A constituent-based model of age-related changes in conduit arteries

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Submitted 14 June 2010; accepted in final form 28 June 2011

Tsamis A, Rachev A, Stergiopulos N. A constituent-based model of age-related changes in conduit arteries. Am J Physiol Heart Circ Physiol 301: H1286–H1301, 2011. First published July 1, 2011; doi:10.1152/ajpheart.00570.2010.—In the present report, a constituent-based theoretical model of age-related changes in geometry and mechanical properties of conduit arteries is proposed. The model was based on the premise that given the time course of the load on an artery and the accumulation of advanced glycation end-products in the arterial tissue, the initial geometric dimensions and properties of the arterial tissue can be predicted by a solution of a boundary value problem for the governing equations that follow from finite elasticity, structure-based constitutive modeling within the constrained mixture theory, continuum damage theory, and global growth approach for stress-induced structure-based remodeling. An illustrative example of the age-related changes in geometry, structure, composition, and mechanical properties of a human thoracic aorta is considered. Model predictions were in good qualitative agreement with available experimental data in the literature. Limitations and perspectives for refining the model are discussed.

arterial remodeling; vascular mechanics; elastin fatigue damage; collagen cross-linking

AGING AFFECTS THE MECHANICAL FUNCTION of human conduit arteries such as the aorta, the iliac arteries, and the carotid arteries. It manifests as a change in the vessel geometry and material properties of the vascular tissue, accompanied by alterations in loading conditions. Geometric and structural alterations in the tissue of conduit vessels with progressing age cause a decrease in the total arterial compliance (66), which, in turn, leads to an increase in pulse pressure. The increase in pulse pressure has been shown to be the strongest predictor for cardiovascular mortality, for it augments the mechanical load on the left ventricle (9). Furthermore, the decrease in diastolic pressure observed in late middle age, which reduces the coronary arterial perfusion, raises the demands on the left ventricle (25).

Geometric changes observed in aging are associated with an increase in arterial volume (7) characterized by increased lumen area (63) and wall thickening (43) and decreased axial stretch associated with loss in longitudinal stiffness (65). An increase in the opening angle has been observed, which was obtained after residual stress was relieved in an isolated arterial ring by a radial cut (54). Simultaneously, the content of collagen increases and the number of smooth muscle (SM) cells decreases (55). Furthermore, mean aortic pressure gradually increases with advanced age (27). The interrelation among the aforementioned processes is unknown. Additionally, the stiffness of the elastin structure gradually increases with advanced age due to a nonatherosclerotic mineralization mechanism called the medial elastocalcinosis (MEC), during which calcium salts bind to the elastin of the aortic media (15). Also, elastin is fragmented with progressing age, and the damage appears to be related to mechanical fatigue failure caused by cyclic stretch (25) as well as chemical degradation caused by the upregulation of matrix metalloproteinases (MMPs), which is due to an imbalance between proteases and their inhibitors (64). There is some evidence that the increased expression of MMPs accompanies the aforementioned calcification of elastin (8). Moreover, increased cross-linkage of collagen fibers by advanced glycation end-products (AGEs) raises the stiffness of the collagen fiber network (56). In vitro studies (35, 67) have shown that the accumulation of AGEs over time similarly affects the stiffness of the elastin structure. A comprehensive review on the aging of arteries is can be found in Ref. 25.

Zulliger and Stergiopulos (72) examined the changes in elastic and structural properties of the human aortic wall with aging by applying a structure-based constitutive law to the experimental data published by Langewouters et al. (36) and Wuyts (69). The data referred to 43 human thoracic aortas obtained postmortem from subjects 30–88 yr old. Zulliger and Stergiopulos (72) made some basic assumptions about the evolution of the opening angle (Φ) and axial stretch ratio (λ₃) with age, because neither Langewouters et al. (36) nor Wuyts (69) reported Φ and λ₃ of the aortas. The fitting to experimental data by means of two parameters describing the statistical distribution of collagen engagement revealed that collagen fibers engage in bearing load at lower levels of stretch and much more abruptly in old subjects than in young subjects, causing a decrease in aortic compliance with progressing age.

There is experimental evidence that the fragmentation of aortic elastin with age is associated with mechanical fatigue caused by the pulsatile wall strain over the number of cardiac cycles during lifetime (5, 55). Also, cross-linkage of collagen fibers by AGEs, which is known to increase with age (37), would make the fiber engagement occur at lower strains and more abruptly (72). As aforementioned, it could also be possible for the elastin structure to be similarly affected by AGEs. It would therefore be reasonable to link the damage of elastin with mechanical fatigue, and the stiffening of collagen and elastin network with AGEs cross-links, when building models for aging-induced remodeling of aortas.

It is reasonable to expect that not all age-related changes of conduit arteries exist independently of one another. The central premise of this study is that given the time course of the load on an artery and the accumulation of AGEs in the arterial tissue, the initial geometric dimensions and properties of the arterial tissue can be predicted by a solution of a boundary value problem for the governing equations that follow from the finite elasticity, structure-based constitutive modeling within...
the constrained mixture theory, continuum damage theory, and global growth approach for stress-induced structure-based remodeling.

**METHODS**

We formulated two major groups of equations for a model of age-related changes in conduit arteries. The first group is composed of the evolution equations that prescribe the variation over age of the mean arterial pressure (P_m), pulse pressure, heart rate (HR), in vivo λ_c, and accumulation of AGEs. The second group includes calculated model parameters from the governing equations for kinematics, constitutive modeling and equilibrium of arteries, damage of the arterial tissue, and stress-induced remodeling of arteries.

**Prescribed Model Parameters**

P_m and pulse pressure. The variation of P_m with age was taken according to the diastolic pressure (P_d) and systolic pressure (P_s) data of Ref. 27. At 20, 40, 60, and 80 yr of age, P_d is 77, 87, 89, and 81 mmHg and P_s is 110, 125, 137, and 156 mmHg, respectively. A best fit of the data was performed, and the time course of P_d, P_s, and P_m was described according to the following equations:

\[
P_d(t) = 57.5 + 1.195t - 0.0113t^2
\]

\[
P_s(t) = 94.5 + 0.75t
\]

\[
P_m(t) = \frac{2P_d(t)+P_s(t)}{3}
\]

where t is age (in yr).

HR. HR was taken to increase linearly with age according to the data reported by Nichols et al. (45), as follows:

\[
HR(t) = 73.64 + 0.0486t \text{ (in beats/min)}
\]

In vivo λ_c. Experimental observations have shown that there is a tendency for the axial stretch of the aortas to decrease with progress of age associated with a loss in axial stiffness (65). We prescribed the following decrease in λ_c with age:

\[
\frac{dλ_c(t)}{dt} = -β_1(t-t^*)
\]

where β_1 > 0 is a rate parameter and t^* is at a young age.

