A constitutive formulation of arterial mechanics including vascular smooth muscle tone

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A constitutive formulation of arterial mechanics including vascular smooth muscle tone. Am J Physiol Heart Circ Physiol 287: H1335–H1343, 2004. First published May 6, 2004; 10.1152/ajpheart.00094.2004.—A pseudo-strain energy function (pseudo-SEF) describing the biomechanical properties of large conduit arteries under the influence of vascular smooth muscle (VSM) tone is proposed. In contrast to previous models that include the effects of smooth muscle contraction through generation of an active stress, in this study we consider the vascular muscle as a structural element whose contribution to load bearing is modulated by the contraction. This novel pseudo-SEF models not only arterial mechanics at maximal VSM contraction but also the myogenic contraction of the VSM in response to local increases in stretch. The proposed pseudo-SEF was verified with experimentally obtained pressure-radius curves and zero-stress state configurations from rat carotid arteries displaying distinct differences in VSM tone: arteries from normotensive rats displaying minimal VSM tone and arteries from hypertensive rats exhibiting significant VSM tone. The pressure-radius curves were measured in three different VSM states: fully relaxed, maximally contracted, and normal VSM tone. The model fitted the experimental data very well ($r^2 > 0.99$) in both the normo- and hypertensive groups for all three states of VSM activation. The pseudo-SEF was used to illustrate the localized reduction of circumferential stress in the arterial wall due to normal VSM tone, suggesting that the proposed pseudo-SEF can be of general utility for describing stress distribution not only under passive VSM contraction but also under physiological and pathological conditions with varying levels of VSM tone.

biomechanical properties; constitutive equation; myogenic response; nonlinear elasticity

SOFT BIOLOGICAL TISSUES such as an arterial wall exhibit a complex mechanical behavior. A reasonable model for describing arterial tissue under physiological loads is a highly nonlinear elastic, orthotropic, and incompressible solid that undergoes finite deformations. Within this model the constitutive stress-strain relations are not independent relations. For isothermal deformation processes there exists a scalar, the strain energy function (SEF), from which the stress-strain relations are derived. Thus the constitutive formulation of the arterial tissue reduces to the identification of a relevant SEF.

The most widely known SEF for arteries is probably the exponential-polynomial SEF of Chuong and Fung (9). Many other SEFs have been proposed, and we refer the reader to the works of Hayashi (27), Humphrey (31, 32), and Holzapfel and Gasser (29) for more detailed presentations and discussions thereof. With possibly the sole exception of that of Eude and Ohayon (19), none of the previously proposed SEFs accounts for the effects of vascular smooth muscle (VSM), even though it is well known that the dynamics of VSM alter the mechanical properties of arteries (16–18, 26, 30). Rachev and Hayashi (38) have studied the effect of VSM on strain and stress distribution in the arterial wall by using a SEF to formulate passive stress, to which they added an active stress developed by the VSM with variable tone in the circumferential direction. Furthermore, Rachev and Hayashi (38) used their approach to modeling the arterial wall to predict variations in opening angles with changes in VSM tone.

The level of VSM activation or tone may change in response to biomechanical stimuli such as flow (4, 11, 13) or pressure (4, 21, 33, 36, 40), hormonal stimuli, neural stimuli, and drugs. Furthermore, VSM tone has been proposed to be a very important parameter in vascular remodeling. Changes in flow, which the VSM senses via signaling molecules received from endothelial cells (see Ref. 13 for a review), cause changes in VSM tone, which has been hypothesized to be associated with synthetic and proliferative activity of the VSM cells leading to shear stress-induced remodeling of the artery (37). Changes in lumen pressure lead to alteration of the wall in stress and strain (36, 45), which is followed by remodeling of the wall. At the same time, changes in VSM tone can be observed (20, 50). Both shear stress and hypertension-induced wall adaptation have been successfully modeled as a function of VSM tone by Rachev (37) and Fridex et al. (22), respectively. In both studies, the effective stress of the VSM cells is averaged over the entire deformed cross section. Variations in the artery’s mechanical properties are described by VSM tone changes alone in both models, and altered composition of the wall is not taken into account. Especially in the case of flow-related remodeling of adult arteries, these assumptions are valid. However, composition varies during development and maturation and therefore a constitutive formulation of the arterial tissue accounting for the contribution of its structural constituents including VSM is required (44). As remodeling in response to hypertension has been shown to be inhomogeneous across the wall cross thickness (23, 34), one would thus expect that the VSM tone and changes in local stress and strain acting on the VSM cells would be inhomogeneous during the remodeling process. Furthermore, we have observed (49) changes of VSM tone in...
response to axial elongation of the porcine carotid artery in addition to the widely appreciated sensitivity to circumferential deformation or myogenic response (3, 6, 7, 33, 40, 41). We thus identified the need for a more detailed description of the arterial wall mechanics through a SEF that describes the orthotropic and dynamic VSM embedded in the passive arterial matrix. Such a model could be used to derive the distribution of stress within the arterial wall and describe its biomechanical properties not only under passive conditions but also under any level of VSM tone.

