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SPECIAL ISSUE

ARTERIAL SOLID MECHANICS. A BRIEF REVIEW AND BULGARIAN “IMPRINT”*

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ABSTRACT: This paper provides an overview of research in arterial solid mechanics for readers who may not have expertise in the field of biomechanics. The review explores whether a healthy artery functions as an ”intelligent” organ. A brief description of the biological and mechanical processes that govern arterial performance is followed by an overview of typical experimental findings and mathematical models describing the passive, active, and remodeling behavior of healthy arteries. The review includes critical commentary based on the author’s perspective. The term ”Bulgarian imprint” highlights the significant contributions of Bulgarian scientists, frequently in collaboration with international partners, to arterial biomechanics. When cited, the corresponding papers are denoted in the reference list by an asterisk.

KEY WORDS: vascular mechanics, finite elasticity, residual strains, smooth muscle contraction, remodeling, stenting and grafting.

1 INTRODUCTION

In short, biomechanics is the application of mechanics to biology and medicine, focusing on mechanical processes within living organisms. The function of arteries to convey and distribute oxygenated blood to organs and tissues meets this definition. Investigations encompass experimental studies that aim to describe and analyze the mechanical aspects of biological events, as well as the development of mathematical models to yield predictive results.

The importance of biomechanics is evident in its ability to expand the horizon of knowledge and provide a scientific foundation for developing new diagnostic and therapeutic methods and devices that improve, prevent, or replace an organ or physiological function. A better understanding of biological processes is essential for advancements in medical treatment and care.

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As an illustrative example, consider the strong correlation, documented in human post-mortem reports, between the progression of atherosclerosis and the gradual increase in arterial stiffness. However, it is not currently feasible to directly assess an artery's mechanical properties for diagnosing potential pathologies. Within the biomechanics framework, the function of large arteries to convey blood is modeled as the propagation of flow and pressure waves through an elastic tube filled with a viscous fluid. Solving the corresponding mathematical problem yields a relationship between the pulse wave velocity (PWV) and the value of the arterial stiffness (e.g., [1*]). Because PWV can be determined non-invasively by dividing the distance between two fixed points along an artery by the time delay of the pulse signal, it can be used to quantify the vessel's stiffness. Details about the recording methodology and the clinical application of PWV can be found in the medical literature (e.g., [2]).

1.1 Anatomy and Histology of Conduit Arteries

The arterial system resembles a tree-like branching tube network, with diameters ranging from 2.5 cm (in the human aorta) to 200 µm (in arterioles). Arterial tissue is composed of cells and an extracellular matrix (ECM). The ECM maintains the integrity and strength of the arterial tissue and serves as a home for vascular cells. In turn, vascular smooth muscle cells (VSMCs) produce the ECM.

An artery has three main layers: the intima, media, and adventitia. The intima is composed of endothelial cells (ECs) that are in direct contact with flowing blood. The media consists mainly of circumferentially oriented VSMCs, a system of highly deformable elastin fibers with no preferred orientation, and four stiffer collagen fiber families aligned circumferentially, axially, and in two symmetric helical directions. The media is the primary load-bearing part of the arterial wall. The adventitia is composed of collagen and fibroblast cells and functions as a protective layer against high pressures. The structural components and cells are smaller than 1/100th the size of the artery, which justifies modeling arteries using continuum mechanics.

1.2 Loads and Stresses

Arteries are subjected to arterial pressure (approximately 13.33 ± 2.66 kPa), axial forces from surrounding tissues, and shear forces resulting from the friction between flowing blood and the arterial wall. The forces generate stresses. Considering an artery as a long cylindrical tube that undergoes finite deformations, the mean circumferential wall stress $\langle t_{\theta\theta} \rangle$ is calculated from a formula often known as the law of Laplace. Assuming a developed flow of a Newtonian fluid, the flow-induced shear stress at the inner arterial surface τ is given by the relation, usually named Poiseuille's law

$$\langle t_{\theta\theta} \rangle = \frac{Pr_i}{h}, \qquad \tau = \frac{4Q\mu}{\pi r_i^3}, \tag{1}$$

where P is the arterial pressure, r_i – deformed inner radius, h – wall thickness, Q – flow rate, and μ – blood viscosity.

Cells are mechanosensitive and tend to maintain specific stress levels, known as *target stresses*. These are approximately 100–150 kPa for circumferential wall stress and 1.5 Pa for shear stress, and they remain virtually constant along the entire arterial tree.