Accumulation of AGEs. Cross-linking of collagen fibers by the accumulation of AGEs over time raises the stiffness of the collagen fiber network (2, 56). We assume that the collagen fibers themselves do not alter their inherent material properties to yield a stiffer structure. Attaching fibers to one another can stiffen the fiber ensemble by shifting the recruitment of the fibers to lower strains and forcing the engagement to occur more abruptly. Evidently, the data-fitting study of Zulliger and Stergiopoulos (72) revealed that the elastic modulus of the individual collagen fiber does not vary with age; however, there is a clear decrease in the mean fiber engagement strain and an even more pronounced decrease in fiber engagement variance with age. We introduced the function C_AGE to account for the accumulation of AGEs over time. We postulate the following relation to prescribe the increase of C_AGE with age t:

\[
\frac{dC_AGE(t)}{dt} = β_2(t-t^*)
\]

where β_2 > 0 is a rate parameter.

**Calculated Model Parameters**

To calculate the remaining model parameters, we first derived the governing equations for kinematics, constitutive modeling and equilibrium of arteries, damage of the arterial tissue, and stress-induced remodeling of arteries.

**Kinematics.** An artery is considered to be a thick-walled cylindrical tube made of nonlinear, elastic, and incompressible material. Under applied internal pressure and axial stretching to in vivo length, the artery undergoes finite axisymmetric deformations in the state of plane strain. In the traction-free configuration of an arterial segment, there exist residual stresses, which are released by a radial cut (18, 26, 60). The zero-stress (B_o) and deformed (B) configurations of the artery cross-section are shown in Fig. 1. As shown in Fig. 1, C_o and C are the inner and outer arc lengths in the zero-stress state (ZSS), H is the wall thickness, Φ is the opening angle as defined in Ref. 59, R_o the radius of curvature of C_o, R is the radius of curvature of C, r_i is the deformed inner radius, and r_o is the deformed outer radius. Finite deformation that maps B_o into B has been considered in many published reports (1, 49, 57). Briefly, for the incompressible wall, the stretch ratios (λ) in the radial (subscript r), circumferential (subscript θ), and axial (subscript z) directions are as follows:

\[
λ_r = \frac{r}{r_o}, \quad λ_θ = \frac{R}{R_o}, \quad λ_z = λ
\]

and the Green strains (E) are as follows:

\[
E_i = \frac{1}{2}(λ_i^2 - 1) \quad (i = r, θ, \text{ or } z)
\]

where r and R are an arbitrary radius in states B_o and B, respectively; μ, χ, and λ are deformation parameters; and l and L are the deformed and undeformed axial length, respectively. Given the dimensions of the vessel in the ZSS and λ, the only unknown parameter is μ.

**Constitutive equations: equilibrium.** The calculation of stresses requires specification of the strain energy function (SEF) W, which describes the passive mechanical properties of the arterial tissue. Similar to the models in Refs. 1, 22, 23, and 59, the tissue was modeled as a constrained mixture of elastin, collagen, SM cells, and water. Therefore, the total stress was given by the rule-of-mixtures relation, which implies that the SEF is as follows:

\[
W = W_{elast}W_{elast} + W_{coll}W_{coll} + f_{SM}W_{SM}
\]

where W_{elast}, W_{coll}, and W_{SM} are the corresponding SEFs for elastin, collagen, and passive SM and f_{elast}, f_{coll}, and f_{SM} are the corresponding mass fractions defined as follows:

\[
\begin{align*}
β_{elast} &= \frac{2E_i}{3(1-2ν_i)}
\end{align*}
\]

\[
β_{coll} = \frac{2E_i}{3(1-2ν_i)}
\]

\[
β_{SM} = \frac{2E_i}{3(1-2ν_i)}
\]

**Fig. 1. Zero-stress (B_o) and deformed (B) configurations of an artery cross-section. Θ, zero-stress angular coordinate; Φ, opening angle; 0 ≤ Θ ≤ π - Φ; R_o, zero-stress radius; R, radius of curvature of the inner arc length; R_i, radius of curvature of the outer arc length; H, thickness; r, deformed radius; r_i, deformed inner radius; r_o, deformed outer radius; Θ, deformed angular coordinate; Θ = πΘ/(π - Φ). [Duplicated from Ref. 59.]**
where \( M \) is the total mass and \( M_i \) is the mass of an individual structural component (where \( s = \) elastin, collagen, SM, or water). Evidently

\[
f_{\text{elast}} + f_{\text{coll}} + f_{\text{SM}} + f_w = 1 \tag{10}
\]

where \( f_w \) is the mass fraction of water. In this study, we use the SEF proposed in Ref. 72, which is expressed as follows

\[
W = f_{\text{elast}} c_{\text{elast}} \sqrt{(I_1 - 3)^2} + f_{\text{coll}} c_{\text{coll}} E_{\text{coll}} b^2 k (E_0 - E)^{k-1} \left[ b^2 + (E_0 - E)^2 \right] \tag{11}
\]

The first term represents the SEF of elastin, \( c_{\text{elast}} \) is the material constant of elastin, and \( I_1 = 2(E_s + E_o) \) is the first strain invariant. The second term represents the SEF of collagen, \( c_{\text{coll}} \) is the material constant of collagen, \( E \) is the local strain in the direction of the collagen fiber, and \( b \) and \( k \) are parameters of the collagen engagement distribution. Parameters \( b \) and \( k \) are related to the mean fiber engagement strain (\( \mu_{\text{eng}} \)) and fiber engagement variance (\( \sigma_{\text{eng}} \)) of the statistical distribution of collagen engagement, as follows:

\[
\mu_{\text{eng}} = b \pi \csc \frac{\pi}{k} \tag{12a}
\]

\[
\sigma_{\text{eng}} = b^2 \left( \frac{2 \pi}{k} \csc \frac{\pi}{k} - \left( \frac{\pi}{k} \csc \frac{\pi}{k} \right)^2 \right) \tag{12b}
\]

We neglect the SEF for the passive properties of SM cells, because it has been reported that its contribution to the circumferential wall stress is about one order of magnitude less than that of the SEF for elastin (10, 62).