**Glossary**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
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<tbody>
<tr>
<td>$e_0$, $e_z$, $e_r$</td>
<td>Local base of cylindrical coordinate system</td>
</tr>
<tr>
<td>$\lambda_0$, $\lambda_z$, $\lambda_r$</td>
<td>Circumferential, axial, and radial stretch ratios</td>
</tr>
<tr>
<td>$E_0$, $E_z$, $E_r$</td>
<td>Circumferential, axial, and radial Green's strains</td>
</tr>
<tr>
<td>$I_1$</td>
<td>2$E_0$ + 2$E_z$ + 2$E_r$ + 3, first invariant of the Cauchy-Green deformation tensor</td>
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<tr>
<td>$\Theta$</td>
<td>Opening angle</td>
</tr>
<tr>
<td>$r_i$</td>
<td>Inner radius (loaded state)</td>
</tr>
<tr>
<td>$r_o$</td>
<td>Outer radius (loaded state)</td>
</tr>
<tr>
<td>$r$</td>
<td>Radius of a wall point (loaded state)</td>
</tr>
<tr>
<td>$R_i$</td>
<td>Inner radius (zero-stress state)</td>
</tr>
<tr>
<td>$R_o$</td>
<td>Outer radius (zero-stress state)</td>
</tr>
<tr>
<td>$R$</td>
<td>Radius of a wall point (zero-stress state)</td>
</tr>
<tr>
<td>$l$</td>
<td>Axial length (loaded state)</td>
</tr>
<tr>
<td>$L$</td>
<td>Axial length (zero-stress state)</td>
</tr>
<tr>
<td>$P$</td>
<td>Local hydrostatic pressure within wall</td>
</tr>
<tr>
<td>$\sigma_0$, $\sigma_z$, $\sigma_r$</td>
<td>Local wall stresses in principal directions</td>
</tr>
<tr>
<td>$P_{\text{mod}}$</td>
<td>Intraluminal pressure</td>
</tr>
<tr>
<td>$r_{i,\text{exp}}$</td>
<td>Internal arterial radius as given by model</td>
</tr>
<tr>
<td>$r_{i,\text{mod}}$</td>
<td>Internal arterial radius as measured experimentally</td>
</tr>
<tr>
<td>$\Psi$</td>
<td>Full strain energy function</td>
</tr>
<tr>
<td>$\Psi_{\text{coll}}$</td>
<td>Strain energy function representing collagen mesh</td>
</tr>
<tr>
<td>$\Psi_{\text{fiber}}$</td>
<td>Strain energy function representing individual collagen fiber</td>
</tr>
<tr>
<td>$\rho_{\text{fiber}}$</td>
<td>Collagen fiber engagement strain distribution</td>
</tr>
<tr>
<td>$\Psi_{\text{VSM}}$</td>
<td>Strain energy function representing VSM</td>
</tr>
<tr>
<td>$f_{\text{elast}}$</td>
<td>Area fraction of load-bearing elastin</td>
</tr>
<tr>
<td>$f_{\text{coll}}$</td>
<td>Area fraction of load-bearing collagen</td>
</tr>
<tr>
<td>$f_{\text{VSM}}$</td>
<td>Area fraction of load-bearing VSM</td>
</tr>
<tr>
<td>$c_{\text{elast}}$</td>
<td>Elastic constant of elastin</td>
</tr>
<tr>
<td>$c_{\text{coll}}$</td>
<td>Young’s modulus of collagen</td>
</tr>
<tr>
<td>$k$, $b$</td>
<td>Constants defining collagen fiber engagement</td>
</tr>
<tr>
<td>$c_{\text{VSM}}$</td>
<td>Elastic constant of maximally contracted VSM</td>
</tr>
<tr>
<td>$L_0$</td>
<td>Length of a fully relaxed VSM cell</td>
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<tr>
<td>$L_c$</td>
<td>Length of a maximally contracted VSM cell</td>
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**METHODS**

In contrast to previous models that included the effects of smooth muscle contraction through generation of an active stress, in this study we consider the vascular muscle as a structural element whose contribution to load bearing is modulated by the contraction. The model is based on the following assumptions: 1) the extracellular matrix and the VSM operate in parallel, each weighted by their contribution to load bearing; 2) VSM exhibits a linear mechanical response in terms of Cauchy-stress engineering strain when the VSM is maximally contracted; 3) when the VSM is maximally contracted at zero load, the length of the circumferential VSM cells is less than the length of the corresponding extracellular matrix in the zero-stress state (ZSS); 4) variation of the VSM tone in function of external stimulation (biochemical or mechanical) and the length-tension relationship are taken into account through a variation of the stress-strain relationship of the VSM in the circumferential direction; and 5) the contribution of the fully relaxed VSM to stress-bearing structures is negligible.

**Assumption 1** is similar to Hill’s model shown in Fig. 1 (25, 28). However, the weighting by the cross-sectional areas of each component will result in a description of their effective stresses and not, as in Hill’s model, in the passive and active stress per unit area of the wall cross section. **Assumptions 2** and 3 allow the formulation of the maximally contracted VSM mechanics in a SEF context. However, as indicated by assumption 3, the reference circumferential stretch is not the same for the VSM as for the extracellular matrix.