1.3 Residual strains and stresses

When a ring segment of an artery is cut radially in its unloaded (traction-free) state, it springs open into a shape resembling a circular sector. This behavior reveals the presence of residual strains and stresses within the arterial wall. The phenomenon was first reported by Vaishnav and Vossoughi [3], and independently by Chuong and Fung [4]. The sector's opening angle, as defined in [4], serves as an indicator of these residual mechanical effects. It is typically assumed that a single radial cut releases all residual strains and stresses, and that the resulting opened configuration represents the artery's natural (stress-free) state. Consequently, this configuration is often used as the reference state for calculating strain measures.

Over the past decades, numerous studies have examined the variation in the opening angle of arteries across different anatomical locations, age groups, sexes, levels of muscular tone, and pathological conditions. One of the most frequently cited studies [5*] presents observations on the change in the opening angle after progressive removal of arterial wall layers from a bovine carotid artery, as well as following the selective elimination of collagen or elastin using chemical methods. A comprehensive review of residual strains in conduit arteries is provided in [6*].

The residual strains resulting from the finite deformation between the zero-stress and the traction-free configurations have important biological consequences. They modulate the actual strain field in the deformed state such that, under physiological loads, the circumferential strain and stress distributions across the arterial wall are nearly uniform. This ensures effective load-bearing and provides a nearly identical stress environment for the mechanosensitive VSMCs, thereby supporting optimal mechanical operation. As shown in [7], in addition to the systemic requirement for flow distribution, this principle governs the simultaneous variation of the deformed inner diameter, axial stretch ratio, and area compliance along the aorta. Otherwise, if the traction-free configuration is taken as the reference, the inflation of an artery under physiological pressure leads to a pronounced stress gradient across the wall thickness due to geometric and physical nonlinearities.

Surprisingly, there is one widespread but unfortunately incorrect explanation of the cause of stress homogenization in arteries. Several scientific articles from prestigious labs are entitled "Effects of residual stresses on...", suggesting that residual stresses cause stress homogenization. However, stress depends on strains at a given point in the continuum, not on the stress that exists at that point in a different deformed state. The origin of this misunderstanding is the existence of one particular case in which the total circumferential stress in an inflated tube is indeed equal to the sum of the residual stress due to deformation from the opened-up to the traction-free configuration and the stress due to the successive deformation to the final deformed configuration. This occurs when an inflated elastic tube undergoes small deformations and the wall material is a linearly elastic solid. However, the fact that this statement holds in that specific case does not imply a causal connection between the total and residual stresses. In this case, homogenization is a result of the superposition of two successive strains.

1.4 General Characteristics of Arterial Response

Arterial function is governed by an artery's ability to adjust its lumen in response to changes in load magnitude, duration, and certain non-mechanical factors. Under normal loading conditions, considering the deformation as a quasi-static process, a healthy artery is in a steady state, and vascular cells experience preferred target stresses. A portion of vascular smooth muscle cells (VSMCs) is contracted and develops the so-called *basal muscular tone*.

To illustrate different modes of arterial performance, consider the case when the transmural pressure is increased. The artery undergoes an instantaneous elastic deformation, manifesting as an increase in the vessel's lumen. This is the so-called *passive response*, characterized by large deformations and mechanical nonlinearity. However, the passive response does not imply that the deformation occurs in a living biological tissue. The stresses sensed by the vascular cells alter, but the basal tone remains unchanged.

If the change in the mechanical environment persists for a few minutes, the passive response may be followed by a change in the contractile state of the VSMCs. This response is called the *active response*. The increase in circumferential wall stress causes contraction of the SMCs, which initiates a constriction of the artery, manifesting the so-called *myogenic effect*. On the other hand, the passive increase in lumen diameter leads to a decrease in the shear stress sensed by endothelial cells (ECs). They respond by reducing the production of the so-called *endothelium-derived relaxing factor* (EDRF), whose main component, nitric oxide (NO), has a vasodilator effect. Through this pathway, the VSMCs are forced to contract synergistically. This discovery was awarded the Nobel Prize in Physiology or Medicine in 1998. Therefore, in the short term, the artery responds to cope with the altered pressure, tending to restore, at least in part, the cells' basal stress environment, except for an abnormally increased muscular tone. The artery behaves as an open thermodynamic system.

If pressure changes persist for weeks or months, the artery undergoes gradual changes in mass, structure, and composition. This long-term response is called *remodeling* and leads to changes in arterial dimensions and, in some cases, in the mechanical properties of the arterial tissue. As a result, a healthy artery restores both the target stress of the VSMCs and ECs, as well as the basal muscular tone.

