptive remodeling (Fig. 5(*a*)), and it becomes more significant if the artery completed inward eutrophic remolding at higher critical pressure (Fig. 5(*b*)). This conclusion is supported by the experimental observations in Ref. [17], which is the only published paper in which we found a graphic illustration of remodeling-caused decreased deformability of a resistive vessel.

4.2 Limitations and Perspectives. To focus on the novelty of the proposed model we introduced assumptions that simplify the numerical calculations and facilitate the interpretations of the predictions. There are many ways how the proposed mathematical model can be generalized and improved as was done after publishing the first models on adaptive remodeling of large arteries in 1996 [8,9]. Considering an artery as thick-walled two-layered tube, using refined constitutive models that account for the tissue composition and stress interaction between constituents [37], and including the effects of residual strains, are some but not all possible directions to refine the model. However, the lack of available experimental data for quantification of model parameters does not allow performing numerical simulations needed for verification of these modes. In contrast to large elastic arteries, there are only a few published constitutive models referring to muscular arteries [30,38] and to our knowledge none to arterioles. Provided that quantitative histological data is available, due account of remodeling-mediated changes in mass fractions of the load-bearing constituents and VSMCs could be incorporated into the modeling framework as done in Ref. [37]. Therefore, how eutrophic remodeling might be accompanied by a change not only in the geometry but also in the structure and composition of the arterial wall is still an open issue. Moreover, the analytical expressions for the relationship between the muscular tone and hypertensive pressure and between a descriptor of the chronic muscular contraction of VSMCs and the outcomes of their synthetic activity, postulated to be linear in this paper, need specification based on collection and analysis of model-oriented biological data. Though it is accepted that the change in arterial geometry is due mainly to inward eutrophic remodeling that originates from the impaired synthetic activity of VSMCs, other factors such as switching apoptosis, low-grade inflammation, and vascular fibrosis are processes, as suggested in Ref. [32], that wait to be incorporated into future models. Finally, it is worth noting that not only persistent elevation of VSMCs contractility appears to be a determinative factor for development of a maladaptive arterial response in hypertension. A recent study showed that diminished vasoactive capacity observed in a nonpharmacologic mouse model of induced hypertension might also compromise effective adaptations of a common carotid artery and result in Marfan syndrome [39].

4.3 Conclusion. In conclusion, we proposed a relatively simple two-dimensional mathematical model as a first step in understanding the mechanism of development and progression of maladaptive inward eutrophic remodeling in muscular arteries. Two features make the approach different from the traditional modeling of adaptive remodeling done so far. First postulates a continuum mechanics-based equation that relates the magnitude of the chronic increase in the VSMCs tone with the arterial CSA considered as a generalized descriptor of the geometrical output of remodeling induced growth; and second, postulates a relationship between tone and high arterial pressure. It was shown that the elevated VSMCs tone initiates and is the major cause of maladaptive remodeling, but the process is driven by the magnitude of arterial pressure aiming ultimately to normalize the circumferential wall stress. We expect that some open questions that the model provokes would stimulate further theoretical studies, which in concert with medical and biological investigations, will better elucidate how inward eutrophic remodeling is associated with and has an influence on the development and progression of hypertension.

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