The strains in the arterial wall produce stresses. The non-zero components of Cauchy stress (\( \sigma \)) are as follows:

\[
\sigma_r = \left( \frac{\partial W}{\partial E_r} - \lambda_1 \frac{\partial W}{\partial E_r} \right) \frac{1}{r} - P \tag{13a}
\]

\[
\sigma_\theta = \sigma_r + \left( \frac{\partial W}{\partial E_\theta} - \lambda_1 \frac{\partial W}{\partial E_r} \right) \tag{13b}
\]

\[
\sigma_z = \sigma_r + \left( \frac{\partial W}{\partial E_z} - \lambda_1 \frac{\partial W}{\partial E_r} \right) \tag{13c}
\]

where \( P \) is the arterial pressure applied at the inner surface, with \( P \) being equal to

\[
P = \int_0^{\theta_0} \left( \lambda_1 \frac{\partial W}{\partial E_\theta} - \lambda_1 \frac{\partial W}{\partial E_r} \right) \frac{1}{r} \, dr \tag{14}
\]

Linearized mechanical response. Measures of the linearized mechanical response of an artery around certain deformed state are the area compliance (\( C_A \)) and area distensibility (\( D_A \)), which were given by the following equations:

\[
C_A = \frac{\Delta A}{\Delta P} \tag{15a}
\]

\[
D_A = \frac{1}{A} \frac{\Delta A}{\Delta P} \tag{15b}
\]

where \( \Delta A \) is the small increase in the luminal area \( A \) due to a small increase in pressure \( \Delta P \) (66). \( C_A \) was related to the pulse wave velocity (PWV) and characteristic impedance (\( Z_c \)) as follows:

\[
\text{PWV} = \sqrt{\frac{A}{\rho \times C_A}} \quad Z_c = \frac{\rho \times \text{PWV}}{A} \tag{16}
\]

where \( \rho \) is the blood density. When pressure varies between diastole and systole, the change in the diameter is relatively small, and the pressure-diameter relationship is virtually linear (31). Therefore, the pulsatile strain \( \Delta E = \Delta r_0 / r_0 \) experienced by the arterial wall during the cardiac cycle, with \( \Delta r_0 \) being the small increase in the outer deformed radius \( r_o \) due to a small increase in pressure \( \Delta P \), can be calculated using the linearized measures given by Eqs. 15a and 15b, provided that they are calculated at \( P_m \). By accounting for material incompressibility (\( r_o^2 - r_i^2 = \text{constant} \)) and after some algebra, it follows that

\[
\Delta E = \frac{C_A \Delta P}{2 \pi r_o^2} \tag{17}
\]

Damage of arterial tissue due to elastin fragmentation. The fragmentation of aortic elastin with age appears to be related to mechanical fatigue caused by the repeated cyclic deformation (pulsatile wall strain) (5, 35). The number of cardiac cycles (\( n \)) between \( t^* \) and some maximum age (\( t_{\text{max}} \)) was given as follows:

\[
n_{\text{max}}^* = \int_{t^*}^{t_{\text{max}}} \frac{1}{n(t)} \, d\tau \tag{18}
\]

where \( n(t) \) is the HR as a function of age \( t \). By adopting the S-N criterion (Wöhler criterion) for fatigue damage, the number of cardiac cycles to failure decreases when the pulsatile strain increases (25), suggesting that the determining factor for fatigue is the product of pulsatile strain times the number of cardiac cycles. We hypothesized that the failure in elastin is the result of a gradual isotropic damage caused by the repeated cyclic deformation. Following the approach of continuum damage mechanics, we introduced a nonobservable damage parameter (\( D \)). It represents the relative loss of load-bearing volume of elastin in the vascular tissue; \( D = 0 \) when there is no damage and \( D = 1 \) when the entire volume of elastin is damaged and the material has failed. To describe the process of damage that occurs with repeated cyclic deformation, the following evolution equation was introduced, which phenomenologically accounts for the causal link among the rate of change of \( D \), the pulsatile strain, and the number of cardiac cycles as follows:

\[
\frac{dD(t)}{dt} = \frac{1}{T_1} \left( 1 - D(t) \right) \frac{\Delta E(t) - \Delta E_0}{\Delta E_0} n_{\text{max}}^* \tag{19}
\]

where \( T_1 \) is a time constant and \( \Delta E_0 \) is a lower bound pulsatile strain below which no elastin failure occurs. According to Eq. 19, an increase in the pulsatile strain or in the number of cardiac cycles raises the magnitude of \( D \), which cannot exceed the value of one, corresponding to the total fragmentation of elastin.

Damage-related evolution of the arterial geometry. The damage of elastin may cause residual (plastic) deformation in the vascular tissue resulting from rearrangement of the wall structural components (48). An increased lumen area at zero pressure with progressing age has also been observed by Langewouters (35). In this study, we hypothesized that the aging-induced increase in lumen radius at the load-free configuration is caused by the gradual degradation of the elastin structure. We postulated the following equation to prescribe the evolution of the inner radius at zero pressure with age:

\[
r_{\text{i}}(t) = \tilde{r}_{\text{i}} + \beta_1 \times D(t) \tag{20}
\]

where \( \tilde{r}_{\text{i}} \) is the current lumen radius at zero pressure, \( \tilde{r}_{\text{i}} \) is the lumen radius at zero pressure at young age, and \( \beta_1 > 0 \) is a parameter having units of length. According to Eq. 20, an increase in the magnitude of \( D \), which corresponds to augmented fragmentation of the elastin structure, causes an increase in the lumen radius at the load-free state.
A MODEL OF AGE-RELATED CHANGES IN ARTERIES

Geometric remodeling induced by augmented \( P_m \) and elastin fragmentation. \( P_m \) is increased with progressing age (66). Pulse pressure also increases with age (4). In particular, \( P_m \) is gradually augmented, whereas \( P_t \) initially increases to a level out at about middle age and decreases thereafter (27). To describe the geometric changes associated with remodeling, we followed the global growth approach proposed in Refs. 49, 50, and 59, according to which we tracked the evolution of the dimensions of the ZSS of the artery. We considered wall remodeling caused by the gradual change in \( \sigma_0 \) caused by the variation in \( P_m \) and changes in the structure of arterial tissue. Initially, at a young age (e.g., 30 yr old), the artery is subjected to normal blood pressure and is kept at a constant deformed length. The magnitude of \( \sigma_0 \) in the arterial wall is considered as the baseline value. Blood flow is assumed to remain unchanged. The gradual increase in \( P_m \) with age causes a gradual increase in the lumen radius value. Blood flow is assumed to remain unchanged. The gradual

\[
\sigma_{b,t}(t) = \sigma_{b,i} \quad \sigma_{b,o}(t) = \sigma_{b,o} \tag{21}
\]

where \( \sigma_{b,i} \) and \( \sigma_{b,o} \) are \( \sigma_0 \) at the inner and outer surface, respectively, under \( P_m \) and \( \sigma_{b,i} \) and \( \sigma_{b,o} \) denote baseline values of \( \sigma_{b,i} \) and \( \sigma_{b,o} \) at a young age. According to Eq. 21, \( \sigma_{b,i} \) and \( \sigma_{b,o} \) depend on all three geometric parameters of the ZSS (\( C_i, C_o, \) and \( H_i \)), \( \lambda_i \), and the material properties, can be maintained at control levels with increasing pressure.

The geometric remodeling due to aging leads to an increase in arterial mass. Accepting that the structural components of the vascular tissue have similar mass densities, the mass production is proportional to the increase in the total arterial volume. If we further assume that the deformed length of the artery does not change with aging, which holds true because the thoracic aorta is tethered to the spine, the current mass of an artery \( M(t) \) is related to the mass at a young age (\( M^* \)) as follows:

\[
M(t) = \kappa(t) M^* = \frac{[r_o(t)]^2- [r_t(t)]^2}{[r_o]_0^2 - [r_t]_0^2} M^* \tag{22}
\]

In Eq. 22, \( \kappa(t) \) is the ratio of the current arterial volume over the volume at a young age; \( r_o(t) \) and \( r_t(t) \) are the current deformed inner and outer radii, respectively; and \( r_o \) and \( r_t \) are the deformed inner and outer radii at a young age, respectively.