At the microscopic level, remodeling is driven by changes in cell number (due to unbalanced replication and cell death), alterations in cell size, cell migration, imbalances in extracellular matrix synthesis and degradation, and a shift in VSMC phenotype from the contractile to the synthetic mode. These processes involve the interaction of multiple ionic and enzymatic pathways.

The reader can find more comprehensive information on the structure, composition, and mechanical response of arteries in the excellent books by Y.C. Fung [8, 9] and J. Humphrey [10], and in numerous review articles (e.g., [11*, 12*]).

In the following sections, we consider the specific modes of arterial response to answer two basic questions: What happens? (which requires mainly experimental investigations); and Why does a certain event happen? (which also involves mathematical modeling in the framework of continuum mechanics)

2 Passive Arterial Response

Examining how the geometrical parameters, structure, and composition of arteries affect their passive mechanical response is essential for understanding arterial function. This involves solving appropriate boundary-value problems for mathematical models developed within the framework of the theory of finite elasticity. Moreover, it enables the calculation of the local stress environment of cells, which cannot be measured experimentally. The key point in this task is the identification of the constitutive equations (CEs), which quantify the passive mechanical properties of arterial tissue when the contractile activity of vascular smooth muscle cells is neglected.

CEs are typically derived from *in vitro* two-dimensional mechanical experiments, often replicating physiological loading conditions. Tubular specimens are subjected to longitudinal extension and internal pressurization, while parameters such as internal pressure and longitudinal stretch are controlled. Measurements of outer diameter and axial force are recorded at various deformation states.

The results obtained have shown that arterial tissue exhibits elastic properties, high deformability, and curvilinear orthotropy, as supported by histological observations, as well as material incompressibility, which is explained by tissue's high water content. Due to the specific mechanical properties of the conduit arteries, the arterial system functions as an elastic reservoir, transforming the discrete output of blood from the heart into a flow with moderated fluctuations. The passive mechanical properties of arterial tissue vary due to changes in structure and composition, age, and progression of arterial diseases.

Data from mechanical testing suggests modeling CEs within the framework of finite elasticity theory as analytical expressions relating stress and strain measures. Accordingly, the CEs are quantified in terms of the so-called *strain energy density function* (SEF) $W(C)$ as follows:

$$\boldsymbol{t} = -p\boldsymbol{I} + 2\boldsymbol{F} \cdot \frac{\partial W}{\partial C} \cdot F^T \,, \tag{2}$$

where $\boldsymbol{t}$ is the Cauchy stress tensor, $\boldsymbol{F} = \text{diag}\,\{\lambda_r,\, \lambda_\theta,\, \lambda_z\}$ – the deformation gradient tensor, $\boldsymbol{C} = \boldsymbol{F}^T\boldsymbol{F}$ – the right Cauchy-Green stress tensor. $\boldsymbol{I}$ – the second-order identity tensor $\lambda_r,\, \lambda_\theta$, and λ_z are the stretch in the radial, circumferential, and axial direction, p is an unknown scalar function that follows from the material incompressibility enforced on the third invariant of tensor $\boldsymbol{C}$ by the relation $\det(\boldsymbol{C}) = 1$. It has to be determined from the equations of equilibrium and the boundary conditions.

In most biomechanical studies of arteries, the existence of an SEF characterizes the tissue as *hyperelastic* (Green-elastic). While some suggest that hyperelasticity is a subset of general elasticity, wherein stress depends solely on strain, the existence of an SEF fundamentally stems from the assumption that elastic deformation is a reversible thermodynamic process. As shown in [13], in vitro inflation-extension test data can validate the SEF and support the assumption of arterial elasticity.

The analytical form of the strain energy function (SEF) and its material parameters are determined from the best fit between theoretical predictions and experimental data from inflation-extension tests. Investigations have focused on two primary objectives: (i) adopting a specific analytical form and identifying SEF parameters across arterial locations, species, age groups, and pathological states; and (ii) refining SEF analytical forms to reflect tissue structure and composition more accurately. These refinements facilitate the assessment of factors influencing the passive response and provide insights into pathological alterations. Typical examples of SEFs, taken from published papers, are given chronologically below.

Chuong and Fung proposed the SEF of the rabbit carotid artery as [4]:

$$\begin{aligned} &W = \frac{1}{2} c \, \exp{(Q)} \,, \\ &Q = b_1 E_r^2 + b_2 E_\theta^2 + b_3 E_z^2 + 2b_4 E_r E_\theta + 2b_5 E_\theta E_z + 2b_6 E_z E_r \,, \end{aligned} \tag{3}$$

where $\boldsymbol{E} = \frac{1}{2}(\boldsymbol{C} - \boldsymbol{I})$ is the Green strain tensor. The model is *phenomenological* because the material constants $c, b_1, \ldots, b_6$ do not have physical meaning.