**Strain energy function for fully relaxed arterial wall.** A SEF describing the elastin and collagen matrix of the arterial wall, which we have presented elsewhere in a slightly modified form (48), is used to describe the passive components of the arterial wall. We recapitulate the important features of this SEF here.

The SEF is expressed in a cylindrical coordinate system in terms of local Green strains ($E_0$, $E_z$, $E_r$) or stretch ratios ($\lambda_0$, $\lambda_z$, $\lambda_r$) which are related to each other via

$$\lambda_i = \sqrt{2E_i + 1} k = \theta, z, r$$

The general approach is a separation of the SEF ($\Psi$) into an isotropic and an orthotropic part representing elastin and collagen acting in parallel, respectively:

$$\Psi_{\text{passive}} = f_{\text{elast}}\Psi_{\text{elast}} + f_{\text{coll}}\Psi_{\text{coll}}$$

Each part is weighted by the fractions of the total wall cross-sectional area ($f_{\text{elast}}$ and $f_{\text{coll}}$, respectively) that the component occupies, so we later obtain effective stresses for the parallel element. VSM in its fully relaxed state is neglected (48). Schematically, this is shown in Fig. 2, left.
Constitutive arterial mechanics including VSM tone

For the isotropic elastin we write

$$\Psi_{\text{elast}} = c_{\text{elast}} (I_1 - 3)^{3/2}$$  \hspace{1cm} (3)

with the elastic constant $c_{\text{elast}} > 0$ describing the elastin. $I_1 = 2E_0 + 2E_c + 2E_r + 3$ is the first invariant of the Cauchy-Green deformation tensor.

The collagen fibers appear to be coiled and wavy in their unloaded state (10, 15), and we assume that the engagement of the collagen fibers when stretched is distributed in some statistical manner (14, 46, 47) and that the collagen fibers are oriented circumferentially (15, 46).

We have selected the log-logistic probability distribution function ($p_{\text{fibers}}$) of the engagement strain in circumferential direction $E_{\text{fibers}}$, which has lower bounds at a given value $E_0$

$$p_{\text{fibers}} (E_{\text{fibers}}) = \begin{cases} 
  k \left( \frac{E_0 - E_{\text{fibers}}}{b} \right)^{k-1} & \text{for } E_0 \leq E_{\text{fibers}} \\
  B \left[ 1 + \left( \frac{E_0 - E_{\text{fibers}}}{b} \right)^{k-1} \right]^{-k} & \text{for } E_{\text{fibers}} > E_0 
\end{cases}$$  \hspace{1cm} (4)

where $b > 0$ is a scaling parameter and $k > 0$ defines the shape of the distribution. We set $E_0 = 0$ to prevent any collagen fibers being loaded and thus exerting a force when the tissue is in its ZSS. An individual collagen fiber’s SEF is described by

$$\Psi_{\text{coll}} (E') = \begin{cases} 
  0 & \text{for } E' \leq 0 \\
  c_{\text{coll}} \frac{1}{2} E'^2 & \text{for } E' > 0 
\end{cases}$$  \hspace{1cm} (5)

where $c_{\text{coll}}$ is the elastic constant associated with the collagen and $E'$ is the local strain in direction of the fiber. To describe the ensemble of circumferentially oriented collagen fibers we can fold the individual fiber SEF ($\Psi_{\text{fibers}}$) with the fiber distribution ($p_{\text{fibers}}$)

$$\Psi_{\text{coll}} (E_{\text{fibers}}) = \Psi_{\text{fibers}} \cdot p_{\text{fibers}} = \int_{-\infty}^{\infty} \Psi_{\text{fibers}} (E') \cdot p_{\text{fibers}} (E_{\text{fibers}} - E') dE'$$  \hspace{1cm} (6)

Equation 2 now becomes

$$\Psi_{\text{passive}} = f_{\text{elast}} c_{\text{elast}} (I_1 - 3)^{3/2} + f_{\text{coll}} \Psi_{\text{coll}} (E_{\text{fibers}} - E') dE'$$  \hspace{1cm} (7)

Pseudo-SEF for active mechanical VSM properties. Under physiological conditions VSM displays some residual contraction. This level of contraction, situated between the fully relaxed VSM state and the maximally contracted VSM state, is often called normal VSM tone or simply normal tone. Even when the vessel is under no load, a slight VSM contraction, called basal tone, can be observed (3, 22, 50). In many arteries normal tone increases when pressure is increased, signifying the presence of a myogenic response (4, 21, 33, 36, 40). Under normal VSM tone and at physiological pressures, an artery appears stiffer than when fully relaxed but is more distensible than in its maximally contracted state (1, 49).

To extend the mechanical description of the arterial wall to include the effects of VSM tone, we propose adding an additional term to the above-mentioned SEF (Eq. 2)

$$\Psi = f_{\text{elast}} \Psi_{\text{elast}} + f_{\text{coll}} \Psi_{\text{coll}} + S_1 S_2 \Psi_{\text{VSM}}$$  \hspace{1cm} (8)

where $f_{\text{VSM}}$ is the cross-sectional area fraction of VSM and $\Psi_{\text{VSM}}$ is a SEF describing the VSM when maximally contracted. $S_1$ is a nondimensional function describing the level of VSM tone. $S_2$ incorporates the range of stretch at which the VSM develops maximal force under isometric contraction (35a).