Aging-induced alterations in material properties. With progressing age, large conduit arteries such as the aorta alter not only their geometric dimensions but also their material properties. The remodeling of material properties is due to differential mass production in the arterial wall components and due to structural reorganization in the vascular tissue. Here, we separately modeled these two processes.

The new mass produced with ageing (Eq. 22) affects the values of mass fractions (Eqs. 9 and 10) and thereby the mechanical response of the artery (Eq. 11). Based on histological evidence, we assumed that \( f_w \) remains constant during the entire process of remodeling (13). We further considered arteries of matured organisms, for which the turnover of elastin is a very slow process. Therefore, the mass of the elastin was taken to be constant during remodeling. It is generally accepted that the number of SM cells in the adult aorta decreases with age (25, 55). Degeneration of SM cells in the aortic media with increasing age has been reported by Toda et al. (58). Animal experiments have revealed that the aortic medial SM cells not only decrease in number but also become hypertrophic with advanced age (71). Since the decrease in the number of SM cells in the adult aorta could be accompanied by hypertrophy of the cells, it would be possible for the mass of SM to remain unchanged with aging. Therefore, we assumed in this study that the mass of the SM in the human aorta remains constant with increasing age. Taking into account Eqs. 9, 10, and 22, the current \( f_{elast}, f_{SM}, \) and \( f_{coll} \) were as follows:

\[
f_{elast}(t) = \frac{f_{elast}}{\kappa(t)} \tag{23a}
\]

\[
f_{SM}(t) = \frac{f_{SM}}{\kappa(t)} \tag{23b}
\]

\[
f_{coll}(t) = 1 - f_{elast}(t) - f_{SM}(t) - f_w \tag{23c}
\]

where \( f_{elast} \) and \( f_{SM} \) are \( f_{elast} \) and \( f_{SM} \) at a young age, respectively. Since the volume ratio \( \kappa(t) \) is augmented with age, \( f_{elast} \) and \( f_{SM} \) will decrease with age, giving rise to an increase in \( f_{coll} \) according to Eq. 23c. An increased collagen content with respect to the wet weight of the aortic vessel has been reported by Sans and Moragas (55). Toda et al. (58) also reported an increase of irregularly arranged collagen fibers with age in the human aorta.

The fragmentation of elastin impacts on the effective \( f_{elast} \) (\( f_{elast,eff} \)), which accounts for the portion of elastin that bears load. The damaged elastin fibers do not bear any load. Nevertheless, they occupy space within the vascular tissue, \( f_{elast} \) given by Eq. 23a accounts for the total content of elastin, i.e., both the undamaged and damaged parts. If we make use of the damage parameter of elastin (\( D \)), we can obtain \( f_{elast,eff} \) as follows:

\[
f_{elast,eff}(t) = \left[ 1 - D(t) \right] f_{elast}(t) \tag{24}
\]

\( f_{elast,eff} \) is then substituted into constitutive Eq. 11 to derive the stress born by the undamaged part of elastin.

The decrease in the variance of the collagen statistical distribution can be caused by an increase in the accumulation of AGEs and a decrease in the pulsatile strain \( \Delta \varepsilon \) with age, which results from the stiffening of the arterial wall. The pulsatile strain is essentially the range of global strains over which new collagen fibers are generated and bear load. Hence, the pulsatile strain \( \Delta \varepsilon \) is intimately associated with the variance of fiber engagement. To account for a structural reorganization in the collagen network, we needed to link the aforementioned decrease in \( \mu_{eng} \) and \( \sigma_{eng} \) of the collagen statistical distribution with the function \( C_{AGE} \) and the pulsatile strain. According to Eq. 12, a decrease in parameter \( b \) causes a decrease in \( \mu_{eng} \). Also, a decrease in parameter \( b \) and/or an increase in parameter \( k \) cause a decrease in \( \sigma_{eng} \). Therefore, we can link the function \( C_{AGE} \) and the pulsatile strain with a decrease in parameter \( b \) and an increase in parameter \( k \) instead. We postulated the following equation for the decrease in the collagen parameter \( b \) caused by the increased accumulation of AGEs over time:

\[
b(t) = b^* - B_4 \times C_{AGE}(t) \tag{25}
\]

where \( B_4 > 0 \) is a dimensionless parameter and \( b^* \) is the value of parameter \( b \) at a young age. According to Eq. 25, increased cross-linkage of collagen fibers by AGEs reduces the magnitude of parameter \( b \), which results in a decrease in \( \mu_{eng} \) (Eq. 12a), shifting the recruitment of the fibers to lower strains. We further postulated the following equation for the increase in the collagen parameter \( k \) caused by the increased accumulation of AGEs over time and decreased pulsatile strain:
where $T_2$ and $T_3$ are time constants. In Eq. 26, the decrease in the pulsatile strain $\Delta E$ at midwall radius and the increased accumulation of AGEs cause an increase in parameter $k$, which leads to a reduction in $\sigma_{\text{eng}}$ (Eq. 12b), making the engagement occur more abruptly.

In vitro studies (34, 67) have shown that elastin is similarly affected by the accumulation of AGEs over time. Elastin cross-links by AGEs increase the stiffness of the elastin network. However, this has not been verified in vivo. In this report, we postulated the following relation for $c_{\text{elast}}$ to account for a structural reorganization of the elastin lamellae:

\[
c_{\text{elast}}(t) = c_{\text{elast}}^* + \beta_3 \times C_{\text{AGE}}(t) \tag{27}
\]

where $c_{\text{elast}}^*$ is $c_{\text{elast}}$ at a young age and $\beta_3 > 0$ is a parameter having units of stress. $c_{\text{elast}}^*$ is the apparent elastic modulus of the ensemble of lamellae and not of a single elastin fiber. Equation 27 shows that, in absence of a mechanism that can intrinsically increase the stiffness of the elastic lamellae, such as MEC, the apparent stiffness of the elastic lamellae increases with age because the structure becomes stiffer.

All governing equations are coupled and represent a highly nonlinear system of equations. A flow diagram that illustrates the interrelations between the prescribed and calculated model parameters is shown in Fig. 2. The time course of the model parameters to be calculated is the solution of the initial value problem of the governing equations with the following initial conditions: $t^* = 0$, $D(t^*) = 0$, $F(t^*) = F_1^*$, $\lambda(t^*) = \lambda_1^*$, $C_{\text{AGE}}(t^*) = 0$, $k(t^*) = k^*$, $b(t^*) = b^*$, and $c_{\text{elast}}(t^*) = c_{\text{elast}}^*$.