Accounting for histological findings that the major load-bearing constituents of the arterial wall are elastin and collagen, several so-called *structure-motivated SEFs* were proposed. The most popular and frequently used model was given by Holzapfel and Weizsäcker [14]. The SEF is composed of a term for elastin (considered an isotropic, incompressible material) and terms for four elastic solids that exhibit a certain type of mechanical symmetry, representing families of collagen fibers in the continuum mechanics framework.

$$W = \frac{c}{2}(I_C - 3) + \sum_{k=1,\ldots,4} \frac{c_1^k}{4c_2^k}\left\{\exp\left[c_2^k\left((\lambda^k)^2 - 1\right)^2\right] - 1\right\}. \tag{4}$$

I_C 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

$$\lambda^k = \sqrt{\lambda_\theta^2 \sin^2(\alpha^k) + \lambda_z^2 \cos^2(\alpha^k)}, \tag{5}$$

where λ_θ and λ_z are the stretches in the circumferential and axial direction, respectively; α^k is the angle between the k^{th} fiber direction and the axial direction.

Except for the angles of the fiber families, the material constants do not have physical meaning. The exponential expressions in the SEF phenomenologically account for the gradual involvement of collagen fibers in load-bearing, as they are in a wavy configuration with varying degrees of undulation in the state of no load. Although the mechanical response at low strain levels is not of primary physiological interest, the model effectively captures the dominant contribution of elastin. Changes in SEF parameters are often used to infer mechanical changes in tissue properties. However, graphics or local measures, such as compliance and incremental moduli, are more informative.

The next step in refining the SEFs was the s*tructure-based models* based on the theory of constrained mixtures. The simplest approach considers the SEF as a sum of postulated analytical functions of elastin W_{el} and collagen W_{col} weighted by their mass fractions φ_{el} and φ_{col}, which are determined by histology

$$W = \varphi_{\text{el}} W_{\text{el}} + \varphi_{\text{col}} W_{\text{col}}, \qquad \varphi_{\text{el}} = \frac{M_{\text{el}}}{M_{\text{el}} + M_{\text{col}}}, \qquad \varphi_{\text{col}} = \frac{M_{\text{col}}}{M_{\text{el}} + M_{\text{col}}}, \tag{6}$$

where M denotes the corresponding mass (e.g. [15]). Again, the individual SEFs of the tissue constituents belong to the class of phenomenological models.

Further improvement of the *structure-based models* accounts for the variable wavy configurations of collagen fibers. Justified by experimental findings or selected *ad hoc*, some papers assume a probability distribution of a collagen mass fraction of fibers with a given orientation and undulation versus the stretch at which they become straightened and are recruited to bear load as the tissue stretches. Zulliger et al. [16] proposed an SEF derived after the convolution of a log-logistically recruitment stretch distribution with a linear stress-strain law of the individual fiber as follows:

$$W = \varphi_{\mathrm{el}} c_{\mathrm{el}} \sqrt{(I_C - 3)^3} + \frac{\varphi_{\mathrm{col}} c_{\mathrm{col}}}{2} \int_0^{E_0} E^2 k \frac{b^k (E_0 - E)}{b^k + (E_0 - E)^k}\,, \tag{7}$$

where c_{el}, c_{col}, k and b^k are model parameters. An advantage of the SEF given by Eq. (7) is that it describes and explains the observed stiffening of arterial tissue due to aging and elastin degradation.

None of the models considered so far can predict the seemingly paradoxical arterial stiffening resulting from reduced elastin mass. This necessitates further development of structure-based models that incorporate *elastin–collagen interaction*. A rationale for this approach lies in findings from several experimental investigations (e.g., [17, 18]) showing that the dimensions of ring or planar arterial specimens change after selective chemical digestion of elastin or collagen. This indicates that the basic structural constituents of arterial tissue exhibit distinct natural configurations, due to their individual turnover times, production rates, and specific disposition stretches at which they are deposited in the tissue. Specifically, in the stress-free state of an intact artery, elastin is extended and collagen is compressed, but the corresponding partial stresses are self-equilibrated.