When maximally contracted, the VSM cells’ contribution to the total SEF is assumed to be described by the following relationship

$$\Psi_{\text{VSM}} = c_{\text{VSM}} \left[ \lambda_{\text{VSM}}^4 - \log (\lambda_{\text{VSM}}^4) - 1 \right]$$  \hspace{1cm} (9)

This yields a stress-strain relationship linear in $\epsilon_{\text{VSM}} = \lambda_{\text{VSM}}$ (engineering strain) and fulfills the requirements of a strain energy potential. The VSM SEF does not depend on deformations in the axial direction and is thus in accordance with previous observations for maximally contracted porcine carotid arteries, which did not alter their circumferential mechanical properties when axial elongation was changed (49). A linear stretch-strain relationship for the maximally contracted VSM describes the ascending part of the experimentally

Fig. 2. The novel strain energy function (SEF) treats the arterial wall as 3 elements acting in parallel. The schematic model for the resulting circumferential stress-strain relationship $\alpha_{\text{VSM}}$ (Eq. 17) is shown here for comparison with the classic Hill model (Fig. 1). Elastin is represented by a nonlinear, elastic collagen as wavy, coiled springs that gradually engage in load bearing with increased stretch and VSM, which when passive is neglected and when contracted is engaged. The VSM elastic element is tunable by myogenic response in the case of normal VSM tone. When the tissue is not loaded externally, the engaged VSM will compress the passive elements until an internal equilibrium of stress is reached. $L_c$, maximally contracted VSM cell length; $L_{cr}$, fully relaxed VSM cell length.
determined active stress-strain relationship well (21). \( \sigma_{VSM} \) takes the role of an elastic modulus. \( \lambda_{VSM} \) is the circumferential stretch of the VSM when the artery is in its maximally contracted state. We assume that when the VSM is maximally contracted at zero load the length of the VSM cells (\( L_c \)) is less than that of the passive components elastin and collagen in the ZSS (\( L_c \); Fig. 2, left and center left). We introduce \( \lambda_{pre} = L_o/L_c \), which allows the stretch experienced by the VSM to be expressed in reference to the stretch of the passive components by the following transformation:

\[
\lambda_{VSM}^f = \lambda_p \lambda_{pre} \tag{10}
\]

For simplicity, \( \lambda_p \) is assumed to be the same across the arterial wall thickness. As an alternative interpretation, \( 1/\lambda_{pre} \) can be understood as length of an isolated VSM cell under the isotonic maximal wall thickness. As an alternative interpretation, 1/

We now turn to \( S_1 \), the VSM tone function. It has been observed that VSM reacts to stretch by initiating a contractile response often termed myogenic response, even in the absence of vasoactive drugs. VSM in its normal tone state appears to be sensitive to both circumferential and longitudinal stretching of the vessel wall (3, 6, 7, 33, 40, 41, 49). We thus make the simplification assumed that normal tone VSM is sensitive to deformation in any direction. \( S_1 \) is a nondimensional indicator of the level of VSM tone and takes on values between 0 (fully relaxed) and 1 (maximally contracted). Mathematically, for the different VSM states, \( S_1 \) is expressed as

\[
S_1 = \begin{cases} 
0 & \text{fully relaxed} \\
1 & \text{maximally contracted} \\
\frac{(S_{basal} + (1 - S_{basal})}{2} & \text{normal tone} \\
\frac{1 + \text{Erf}(\frac{Q - \mu}{\sqrt{2} \sigma})}{2} & \text{normal tone}
\end{cases}
\tag{11}
\]

\( Q \) is a function of the VSM deformation

\[
Q = \alpha_o \varepsilon_i + \alpha_i \varepsilon_i + \alpha_o \varepsilon_o + 3 \tag{12}
\]

\( \alpha_o, \alpha_i, \) and \( \alpha_o \) describe the sensitivity of the VSM to deformations in the corresponding directions. Lacking precise data on the details of \( Q \), we have set \( \alpha_o = \alpha_i = \alpha_o = 2 \) so that \( Q = I_1 \), the first invariant of the Cauchy-Green deformation tensor. In Eq. 11 for vasoactive drugs, only full VSM relaxation and maximal VSM contraction are considered and we do not attempt to describe the VSM dynamics when modified by partial stimulation in this study. When the artery is in its normal VSM tone state, we assume a Gaussian distribution of the VSM cell activation level (myogenic tone) as a function of deformation \( Q \). This Gaussian distribution is characterized by the critical engagement deformation, \( \mu \), and a half-width, \( \sigma \), and is represented by the error function \( \text{Erf} \). \( S_{basal} \) represents the VSM basal tone contraction, which is present even in the absence of any tissue deformation.