RESULTS

We performed an illustrative simulation using literature data for a human thoracic aorta of a 30-yr-old female. The values of the model parameters are shown in Table 1. The governing and remodeling rate equations were solved numerically. The initial value problem has a stable unique solution, which was obtained using an explicit time step on a commercially available solver (MATLAB, Release 2009a, MathWorks). Pressure values are shown normalized in Fig. 3A. The time constant for remodeling Eq. 19 was chosen as $T_1 = 0.8 \times 10^{11}$ cycles·yr to arbitrarily simulate 80% damage in elastin by the age of 90 yr. The lower bound pulsatile strain in Eq. 19 was assigned the sufficiently small value of $\Delta E_0 = 0.01$ so that the difference $\Delta E(t) - \Delta E_0$ was positive during the entire remodeling process. The constant in Eq. 20 was taken as $b_3 = 0.8$ mm to simulate a 10% increase in the lumen radius at the zero-load state by the age of 90 yr. We prescribed a slight decrease in $\lambda_2$ with age by taking $b_1 = 10^{-5}$ yrs$^{-2}$ in Eq. 3. The maximum accumulation of AGEs is prescribed through $b_2 = 3 \times 10^{-4}$ yrs$^{-2}$ in Eq. 4. The constants for Eqs. 25-27 were chosen as $b_4 = 0.3$, $T_2 = 0.9$ yr, $T_3 = 20$ yr, and $b_5 = 50$ mmHg to allow for a 20% decrease in the collagen parameter $b$, a 150% increase in the collagen parameter $k$, and an 8% increase in the elastin parameter $c_{\text{elast}}$ according to the published data of Zulliger and Stergiopulos (72). The simulation was run between $t^* = 30$ yr and $t_{\text{max}} = 90$ yr of age.

Table 1. Model parameters for a human thoracic aorta of a 30-yr-old woman

<table>
<thead>
<tr>
<th>Definition</th>
<th>Parameter</th>
<th>Value</th>
<th>Obtained From Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner radius of curvature, mm</td>
<td>$R_i$</td>
<td>14.75</td>
<td>69 and 72</td>
</tr>
<tr>
<td>Outer radius of curvature, mm</td>
<td>$R_o$</td>
<td>17.99</td>
<td>69 and 72</td>
</tr>
<tr>
<td>Opening angle, $^\circ$</td>
<td>$\Phi$</td>
<td>100</td>
<td>72</td>
</tr>
<tr>
<td>Axial stretch ratio</td>
<td>$\lambda_1$</td>
<td>1.30</td>
<td>72</td>
</tr>
<tr>
<td>Collagen mass fraction</td>
<td>$f_{\text{coll}}$</td>
<td>0.23</td>
<td>72</td>
</tr>
<tr>
<td>Smooth muscle mass fraction</td>
<td>$f_{\text{SM}}$</td>
<td>0.19</td>
<td>72</td>
</tr>
<tr>
<td>Elastin constant, kPa</td>
<td>$c_{\text{elast}}$</td>
<td>43.75</td>
<td>72</td>
</tr>
<tr>
<td>Collagen constant, MPa</td>
<td>$c_{\text{coll}}$</td>
<td>200</td>
<td>72</td>
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<tr>
<td>Distribution parameter</td>
<td>$k$</td>
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<td>72</td>
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<tr>
<td>Distribution parameter</td>
<td>$b$</td>
<td>0.78</td>
<td>72</td>
</tr>
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As prescribed, $P_m$ increases with age and the damage of elastin affects the arterial geometry in the load-free configuration (Fig. 3). The combined effect of pulsatile strain (see Fig. 6B below) and the number of cardiac cycles (not shown) gives rise to an increase in $D$ of elastin (Fig. 3B). An increase in the magnitude of $D$ raises, in turn, the inner radius at the load-free state (Fig. 3C). In this study, the deformed length of the artery was maintained constant. Therefore, the prescribed reduction in $\lambda_z$ (Fig. 3D) led to an increase in the undeformed length of the artery.

Changes in the total arterial volume are dictated by the variation in the geometric dimensions. Assuming that the structural components of the vascular tissue have identical mass densities, the model results showed that total mass increased gradually with age toward a plateau (Fig. 4A). In line with the introduced assumptions, $f_{\text{elast}}$ and $f_{\text{SM}}$ decreased, giving rise to an increase in $f_{\text{coll}}$. $f_{\text{elast,eff}}$ was lower than total $f_{\text{elast}}$ (Fig. 4B).

The geometric alterations were accompanied by a structural reorganization in the vascular tissue. The increased cross-linking of collagen fibers by the accumulation of AGEs over time (Fig. 5A) reduced the magnitude of the collagen parameter $b$ (Fig. 5B). The increased cross-linkage of collagen fibers by AGEs in conjunction with the decrease in pulsatile strain (see Fig. 6B below) caused an augmentation in the magnitude of the collagen engagement parameter $k$ (Fig. 5C). The variation in collagen parameters $b$ and $k$ resulted in a decrease in $\mu_{\text{eng}}$ (Fig. 5D) and $\sigma_{\text{eng}}$ (Fig. 5E), making the recruitment of the fibers occur at lower strains and more abruptly. The stiffening of the elastin structure by AGEs was reflected by the increase in the elastic constant of elastin (Fig. 5F).

The model predicted geometric changes in the deformed and stress-free configuration of the artery with age. The lumen radius under $P_m$ increased monotonically with age (Fig. 6A), and pulsatile strain at the midwall radius exhibited a monotonic decrease (Fig. 6B). These changes were due to the gradual increase in $P_m$ and pulse pressure and alterations in the material properties and ZSS of the artery. The latter, which was obtained by a radial cut of the load-free configuration, changed to maintain $\sigma_{0,i}$ and $\sigma_{0,o}$ under $P_m$ (Eq. 21) and to follow the increase in the lumen diameter at the zero-load state (Eq. 20). $C_i$ and $C_o$ increased monotonically with age (Fig. 6, C and D). Thickness also exhibited a monotonic increase toward an asymptotic value (Fig. 6E). The variation in $C_i$, $C_o$, and...
thickness of the arterial wall affected the magnitude of $\Phi$, which asymptotically increased with progressing age (Fig. 6F).

Changes in geometry and material properties affected the overall mechanical response of the artery, as described by the pressure-diameter and pressure-thickness relationships. The outer diameter under zero pressure increased with age, and the pressure-diameter curve shifted to higher diameters compared with the curve at mid-age. The slope of the pressure-diameter curve with respect to the pressure axis increased at low pressures and slightly decreased at high pressures (Fig. 7A). The model predictions were similar for the pressure-lumen area relationship as well (Fig. 7B). Wall thickness at zero pressure increased. At 20 mmHg, the thickness of the mid-aged artery (40 yr old) was equal to the thickness of the aged artery (80 yr old) and less than the thickness at 60 yr old. The thickness-pressure curve at high pressures moved to higher thicknesses compared with the curve of the mid-aged artery (Fig. 7C).