In 2005, Humphrey wrote [19, p. 8]: "Finally, the idea of modeling the stress response via a rule of mixture with constituents having individual configurations was suggested long ago in Brankov et al. (1975; cf. [20*])." In 2019, this assumption was refined, and a novel constitutive model was proposed that considers the prestretch of elastin and collagen in the tissue's natural state as model parameters [21*]

$$W = \varphi_{\mathrm{el}} W_{\mathrm{el}} + \sum_{j=1}^{4} \gamma^{(j)} \varphi_{\mathrm{col}}^{(j)} W_{\mathrm{col}}^{(J)c} + \frac{1}{2} \sum_{j=1}^{4} c_{\mathrm{col}} \Delta\lambda_r^{(j)} \int_0^{\hat{\alpha}_{(i)}^{(j)}} \varphi_{\mathrm{col}(i)}^{(j)} E_{\mathrm{col}(i)}^{(j)2} d\alpha_{(i)}^{(j)}\,. \tag{8}$$

Details about the specific terms and parameters of Eq. (8) and the model parameters are described in [21*]. An essential part of the model is the system of equations that enforces that the partial stress borne by elastin and collagen fibers are self-equilibrated in the natural state of the intact tissue as follows:

$$
\begin{aligned}
&2\varphi_{\text{el}}c_{\text{el}}\Big((\lambda^0_{\text{el}(\theta)})^2 - \frac{1}{(\lambda^0_{\text{el}(\theta)})^2(\lambda^0_{\text{el}(z)})^2}\Big) + \lambda^0_{\text{col}(\theta)}\sum_{j=1}^{4}\varphi^{(j)}_{\text{col}}\Big\{c_1^{(j)c}\Big[(\lambda^{0(j)}_{\text{col}})^2-1\Big]\\
&\qquad\qquad\qquad\times\exp\Big[c_2^{(j)c}\Big((\lambda^{0(j)}_{\text{col}})^2-1\Big)^2\Big]\Big\}\sin^2\beta_0^{(j)} = 0\,,\\
&2\varphi_{\text{el}}c_{\text{el}}\Big((\lambda^0_{\text{el}(z)})^2 - \frac{1}{(\lambda^0_{\text{el}(\theta)})^2(\lambda^0_{\text{el}(z)})^2}\Big)\lambda^0_{\text{col}(z)}\sum_{j=1}^{4}\varphi^{(j)}_{\text{col}}\Big\{c_1^{(j)c}\Big((\lambda^{0(j)}_{\text{col}})^2-1\Big)\\
&\qquad\qquad\qquad\times\exp\Big[c_2^{(j)c}\Big((\lambda^{0(j)}_{\text{col}})^2-1\Big)^2\Big]\Big\}\cos^2\beta_0^{(j)} = 0\,.
\end{aligned}
\tag{9}
$$

Parameters $\lambda^0_{\text{el}(\theta)}$ $\lambda^0_{\text{el(z)}}$, $\lambda^{0(\text{j})}_{\text{col}}$, $j = 1,\ldots,4$, are the stretches of elastin and collagen fibers in the intact tissue's natural states. Some model parameters are derived from non-mechanical tests (histology, imaging, enzymatic degradation), while others are optimized against experimental data under the constraints of Eqs. (9). An important predictive result of the model is that a reduction in elastin mass diminishes its partial tensile stress, which in turn reduces the compressive stresses borne by collagen. This leads to less collagen fiber undulation and earlier recruitment, resulting in increased arterial stiffness.

Finally, in line with the title of this article, two papers relevant to the passive mechanical response of large arteries are worth mentioning. In [10, p. 303] Humphrey wrote: "Perhaps the first finite elasticity results in the response of an artery to shear was by Kas'yanov and Rachev (1980) [cf. [22*]]". A SEF of human carotid was quantified from an inflation-torsion-extension test. It allows calculation of the arterial response and stress field in the arterial wall under non-axisymmetric loads. On the other hand, the first study on the beam mode dynamic instability of arteries under pulsatile pressure was published in [23*], considering the vessel as a composite beam of an elastic tube with a fluid core. Simulations demonstrated that longitudinal stretch and surrounding tissues prevent arterial buckling under physiological pressures.

3 Active Arterial Response

Vascular smooth muscle cells that exhibit a contractile phenotype govern the active arterial response. In a living organism, these muscle cells are partially contracted, creating the basal tone due to their inherent contractile capability. This tone is further influenced by neurological signals, blood-borne vasoconstrictor substances, myogenic stimuli resulting from pressure-induced wall stress, and opposing factors produced by endothelial cells (ECs) that induce VSMC relaxation. Contraction or relaxation of the VSMCs leads to either constriction or dilation of the arterial lumen, ensuring an adequate blood supply under the metabolic demands of the organs and enabling an acute vasomotor response in the event of an abrupt, short-lasting change in pressure or flow (e.g. [24]).