\( S_2 \) accounts for the length-tension relationship of the individual contractile elements within the VSM cells. When the contractile element is within an optimal range of length it develops maximal force under isometric contraction. From Cox (12) we have obtained the range of maximal force exertion referenced to the circumferential stretch of the composite wall. By division by \( \lambda_{pre} \) we can transform \( \lambda_{VSM}^f \) to the stretch ratios of the wall matrix to utilize the range of maximal force exertion as found by Cox. Above and below this range, we assume that the VSM is not able to develop tension

\[
S_2 = \begin{cases} 
1 & \text{fully relaxed} \\
0.680 < \lambda_{VSM}^f / \lambda_{pre} < 1.505 \\
0 & \text{otherwise}
\end{cases}
\tag{13}
\]

On the basis of the above, \( \Psi \) becomes

\[
\Psi = f_{elast} c_{elas}(I_1 - 3)^{1/2} + f_{int} \int_{-\infty}^{x} \Psi_{int} (x) \cdot p_{elas} (E_q - x) dx \\
+ S_1 S_2 f_{VSM} [\lambda_{VSM}^f - \log(\lambda_{VSM}^f) - 1] \tag{14}
\]

\( \Psi \) is now no longer a SEF in the strict sense, because it does not depend on purely mechanical factors (strains and elastic constants) but can now be modified by the choice of \( S_1 \) (fully relaxed, maximal contraction, or normal tone). At the same time, the ZSS of the relaxed arterial segment is maintained as reference state for the maximally contracted and normal tone VSM, even though this is no longer the equilibrium configuration for the unloaded segments with these choices of VSM tone. Thus the minimum of \( \Psi \) may be shifted by changing \( S_1 \) (i.e., changing the level of VSM tone) and may be nonzero because the VSM, thanks to \( \lambda_{VSM}^f \), has a different ZSS than the passive matrix. For these reasons \( \Psi \) is no longer called a SEF but a pseudo-strain energy function (pseudo-SEF).

Local stress can now be calculated by

\[
\sigma_i = -p + \lambda_i^2 \frac{\partial \sigma_{\text{passive}}}{\partial E_i} + S_1 S_2 f_{VSM} [\lambda_{VSM}^f - \log(\lambda_{VSM}^f) - 1] \tag{15}
\]

\[
\sigma_r = -p + \lambda_r^2 \frac{\partial \sigma_{\text{passive}}}{\partial E_r} + S_1 S_2 f_{VSM} [\lambda_{VSM}^f - \log(\lambda_{VSM}^f) - 1] \tag{16}
\]

\[
\sigma_z = -p + \lambda_z^2 \frac{\partial \sigma_{\text{passive}}}{\partial E_z} + S_1 S_2 f_{VSM} [\lambda_{VSM}^f - \log(\lambda_{VSM}^f) - 1] \tag{17}
\]

where in analogy to Eq. 1

\[
\lambda_{VSM}^f = \sqrt{2E_{VSM}^f} + 1 + k = 0, \sigma, r \tag{18}
\]

and the rightmost summand in Eqs. 15 and 16 representing the VSM contribution to the axial and radial stress, respectively, is equal to 0 in the case of the proposed pseudo-SEF because VSM is assumed to be oriented circumferentially. The schematic model of Eq. 17 is shown in Fig. 2.

Experimental data used for verification of pseudo-SEF. We tested the utility and appropriateness of the pseudo-SEF in describing arterial pressure-radius relations of different VSM tone levels. To do so, we used experimental data obtained from carotids of normotensive and hypertensive rats, which exhibit significantly different levels of VSM tone. The animal models and experimental procedures are described in detail elsewhere (21). All animal procedures were conducted in accordance with the “Guiding Principles for Research Involving Animals and Human Beings” of the American Physiological Society. In brief, hypertension was induced by ligation of the aorta between the two kidneys of 8-wk-old Wistar rats, inducing a step increase of blood pressure. After 8 days, the rats were euthanized, the left carotid arterial segments were harvested, and all adventitia and excess tissue were removed (hypertensive group). From an 8-wk-old control group carotids were removed in the same fashion (normotensive group). All segments were mounted on cannulas and placed in Krebs-Ringer solution. Under quasi-static inflation, pressure-radius curves were measured, first under normal conditions (normal VSM tone), then with the VSM under influence of norepinephrine maximally contracting the VSM, and finally fully relaxing the VSM by the addition of papaverine. Pressure-radius relationships were measured at in vivo length. Nearby segments were cut into small rings and used to determine the unloaded and ZSS geometry. The unloaded inner and outer radii, \( r_i \) and \( r_o \), respectively, were measured, and together with the opening angle (OA, \( \Theta \)) of the ZSS were used to calculate the inner \( R_i \) and outer \( R_o \) radii of the ZSS. For this, it was assumed that the wall cross-sectional area remained the same and that the midfielder arc length remained constant as well.