The thickness-to-diameter ratio raised under zero pressure. At low pressures, the thickness-to-diameter ratio decreased with age, whereas at high pressures, the ratio increased with age and remained practically unchanged after the age of 60 yr old (Fig. 7D).

The stiffening of the aortic wall with progressing age is described by the relationship between arterial compliance and pressure. The area compliance-pressure relationship showed that the compliance of the aged artery is higher than that of the mid-aged artery at low pressures and becomes lower than that of the mid-aged artery at high pressures (Fig. 8A). The model predictions were similar for the relationship between $D_A$ and pressure as well (Fig. 8B). The values of PWV and $Z_c$ of the aged artery were lower than those of the mid-aged artery at low pressures and became higher than those of the mid-aged artery at high pressures (Fig. 8C and D). Hence, the aortic wall became stiffer with increased age at high pressures.

We varied the degree of damage in elastin to study its effect on the geometric and material parameters of the aorta. We tried higher values for the time constant $T_1$, such as $T_1 = 2 \times 10^{11}$ cycles·yr (Fig. 9A, solid line) and $5 \times 10^{11}$ cycles·yr (Fig. 9A, dashed line) compared with $T_1 = 0.8 \times 10^{11}$ cycles·yr (Fig. 9A, dotted line), which we had used before, to achieve lower levels of damage in elastin. The model predicted that pulsatile strain decreases nonmonotonically with age when elastin damage is low (Fig. 9B). An increase in $D$ gives rise to a further increase in the inner radius at $P_m$ (Fig. 9C) and the inner radius at the load-free configuration (Fig. 9D). The impact of elastin damage on parameters of the ZSS is shown in Fig. 10. $C_i$, $C_o$, thickness, and $\Phi$ were further increased when the extent of elastin damage was high. The more the elastin is damaged, the

Fig. 5. Time course of cross-link function ($A$), collagen parameter $b$ ($B$), collagen parameter $k$ ($C$), mean collagen fiber engagement strain ($D$), collagen fiber engagement variance ($E$), and elastin constant $c_{\text{elast}}$ ($F$). Values in $B$–$F$ were normalized.

AJP-Heart Circ Physiol • VOL 301 • OCTOBER 2011 • www.ajpheart.org
more the total arterial mass is raised (Fig. 11A). Increased $D$ caused a slight further increase in $f_{\text{coll}}$ and a slight further decrease in $f_{\text{elast}}$ and $f_{\text{SM}}$. As expected, $f_{\text{elast,eff}}$ exhibited a pronounced further decrease with age when $D$ increased (Fig. 11B). The varied degree of damage in elastin did not affect the time course of $c_{\text{elast}}$ nor the time evolution of collagen engagement distribution (not shown).

We also studied the alterations in geometry and material properties of the aorta caused by a varying accumulation of AGEs over time. We achieved this by trying different values for parameter $N$, such as $1.5 \times 10^{-4}$ yr$^{-2}$ (Fig. 12A, dotted line) compared with the initial value of $N = 3 \times 10^{-4}$ yr$^{-2}$ (Fig. 12A, solid line). We observed that an increased accumulation of AGEs over time caused a further decrease in the collagen parameter $b$ (Fig. 12B) and a further increase in the collagen parameter $k$ (Fig. 12C). The variation in collagen parameters $b$ and $k$ resulted in a further decrease in $\mu_{\text{eng}}$ (Fig. 12D) and $\sigma_{\text{eng}}$ (Fig. 12E) when the cross-linkage of collagen fibers was increased over time. The increase in parameter $\beta_2$ gave rise to a further increase in $c_{\text{elast}}$ (Fig. 12F). The increased accumulation of AGEs over time reduced the inner radius at $P_m$ after 70 yr old (Fig. 13A). The model predicted that pulsatile wall strain in combination with the number of cardiac cycles over the lifetime cause fatigue failure in the elastin structure, which, in turn, gives rise to an increase in the lumen diameter at the load-free configuration. Moreover, aging leads to enhanced cross-linking of collagen fibers by the accumulation of AGEs over time, which raises the stiffness of the collagen fiber network, by making the recruitment of the fibers occur at lower strains and more abruptly. We also assumed that the stiffness of the elastin structure was similarly affected by the accumulation of AGEs over time. Furthermore, the ge-

![Fig. 6. Time course of inner radius at mean pressure (A), pulsatile strain (B), inner arc length (C) and outer arc length (D) at the ZSS, thickness at the ZSS (E), and opening angle (F). Values were normalized.](https://example.com/fig6.png)
ometry of the artery at the ZSS changes to follow the increase in the lumen diameter at the zero-load state and to maintain $\sigma_0$ under $P_m$ at baseline values for a healthy young artery. We used the constitutive law of Zulliger and Stergiopoulos (72), and we applied our model to their data on the aging of the human aorta.

Most of the results from the illustrative example for the human aorta were in agreement with the available experimental

![Fig. 7. Theoretical predictions for the relation between outer diameter and mean pressure (A), lumen area and mean pressure (B), thickness and mean pressure (C), and thickness/outer diameter and mean pressure (D).](image)

![Fig. 8. Theoretical predictions for the relation between area compliance and mean pressure (A), area distensibility and mean pressure (B), pulse wave velocity and mean pressure (C), and characteristic impedance and mean pressure (D).](image)
observations reported in the literature. According to Fung and Liu (18), pressure-induced geometric remodeling of a healthy artery results in the restoration of the magnitude of wall stresses to their baseline values. Similar conclusions have also been reported by others (38, 39). The monotonic increase in $\Phi$ with age (Fig. 6F) was in qualitative agreement with the measurements of Saini et al. (54), who found that $\Phi$ of the human thoracic aorta increases fairly linearly with age. A linear relationship between $\Phi$ and age has also been considered by Zulliger and Stergiopulos (72).

There are several reports in the literature that support the model hypothesis for the damage of elastin. O’Rourke (46) suggested that fatigue failure causes the fragmentation of elastin with increasing age. Also, Sa Cunha et al. (53) linked the high HR with mortality from cardiovascular disease. According to Refs. 5 and 55, pulsatile wall strain and the number

![Fig. 9. Time course of damage parameter of elastin (A), pulsatile strain (B), inner radius at mean pressure (C), and inner radius at the load-free configuration (D). Arrows indicate an increase in the damage of elastin. Values in B–D were normalized. The dashed lines show values for time constant $T_1 = 5 \times 10^{11}$ cycles·yr, solid lines show values for $T_1 = 2 \times 10^{11}$ cycles·yr, and dotted lines show values for $T_1 = 0.8 \times 10^{11}$ cycles·yr.]

![Fig. 10. Time course of inner arc length (A), outer arc length (B), thickness (C), and opening angle (D) at the ZSS. Arrows indicate an increase in the damage of elastin. Values were normalized. The dashed lines show values for $T_1 = 5 \times 10^{11}$ cycles·yr, solid lines show values for $T_1 = 2 \times 10^{11}$ cycles·yr, and dotted lines show values for $T_1 = 0.8 \times 10^{11}$ cycles·yr.]