Most experimental investigations on the active response have been conducted *in* vitro using tubular specimens. To maintain the viability of VSMCs, the artery is immersed in a physiological solution bath with a continuous oxygen supply. By adding specific substances, such as norepinephrine and KCN, the muscle cells are stimulated to contract or relax, resulting in the arterial vessel constricting or dilating. The active response can be evaluated in two experimental scenarios: i) in terms of circumferential tension, calculated from the pressure needed to inflate the stimulated artery to a configuration identical to its state before stimulation (referred to as *isometric contraction*), and ii) in terms of the change in arterial diameter when the pressure is kept at the basal level (referred to as *isobaric constriction*). Given the intensity of stimulation and internal pressure, the configurations taken by the arterial vessel are virtually identical in both scenarios. Experimental results have shown that the active response depends on stimulation, following a dose-response curve with a sigmoidal shape. Moreover, the active response occurs only within a certain range of deformed configurations, exhibiting a non-monotonic relationship between active tension and lumen diameter.

The first constitutive model to include the active arterial response was proposed in [25*] and remains the most cited paper on this topic. The basic assumption is that the total circumferential stress is the sum of passive stress t_p, which follows from a known SEF, and *active stress* t_a generated by the stimulated VSMCs (the second term on the right-hand side of the following equation):

$$t_{\theta\theta} = -p + 2\frac{\partial W}{\partial C_{\theta\theta}} F_{\theta\theta}^{T} F_{\theta\theta} + S\Psi(\lambda_{\vartheta})\,. \tag{10}$$

The parameter S, often referred to as the activation parameter, is a measure of the ability of muscle cells to contract and generate active stress. Depending on the level of stimulation, S varies from 0 (relaxed VSMCs) to $S_{\max}$, which is the absolute maximal value of the active circumferential stress that muscle cells can generate. $\Psi\left(\lambda_{\vartheta}\right)$ is a normalized function that ranges from [0, 1] and describes the influence of the deformed configuration on the active stress according to the lumen-active stress relationship. $\Psi\left(\lambda_{\vartheta}\right)$ was chosen as a parabolic function of λ_{θ}. The operating points under basal physiological conditions lie on the ascending part of the corresponding curve. Both the activation parameter S and function $\Psi\left(\lambda_{\vartheta}\right)$ are determined from data obtained from biaxial mechanical experiments on tubular arterial segments.

It is worth noting that the increase in active stress due to myogenic resonance, caused by elevated arterial pressure, modulates the circumferential stress distribution synergistically with residual strains, promoting its homogenization.

Assuming additivity of active and passive stress, the model given by Eq. (10) has been further developed in two directions: (i) identification of artery-specific analytical expressions for the function Ψ (e.g. [26]), and the model generalization to account for the biaxial active mechanical properties [27, 28].

Finally, the myogenic response of VSMCs was incorporated into a lumped dynamic mathematical model for the mechanical response of an artery perfused with constant flow [29*]. The illustrative results showed that, in some cases, the stationary solution of the governing equations may become unstable, and the model predicts the development of low-frequency diameter oscillations that have been observed in vivo.

4 Remodeling Response

Many experimental investigations on arterial remodeling have been conducted on living animals, following specific protocols to maintain sustained changes in arterial pressure or flow and recording post-mortem changes in arterial geometry, histology, and overall mechanical response (e.g. [30]). The comparison of dimensions in the deformed state before and after remodeling quantifies the *apparent or observed remodeling*. It results from changes in the distribution of arterial mass and the vessel's deformation under altered loads. However, *true or pure remodeling* can only be evaluated when the geometrical dimensions are compared in the zero-stress state, and the VSMCs are completely relaxed.

Another experimental approach to studying remodeling involves keeping a portion of the artery alive in an organ culture system and monitoring remodeling-induced geometrical changes under controlled pressure and flow conditions. The advantage of this approach is that it provides the artery with a well-defined chemical and nutrient environment while eliminating non-mechanical factors. However, the artery can only be kept alive for several weeks.