Histomorphometry was performed as described in more detail by Fridz et al. (23). In brief, the arterial segments were sliced into thin rings, stained, examined under an electron microscope (CM10, Philips), and photographed. The photos were then analyzed with image analysis software (KS400, Carl Zeiss) to determine the cross-sectional areas of each of the arterial wall components. The cross-sectional areas were expressed relative to the total cross-sectional area of the wall, giving the area fractions of collagen, elastin, and VSM.
Analysis. The pseudo–SEF is utilized in the usual continuum mechanical context with a cylindrical coordinate system (Fig. 3, left). For details we refer the reader to the works of Fung (24), Humphrey (32), Rachev and Hayashi (38), and Holzapfel and Gasser (29). The artery is assumed to be cylindrical when loaded with a lumen pressure $P$ and stretched axially by the ratio $\lambda_c$. Furthermore, it is assumed that the arterial wall material is incompressible, so that

$$\lambda_o \lambda_i \lambda_c = 1$$

(19)

where $\lambda_o$, $\lambda_i$, and $\lambda_c$ are the principal stretch ratios (24)

$$\lambda_o = \frac{\pi}{\pi - \Theta} \frac{r}{R}, \lambda_i = \frac{l}{L}, \lambda_c = \frac{\partial r}{\partial R}$$

(20)

where $\Theta$ is the OA, $R$ is a radius to a point in the ZSS, and $r$ is the radius to the same point in the axially stretched and inflated state (Fig. 3). $L$ is the axial length of the segment in the ZSS, and $l$ is the loaded axial length. Solving the system of Eqs. 19 and 20 under the boundary condition that the outer radius in the ZSS $R_o$ should be mapped to the outer radius in the stretched and pressurized state, $r_o = r(R_o)$, we find

$$r(R) = \sqrt{(r_o^2 - (R_o^2 - R^2)} \frac{\pi - \Theta}{\lambda_o^{\Theta}}$$

(21)

Integrating the local stresses (Eqs. 15–17) across the entire wall, we obtain lumen pressure $P$ for a vessel with inner and outer radii $r_i$ and $r_o$, respectively (Fig. 3, right)

$$P = \int_{r_i}^{r_o} \left(\sigma_a - \sigma_z\right) \frac{1}{r} \, dr$$

(22)

The modeled radii were determined by numerically solving Eq. 22 for the radius at the corresponding experimental pressure. Pressure-radius relationships were fitted to the experimental data by minimizing the function (least squares)

$$\Phi = \sum_{i} \left[ \frac{r_i^{\text{mod}} - r_i^{\text{exp}}}{r_i^{\text{exp}}} \right]^2$$

(23)

where $i$ is the data point index and $n$ is the total of experimental points measured in the pressure-radius relationship. On the radii $r$ the indices mod and exp are used to identify the model and experimental values, respectively. We chose to impose a collagen elastic modulus of $c_{\text{coll}} = 200$ MPa (48). Thus only the parameters $c_{\text{pass}}$, $k$, and $b$ remain free to fit for the passive SEF component. We initially determine these parameters minimizing Eq. 23 and the data from pressure-radius curves of fully relaxed state. Subsequently, by utilizing the data from the maximally contracted VSM pressure-radius curves the parameters $c_{\text{VSM}}$ and $\lambda_{\text{pre}}$ are determined. From the pressure-radius curves under the normal VSM tone, the parameters $S_{\text{pass}}$, $\sigma_z$, and $\mu$ are then identified.

To further verify the validity of the fitted parameters, we predicted the OA of arterial segments when VSM is maximally contracted following the methods laid out by Rachev and Hayashi (38). The deformation of a radially cut arterial segment from one OA configuration to another can be defined by the parameters:

$$\lambda_o = \frac{\pi - \Theta^*}{\pi - \Theta} \frac{R^*}{R}, \lambda_i = \frac{\partial R^*}{\partial R}$$

where $\Theta^*$ is the OA and $R^*$ the radius of a point at $R$ in the passive configuration repositioned under maximal VSM contraction. Together with the assumption of incompressibility and the boundary conditions of no external load, the new OA configuration must fulfill the conditions that throughout the wall both circumferential stress $\sigma_z$ and axial stress $\sigma_a$ are zero. $\lambda_o$ and $\lambda_c$ were optimized numerically to minimize $\sigma_a^2 + \sigma_z^2$ for 100 points across the wall thickness. With the known OA from the fully relaxed VSM state, we can solve Eq. 24 for the maximally contracted OA $\Theta^*$.

The analysis was carried out on a personal computer running commercially available software (MatLab, Release 12.1; MathWorks).

RESULTS

The parameters identified from the three least-square fits are summarized in Fig. 4, left. The pressure-radius plots of both the experimental data and the model results are shown in Fig. 4, right. The fully relaxed state pressure-radius curve was well described by the SEF and for both the normotensive ($r^2 = 0.9993$) and the hypertensive ($r^2 = 0.9986$) group. Maximally contracted arteries’ low-pressure radii were overestimated in both groups; however, the overall correlation between experiment and model data is satisfactory ($r^2 = 0.9983$ and 0.9937 for the normotensive and hypertensive groups, respectively). The pressure-radius curves under normal VSM tone model are also described well for both the normotensive ($r^2 = 0.9998$) and the hypertensive ($r^2 = 0.9988$) group. The transition between the almost fully relaxed VSM at low pressures to the almost maximally contracted VSM at high pressures was well described, which is particularly evident in the hypertensive group.