A MODEL OF AGE-RELATED CHANGES IN ARTERIES

AJP-Heart Circ Physiol • VOL 301 • OCTOBER 2011 • www.ajpheart.org
Our model predicted an increase in the arterial volume and a subsequent change in the mass fractions of the wall components, which were in agreement with experimental observations. As shown Fig. 4A, the total arterial volume (or mass) increased by 73% between the ages of 30 and 90 yr. According to Eq. 22, the increase in aortic mass is caused by the increase in the deformed inner radius and the increase in wall thickness. The deformed inner radius increases due to the damage-modulated increase in the inner radius in the unloaded state (Eq. 20) and due to an age-related increase in \( P_m \). In this study, we assumed that the wall thickness as a result of remodeling, which tends to restore the \( \sigma_0 \) distribution at \( P_m \), as it exists in the healthy young artery. Langewouters (35) observed that the wall volume of the aged (80 yr old) human thoracic aorta is about two times that of the mid-aged artery (40 yr old). Bader (7) also reported a similar increase in the volume of the human thoracic aorta. The increase in the content of collagen and decrease in \( f_{\text{elast}} \) and \( f_{\text{SM}} \) with age (Fig. 4B) were in agreement with literature reports (14, 16, 29, 55). According to Toda et al. (58), aortic remodeling in aging is associated with a fragmentation and decrease of elastin fibers, an increase of irregularly arranged collagen fibers, and a degeneration of SM cells in the media. Nejjar et al. (43) also reported varying degrees of damage in the elastin structure of the human thoracic aorta. Zulliger and Stergiopulos (72) drew no conclusion on the evolution of collagen content with age, although their data-fitting study revealed that \( f_{\text{elast}} \) diminished gradually with progressing age.

The structural reorganization of the vascular tissue by the accumulation of AGEs over time was in agreement with experimental observations. Increased cross-links of collagen fibers by AGEs (Fig. 5A) stiffen the fiber network (2, 25, 37, 56, 68, 70). The predicted change in the magnitude of collagen parameters \( b \) and \( k \) (Fig. 5, B and C) was in perfect agreement with the results of Zulliger and Stergiopulos (72). The consequences of changes in collagen parameters \( b \) and \( k \) are better understood by their effects on the mean value and the variance of the fiber engagement probability density function (Fig. 5, D and E). The decrease in the mean value of the statistical distribution means that the engagement of collagen fibers takes place at lower \( \lambda_0 \). The decrease in the variance means that the recruitment of collagen fibers occurs more abruptly. As a result, when compared at equal strains, the wall material of the remodeled artery is stiffer than the material of the artery at a young age. Zulliger and Stergiopulos (72) obtained similar results on the variation of the mean and the variance of the collagen statistical distribution with age. Based on in vitro studies (34, 67), we assumed that the accumulation of AGEs over time leads to elastin cross-linking, which raises the apparent stiffness of the elastic lamellae (Fig. 5F). The data-fitting study of Zulliger and Stergiopulos (72) revealed that the elastic constant of elastin increased with age, although the linear regression was not significant. A carefully designed in vivo study is needed to examine the possible effects of AGEs on the structural reorganization of the elastin structure.

The overall mechanical response of an artery is described by its pressure-diameter relationship. The shifting of the pressure-diameter curve to higher diameters with progressed age (Fig. 7A) was in agreement with the experimental observations of Langewouters (35), who reported that the external diameter of the human thoracic aorta at 100 mmHg increased by 25%.
between the mid-aged and aged artery. Our model predicted a 20% increase in the external diameter at 100 mmHg between the mid-aged and aged artery. Virmani et al. (63) also reported that the outer circumference of the thoracic aorta of occidental and Chinese populations at 100 mmHg increased by 30% and 40%, respectively, between 19–44 and ≥65 yr of age. The behavior of the pressure-lumen area relationship with age (Fig. 7B) was similar to that of the pressure-outer diameter curve. The maximum lumen area, as predicted by our model, increased by 22% between the mid-aged and aged artery. Lange-wouters (35) observed that the maximum lumen area of the human thoracic aorta increased up to 25% between the mid-aged and aged artery at 100 mmHg. Our model predicted a 30% increase in wall thickness (Fig. 7C) and a 10% increase in the thickness-to-diameter ratio (Fig. 7D) between the mid-aged and aged artery. The result was in agreement with the experimental observations of Langewouters (35), who found a 100% increase in maximal compliance between the mid-aged and aged human thoracic aorta. Our model predicted a 350% increase in maximal \( C_A \) between the mid-aged and aged artery. At physiological pressures, compliance decreases with age. Our model predicted a 50% decrease in \( C_A \) between the mid-aged and aged artery at 100 mmHg. According to Langewouters (35), \( C_A \) of the aged human thoracic aorta at 100 mmHg is about one-third of that of the mid-aged aorta. The compliance of large human conduit arteries at operating pressure decreases with age, according to several other reports in the literature (11, 20, 30, 42, 44, 51, 61). \( D_A \) of the human aorta also decreases with age at operating pressure. According to our model, \( D_A \) at 100 mmHg decreased by 63% between the mid-aged and aged artery (Fig. 8B). Langewouters (35) found that the distensibility of the aged aorta at 100 mmHg is about one-third of that of the mid-aged aorta. Hallock and Benson (28) also reported that, by the age of 75 yr old, \( D_A \) is 25% of that of a mid-aged specimen. Other investigators have also reported that large elastic arteries lose

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Fig. 12. Time course of cross-link function (A), collagen parameter \( b \) (B), collagen parameter \( k \) (C), mean collagen fiber engagement strain (D), collagen fiber engagement variance (E), and \( c_{\text{elast}} \) (F). Arrows indicate an increase in the accumulation of AGEs over time. Values in B–F were normalized. The dashed lines show values for rate parameter \( \beta_2 = 1.5 \times 10^{-4} \) yr\(^{-2}\), solid lines show values for \( \beta_2 = 3 \times 10^{-4} \) yr\(^{-2}\), and dotted lines show values for \( \beta_2 = 4.5 \times 10^{-4} \) yr\(^{-2}\).
Arterial compliance is associated with the magnitudes of PWV and $Z_c$. The raise in the magnitude of PWV at operating pressure as predicted by our model (Fig. 8C) was in agreement with literature reports. According to Langewouters (35) and Gozna et al. (24), PWV at 100 mmHg of the aged artery is about two times that of the mid-aged artery. Our model predicted a 65% increase in PWV at 100 mmHg between the mid-aged and aged artery. Avolio et al. (3) carried out a study on a large population of Chinese of both sexes aged 3 to 89 yr old and living in urban Beijing, which is an area with a known high prevalence of hypertension. They found that aortic PWV increased by $\sim$37% between the mid-aged and aged artery at operating pressure. Later, Avolio et al. (4) carried out a similar study on a large population of Chinese of both sexes aged 2 mo to 94 yr old and living in rural Guangzhou, which is an area with a known low prevalence of hypertension.