Results from animal investigations have shown that healthy arteries undergo *adaptive remodeling*. A sustained increase in arterial pressure (hypertension), while keeping blood flow at baseline levels, causes no change in the inner deformed radius and an increase in the wall thickness. As a result, the calculated flow-induced shear stress at the intima and pressure-induced average circumferential stress in the media revert to their baseline target values (e.g., [31, 32]). When blood flow is altered but pressure is kept constant, the deformed inner diameter changes to restore the target shear stress, and the wall thickness adjusts accordingly to maintain target wall stress (e.g. [33, 34])

For adaptive remodeling, the parameters describing apparent remodeling are calculated from Eqs. (1) and (2) as follows:

$$(11)\quad r_{i(h)} = r_{i(b)}\,, \qquad h_{(h)} = h_{(b)}\frac{P_{(h)}}{P_{(b)}}\,, \qquad \text{if } P = P_{(h)} \text{ and } Q = Q_{(b)}\,,$$

$$(12)\quad r_{i(q)} = r_{i(b)}\sqrt[3]{\frac{Q_{(q)}}{Q_{(b)}}}\,, \quad h_{(q)} = h_{(b)}\sqrt[3]{\frac{Q_q}{Q_{(b)}}}\,, \qquad \text{if } P = P_{(b)} \text{ and } Q = Q_{(q)}\,,$$

where the subscripts (b), (h) and (q) denote the basal deformed state, remodeled deformed states due to hypertension, and change in blood flow, respectively.

Equations (11) and (12) show that the outcomes of apparent remodeling do not depend on the mechanical properties of the arterial tissue or the magnitude of muscular tone. However, to obtain predictive results regarding the dynamics and outcomes of true remodeling, it is necessary to solve initial-value problems using mathematical models based on the equations of equilibrium, the constitutive equations of the arterial tissue, and a mathematical description of mass changes.

As Humphrey wrote in [10, p. 547]: "Remarkably, attempts to quantify the growth and remodeling that occurs in the arterial wall during, and in response to, hypertension are relatively recent. Moreover, most of this work has come from one group, that of Rachev (1997) and Rachev et al. (1996, 1998) (cf. [35*–37*])." These papers proposed a *global growth approach* based on the decomposition of observed remodeling into true remodeling and deformation of the remodeled vessel under altered loads. The artery is considered a first-order dynamic system. During hypertension-induced remodeling, the inner and outer arc lengths of the arterial cross-section, axial length, and deformed inner radius change according to postulated evolution equations. The rate of change of the geometrical parameters depends on the deviation of the current axial stress, circumferential wall stress at the inner and outer surfaces, and flow-induced shear stress from their target values. Finally, motivated by experimental findings that the mechanical properties may change due to remodeling, a variable constitutive parameter and an associated evolution equation were introduced, under the assumption that arterial compliance is preserved at the baseline level.

The global growth approach was further refined by specifying a structure-motivated description of arterial tissue remodeling [38]. It was also applied to study other remodeling-related problems, such as adaptive remodeling to changes in blood flow [39*] and variations in arterial geometry and mechanical response during aging [40]. Recently, a novel structure-based two-dimensional mathematical model of hypertension-induced arterial remodeling was proposed, accounting for the stress interaction between elastin and collagen [41]. The key predictive result is that, when remodeling alters the elastin-to-collagen fraction ratio, it leads to structural reorganization of collagen through changes in fiber undulation as well as the orientation of helically arranged fibers. Illustrative simulation results showed that collagen reorganization, rather than an increase in its mass fraction, is the primary cause of the observed stiffening in the remodeled arteries.

In 1996, independently, mathematical models of arterial remodeling due to hypertension were developed in [42] using a more general *volumetric growth approach* [43]. The body is considered a collection of infinitesimal elements. Each element undergoes finite volumetric growth described by a growth gradient tensor. The rate of change of the growth tensor components depends on the deviation of the components of the Cauchy stress tensor from selected target values. The grown elements may not fit together exactly, but growth does not destroy material continuity. Reassembling the elements requires deformation, described by a deformation gradient tensor, which generates residual strains and stresses. Finally, under external loads, the configuration transforms into the deformed grown configuration, and the mapping is described by another deformation gradient tensor.

Both the volumetric and global growth approaches are based on the kinematics of remodeling, disregarding the underlying processes. To account for the causes, rather than just the results, of remodeling, a research strategy based on a constrained mixture was proposed in [44, 45]. This approach focuses on the dynamics of the growth process. The basic structural constituents (elastin and collagen) are considered to have individual rates of production and removal, as well as evolving natural configurations. The rate of change in vascular mass is not explicitly related to wall stress, although the remodeling process is acknowledged to be stress-driven. The advantage of this approach is that it can provide predictive results based on variations in the parameters that govern the remodeling response.

The results from the considered models yield the time course of arterial geometry during remodeling, which is predetermined by the choice of evolution equations and growth laws. Since the outcomes of the remodeling process are single-valued, all approaches must predict identical stationary remodeled states. Given the lumen, stress field, and structural stiffness of an artery, solutions to inverse problems of vascular mechanics formulated in [35*, 46] yield the initial dimensions and mechanical properties of an artery after the completion of adaptive remodeling to pressure and flow.