Fig. 3. Coordinate system (left) and parameters characterizing the loaded state (right) and the zero-stress state (center) geometry of an artery. $L$, zero-stress state axial length; $l$, loaded state axial length; $e_o$, $e_c$, $e_z$, local base of cylindrical coordinate system; $R_0$, zero-stress state inner radius; $R_o$, zero-stress state outer radius; $R$, zero-stress state radius of wall point; $\Theta$, opening angle; $r_o$, loaded state inner radius; $r_o$, loaded state outer radius; $r$, loaded state radius of wall point.
The VSM normal tone function $S_1$ (Eq. 11) reflects the differences in VSM behavior. $S_1$ was plotted for the normotensive and hypertensive groups (Fig. 5). The basal tone, $S_{basal}$, of the hypertensive group is doubled compared with the normotensive group (from 0.052 to 0.105), whereas the critical engagement deformation is lowered from 4.81 to 4.57 and the distribution half-width is increased from 0.13 to 0.42, meaning that the deformation range over which the VSM engage is wider.

The experimentally determined OA under maximal VSM contraction was 160.5° ± 8.8° (means ± SD). The model predicted the OA with maximal VSM contraction to be 148.8° (Fig. 6).

To illustrate the effect of incorporating VSM tone and myogenic response into the model, circumferential stress was calculated by Eq. 17 at the mean in vivo operating pressure $\bar{p}$. Figure 7 shows $\sigma_0$ for both fully passivated VSM and normal-tone VSM as function of normalized wall thickness for the control group (Fig. 7, left; $\bar{p} = 91$ mmHg) and the hypertensive group (Fig. 7, right, $\bar{p} = 141$ mmHg).

**DISCUSSION**

In a previous study (48) we proposed a SEF to describe the passive elements of the arterial wall. The advantage of the previously presented SEF was that its parameters represented physical properties such as elastic moduli and collagen fiber orientation. We have expanded along the same lines to include the effects of VSM contraction. We have tested this novel pseudo-SEF on two distinctly different pressure-radius curve types, one with little normal tone (normotensive) and the other with significant VSM tone (hypertensive). The pseudo-SEF presented here describes the arterial response very well, $r^2$ correlation coefficients of all the data fits being higher than 0.99. We do not intend to discuss the parameters obtained under fully relaxed VSM conditions, because we have done so in detail elsewhere (48). It is sufficient to say that the obtained values describing the passive matrix compare to those found previously (48) and are near to what would be expected from the literature. Instead, we will discuss in more detail the significance of the parameters describing the VSM tone.

The values obtained for the VSM elastic modulus, $c_{VSM}$, are 73.2 and 144 kPa for the normotensive and hypertensive artery groups, respectively. These estimates are at the lower end of the values obtainable from the literature, ranging from 100 to 1.48 MPa estimated by various different methods, species, and arteries (1, 2, 16, 30). The overestimation of the radius at low pressures under maximal contraction (Fig. 4) might be due to this relatively low $c_{VSM}$. A maximal isotonic contraction would reduce the VSM length to $1/\lambda_{pre}$ or 55% and 63% of its initial
length for the normotensive and hypertensive groups, respectively. This compares very well to values reported in the literature. For example, isolated bovine coronary VSM cells have been shown to contract maximally to 47.8% and 61.7% of their initial length under electrical and K\(^+\)-induced depolarization, respectively (43). \(S_2\) defines the range of VSM stretch at which the contractile elements exert maximal force. The values of \(\lambda_{ps}\), make the upper and lower bounds of these ranges lie at the extremes of the circumferential stretch ratios actually encountered by the muscle.

Fridez et al. (20) utilized a simplified one-dimensional model, based on mean circumferential wall strain and stress, to analyze effects of normal VSM tone activation for the same experimental data set used here. The presented pseudo-SEF improves the analysis by providing a model in the context of continuum mechanics. The VSM tone function \(S_1\) (Fig. 5) reflects the short-term remodeling of the VSM properties already observed (20) but in a three-dimensional instead of a one-dimensional context. The basal tone parameter \(S_{basal}\) is elevated after 8 days of induced hypertension. Furthermore, the onset of myogenic response takes place at lower deformations (Fig. 5). This is reflected by the lower \(\mu^{\text{norm}}\) value obtained for the hypertensive group. This confirms the observations that Fridez et al. (20) made with a one-dimensional stress-strain model. The rate of increase in myogenic tone with increasing deformation is, however, lower in the hypertensive artery (Fig. 5). This observation differs from the results of Fridez et al. and is most probably due to the differences in the mathematical modeling of the myogenic tone \(S_1\).

The model proposed here, to the best of our knowledge, the only model offering a three-dimensional structural description of arterial wall mechanics at the continuum mechanics level including VSM tone. The model allows us to study the effects of VSM normal tone on, for example, circumferential stretch \(\sigma_0\) (Fig. 7). The normotensive arteries show a fairly equal distribution of \(\sigma_0\), and the introduction of normal VSM tone, which for the normotensive arteries is minimal, barely matters (Fig. 7, left). The hypertensive group, however, shows a >20% reduction of \(\sigma_0\) at the outer wall radius when the normal VSM tone is taken into account (Fig. 7, right). Thus the difference between the inner and outer \(\sigma_0\) is reduced, providing some stress equilibration across the wall thickness (35, 42). Remodeling, still ongoing, is nonhomogeneous in this case, and tissue growth is more pronounced in the outer regions of the vessel wall in accordance with the higher stress and VSM tone found there (23).