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Fig. 13. Time course of inner radius at mean pressure (A), pulsatile strain (B), damage parameter of elastin (C), and inner radius at the load-free configuration (D). Arrows indicate an increase in the accumulation of AGEs over time. Values in A, B, and D were normalized. The dashed lines show values for $\beta_2 = 1.5 \times 10^{-4}$ yr$^{-2}$, solid lines show values for $\beta_2 = 3 \times 10^{-4}$ yr$^{-2}$, and dotted lines show values for $\beta_2 = 4.5 \times 10^{-4}$ yr$^{-2}$.
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Fig. 14. Time course of inner arc length (A), outer arc length (B), thickness (C), and opening angle (D) at the ZSS. Arrows indicate an increase in the accumulation of AGEs over time. Values were normalized. The dashed lines show values for $\beta_2 = 1.5 \times 10^{-4}$ yr$^{-2}$, solid lines show values for $\beta_2 = 3 \times 10^{-4}$ yr$^{-2}$, and dotted lines values for $\beta_2 = 4.5 \times 10^{-4}$ yr$^{-2}$.
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hypertension. The linear regression revealed that aortic PWV increased by $\sim$27% between the mid-aged and aged artery at operating pressure and was consistently lower than that in the Beijing group when compared between subjects of the same arterial pressure and age. The 25% increase in Zc at 100 mmHg between the mid-aged and aged artery as predicted by our model (Fig. 8D) was in agreement with the experimental results of Langewouters (35), who found that $Z_c$ increased by 34% between the mid-aged and aged thoracic aorta.

According to the proposed model, damage of elastin affects the geometric dimensions of the vessel via its effect on the $\sigma_0$ that drives the vessel remodeling. Both the inner radius at $P_m$ (Fig. 9C) and the inner radius at the zero-load state (Fig. 9D), as well as the dimensions of the ZSS (Fig. 10), increased with the progression of elastin damage. As a result, the total arterial mass increased more (Fig. 11A), mainly due to the synthesis of collagen.

The accumulation of AGEs over time has an impact on both the material and geometric parameters of the aortic wall. The increase in parameter $\beta_2$ caused a further decrease in the collagen parameter $b$ (Fig. 12B) and a further increase in the collagen parameter $k$ (Fig. 12C). This, in turn, resulted in a further decrease in $\mu_{Eng}$ and $\sigma_{Eng}$ distribution (Fig. 12, D and E). Consequently, as mentioned above, the increase in parameter $\beta_2$ resulted in a further stiffening of the wall material of the remodeled artery. The further increase in $c_{Elast}$ (Fig. 12F) due to the increased accumulation of AGEs contributed even more to the stiffening of the aortic wall.

The impact of parameter $\beta_2$ (the rate of accumulation of AGEs with time) on the geometric remodeling is manifested at high ages. The net effect is a decrease in arterial dimensions and mass with aging. The inner radius at $P_m$ decreased after the age of 75 yr as $\beta_2$ increased (Fig. 13A). The stiffening of the aortic wall contributed further to the monotonic decrease in pulsatile strain with age (Fig. 13B). As a result, $D$ and the inner radius at the load-free configuration did not increase as fast after 70 yr of age (Fig. 13, C and D). The dimensions of the ZSS also increased less after 70 yr when parameter $\beta_2$ was higher (Fig. 14). The decrease in arterial dimensions was also manifested by the reduction in total arterial mass after 70 yr (Fig. 15A). It appears that the effect of parameter $\beta_2$ on the time course of the mass fractions of the wall components is negligible (Fig. 15B). This indicates that, although the total arterial volume decreases after 70 yr old, the geometric and structural reorganization of the vascular tissue is done in such a way as to preserve the relative content of the wall constituents. There is a need for more experimental data to verify the conclusions of the above parametric study.

The limitations of this study are associated with the introduced simplifying assumptions. First, we disregarded the multilayer structure of the arterial tissue as well as the composition and structure of collagen fibers of various types and orientations by modeling the artery as a homogeneous one-layered tube, in which collagen fibers of a single type were oriented in the circumferential direction only. A more realistic model could separately account for the structural properties of the media and adventitia, where the orientation of collagen fibers of different types would vary from layer to layer and be statistically distributed around a certain mean value, which would not necessarily be the circumferential one (19). Second, in the present model, we did not consider a spectrum of effects generated by the impact of different AGE compounds on the cross-linkage of collagen. Third, a future study might revise the hypothesis regarding the variation of HR with age, because there is contradicting evidence in the literature (33) that resting (as well as maximum) HR declines with age rather than increases with age, as considered in this report. Fourth, the present model linked the elastin damage to mechanical fatigue failure only, disregarding possible elastolytic mechanisms caused by increased expression of MMPs. A future model could, e.g., account for both mechanical and chemical damage of elastin through different remodeling laws, the time constants of which would control the relative evolution of the two different mechanisms as well as their impact on the wall remodeling process. Fifth, in this report, we attributed the stiffening of the elastin structure to cross-linkage caused by increased accumulation of AGEs only, without considering the effect of MEC. Again, a future model might address both mechanisms of elastin stiffening through separate evolution laws and reveal their effect on the remodeling of the aortic tissue. Finally, in this model, we hypothesized that the instantaneous change of arterial geometry with increasing $P_m$ can maintain $\sigma_{Eng}$ and $\sigma_{Eng_o}$ at control levels. Further evidence on the maintenance of $\sigma_0$ as well as other driving stimuli, such as the cardiac preload or other hemodynamic characteristics, might prove essential in building a model of aortic remodeling in aging.

In summary, in the present report, we proposed a predictive constituent-based model of aortic remodeling during aging. The model accounted for a prescribed time course of some mechanical parameters such as $P_m$, pulse pressure, in vivo $A_{E}$, and HR as well as the accumulation of AGEs. Governing equations that follow from the finite elasticity, structure-based constitutive modeling within the constrained mixture theory,
duration continuum theory, global growth approach for stress-induced remodeling, and remodeling of material properties due to differential mass production in the arterial wall components and due to structural reorganization in the vascular tissue were used. The model predicted the response over age of the deformed dimensions, lumen radius at the traction-free state, ZSS fractions of the basic load-bearing structural constituents of the aortic tissue, wall stress, pulsatile strain, elastin damage, and local measures of the linearized response around the physiological deformed state, such as $C_\lambda$, $D_\lambda$, PWV, and $Z_\mu$. Most of the results of the present study were supported by previous theoretical investigations and published experimental findings. However, there is a pressing need for more experimental data that can be used to refine mathematical modeling. Ultimately, a predictive model can serve as a tool that can be used to simulate abnormal processes during aging, which are difficult to capture experimentally. For instance, the results obtained can shed light on the effects of the individual contribution of abnormal processes, such as maladaptive remodeling or accelerated damage of the aortic tissue associated with certain vascular diseases, on the outcome of aging.

GRANTS

This work was supported by Swiss National Scientific Research Fund Grant 325230_125445/1.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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