In conclusion, this brief description of the passive, active, and remodeling responses of healthy arteries suggests that *they function as "smart" organs, capable of maintaining optimal function (homeostasis) by adapting to moderate alterations in loading.*

Unfortunately, optimal arterial performance is not always a stable biological process. The maintenance of a preferred state of the mechanosensitive vascular cells results from the regulation of steady states in a series of dynamic mechanical and biological processes at the cellular and subcellular levels. The delicate balance between these processes can be disturbed, which is associated with the genesis and progression of certain vascular diseases. For instance, genetic and epigenetic factors may impair endothelial cells' adequate response to flow-induced shear stress (endothelial dysfunction), promote accelerated degradation of elastin, or stimulate abnormal stress-induced collagen synthesis. In these cases, remodeling goes awry, manifesting at the macro level as inward or outward changes in the lumen diameter and as hypertrophic, eutrophic, or hypotrophic changes in the arterial wall area [47]. In contrast to adaptive remodeling, mathematical modeling of maladaptive responses remains an open issue. Based on the global growth approach, a 2D model of hypertension-induced eutrophic inward remodeling was proposed in [48].

Sometimes, the normal functioning of a portion of an arterial vessel is disturbed due to a local narrowing called *stenosis*. One option to restore normal blood flow is to replace the compromised vessel with a synthetic prosthesis. Another possibility is to deploy a metallic stent to restore the arterial lumen. Unfortunately, local thickening, known as *anastomotic intimal hyperplasia*, often occurs at the junction of the healthy host artery and the vascular prosthesis or metallic stent. Similarly, progressive restenosis may develop along stented arteries, compromising the surgical intervention. Due to the mechanical mismatch, high-stress concentrations may occur at the junction between the stent and the host artery and in the regions of arterial tissue between the stent's struts. Similar to hypertension-induced remodeling, it has been speculated that VSMCs respond to the higher wall stress by synthesizing more collagen, creating a local restenosis to revert the stress to target values. To test this hypothesis, a mathematical model was developed in [49*]. The governing equations for small axisymmetric deformations, superposed on the finite inflation and extension of a cylindrical shell, are coupled with a set of evolution equations for the shell's geometry, adopting the global growth remodeling approach. Therefore, the model considers anastomotic hyperplasia as a local adaptive response of healthy muscular cells rather than a manifestation of tissue pathology. Achieving local homeostasis at the cellular level leads to impaired performance at the organ level.

A mechanics-based understanding of anastomotic hyperplasia and in-stent restenosis offers insights into strategies for their prevention. One approach involved the design, fabrication, and animal testing of a metallic stent with gradually decreasing stiffness toward its ends, enabling better compliance matching with the host artery [50*]. Finite Element Method (FEM)-based stent design optimization was proposed in [51*] to maintain stent-induced stresses within targeted stress ranges in the arterial wall. Finally, an innovative pathway for developing a compliance-matched vascular prosthesis tailored to replace a specific artery was introduced in [52]. As proof of concept, a prototype made from a novel synthetic biomaterial demonstrated a robust and reliable technology for graft fabrication.

5 Conclusion

This brief review convincingly demonstrates that solid mechanics is a powerful tool for studying arterial function in both health and disease. Conversely, biological insights motivate the development of new branches of mechanics, such as continua that grow and solids capable of exhibiting "active properties" by responding dynamically to mechanical and chemical stimuli.

The mathematical models discussed herein extend foundational knowledge of arterial systems, deepen the interpretation of experimental findings, and offer predictive insights into arterial performance. Despite significant progress, vascular solid mechanics still faces important challenges and requires further development along several lines. One key objective is the development of patient-specific mathematical models that utilize personalized clinical data, including medical imaging. Incorporating these models into advanced computational platforms enables the generation of individualized outcomes, thereby enhancing diagnostic accuracy and optimizing therapeutic strategies for vascular disorders.

Meanwhile, considerable efforts are focused on fabricating synthetic arterial vessels to replace compromised small arteries. These artificial vessels are seen as a potential "silver bullet" in the fight against the leading cause of death in the developed world: cardiovascular disease. It seems that creating artificial intelligence (AI) may prove easier than making a functional artificial artery. Hopefully, AI will ultimately help achieve this ambitious goal.

In conclusion, it is hoped that this article will stimulate interest among readers with expertise in theoretical and applied mechanics and highlight the "Bulgarian imprint" in the field of vascular biomechanics.

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