There are some limitations to this study. We have constrained ourselves to applying the pseudo-SEF to pressure-radius data at one fixed axial stretch alone. The VSM tone function \(S_1\) describes the changes in VSM tone as a function of overall deformation of the VSM. However, sufficiently precise data on the sensitivity of VSM to deformations in all principal directions are not available, and it was not possible to identify the parameters \(\alpha_o\), \(\alpha_r\), and \(\alpha_c\) from the experimental data of

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**Fig. 5.** VSM tone activation function \(S_1\) as function of the local tissue deformation described by the first Cauchy-Green invariant \(I_1\). Normotensive and hypertensive cases are represented by the solid and dashed lines, respectively. The basal tone \(S_{basal}\) is elevated and the critical deformation \(\mu^{\text{norm}}\) is reduced in the hypertensive group. Superscript H indicates hypertensive values, and superscript N normotensive values.

**Fig. 6.** Opening angle (OA) under full relaxation and maximal contraction, as measured experimentally in the normotensive group (●). ○, Model prediction of the OA under maximal contraction based on the fully passive OA values and the material properties of the normotensive group.

**Fig. 7.** Circumferential stress \(\sigma_0\) for fully relaxed and normal VSM tone states. The radial position across the wall thickness has been normalized to be 0 at lumen radius and 1 at outer radius to enable comparison. Left: normotensive group at their mean operating pressure of 91 mmHg. Right: hypertensive group at their mean operating pressure of 141 mmHg. The level of normal VSM tone in the hypertensive arteries is larger on the outside than near the lumen, and the differences of inner and outer \(\sigma_0\) are thus reduced.
Fridez et al. (20). This forced us to simplify the model finally applied and assume isotropic sensitivity.

We have assumed that the maximally contracted VSM stress is linearly dependent on stretch, $\lambda_0$, over the typical range of deformation. We tried to utilize various nonlinear models (for example, square root, square, or logarithmic) and models with linear or nonlinear dependence on $E_B$, but none succeeded in yielding a better description of the pressure-radius curves under maximal VSM contraction. The model fits the pressure-radius curves well over the entire range of pressure and VSM tone conditions. The only unsatisfactory feature is the poor predictions of the model at the low-pressure range ($0 < p < 5$ kPa; Fig. 4). As possible causes one might list 1) the difficulty in assessing the ZSS configuration because of large variations of the opening angle even within the same specimen; 2) the assumption that the VSM cell contraction is primarily in the circumferential direction; 3) the assumption that the maximal VSM contraction is homogeneous across the wall thickness; 4) the assumption that the SEFs of the individual wall components are additive and that no interaction between VSM and the passive matrix takes place (i.e., parallel model); and 5) the assumption that the range defined in $S_2$ is valid for the rat carotids used. With respect to point 4, there seems to be evidence that the VSM contraction modifies the passive matrix geometry and thus the structural properties of the artery (8, 15).

This is attributed to the fact that VSM cells are embedded and attached to the passive matrix elements elastin and collagen and thus VSM contraction leads to a geometric reorganization of the arterial structure.

Under VSM contraction but in the absence of loads or passive prestress, a new pseudo-ZSS configuration is reached in which the compression of the passive components equilibrates the tension of the contracted VSM. With the methods described by Rachev and Hayashi (38) we can use the pseudo-SEF to predict the OA of arterial segments when the VSM is maximally contracted and compare the predictions with the experimental results. The predicted change in OA after maximal contraction is compared with the experimental value in Fig. 6. The model was found to underestimate the experimental OA (148.8° instead of 160.5°). Bearing in mind the difficulties of obtaining precise OA measurements and that in this case the pseudo-SEF is extrapolating stress below the strains actually measured, the prediction is satisfactory because it shows the correct tendency to increase OA from fully relaxed to the maximally contracted OA.

In conclusion, the pseudo-SEF for VSM has been shown to provide a fair description of the involved wall mechanics of both normal and hypertensive rat carotid arteries. The pressure-radius curves can be predicted over almost the entire measurement range (0–200 mmHg) for both maximally contracted and normal tone VSM conditions with good accuracy. The pseudo-SEF allows the discussion of local wall stress under VSM tone alterations and shows that the nonhomogeneous development of VSM tone and thus VSM stress helps to equilibrate the wall stress in short-term hypertensive rat carotids. Furthermore, it has been suggested frequently that hypertensive arterial remodeling might be driven by the level of stress (see, for example, Refs. 22, 25, and 39) in the wall sensed by the VSM cells. For these reasons, we believe that investigative physiology could profit from this or similar pseudo-SEFs to calculate locally within the wall the effective stress borne by the VSM under complex, three-dimensional deformations. Furthermore, the identified model parameters are in reasonable agreement with previously published values determined by other means. Thus the pseudo-SEF demonstrates its value in the modeling of both physiological and hypertensive arterial wall biomechanics in a continuum mechanical framework.

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