A mechanism for arteriolar remodeling based on maintenance of smooth muscle cell activation

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Submitted 11 June 2007; accepted in final form 8 January 2008

VESSELS OF THE MICROCIRCULATION must continuously meet the changing demands of the tissues. On short time scales, vascular diameter and, hence, tissue perfusion are regulated by variation in smooth muscle cell (SMC) activation. On longer time scales, resistance vessels adapt structurally to maintain dimensions optimal for acute flow regulation. In microvascular networks in vivo, such adaptation depends on a complex interplay between various stimuli, including pressure, shear stress, and metabolic status of the tissue (38).

As noted six decades ago by Folkow and co-workers (15), in human essential hypertension, resistance vessels develop a reduced lumen size and an increased wall thickness. These changes are apparently caused by redistribution of the wall material around a smaller lumen, i.e., inward eutrophic remodeling (33), and allow the vessel to operate at normal or near-normal levels of activation, despite increased pressure (14).

Another example of structural adaptation is the surprising observation by Bakker et al. (7) that, in unbranched segments of first-order rat cremaster arterioles, structural diameter does, in fact, increase distally along the vessel. This increase in diameter is not associated with an increase in wall transsectional area. Rather, analogous with the changes in hypertension, it appears that the same amount of wall material is distributed around a smaller lumen upstream and a larger lumen downstream (7). As a consequence of this structure and the simultaneous decrease in pressure along the vessel, circumferential wall stress is the same at the up- and downstream positions (7). Bakker et al. speculated that this peculiar pattern might be related to the myogenic response (10), which in isolated cremaster arterioles has a negative slope of the pressure-diameter curve (12). Recently, some possible mechanisms in structural adaptation on the level of the SMC and the extracellular matrix that may explain the different manifestations of remodeling as originating through a common mechanism have been revealed.

Through a series of vessel culture studies, Bakker and co-workers (2, 5, 6) showed that sustained contraction leads to structural inward remodeling in microvessels. These studies include the effect of myogenic vasoconstriction in vitro (4, 43), but the process in general appears to be independent of the causes of the constriction (5, 6, 48). This led Bakker and co-workers and vanBavel et al. (48) to hypothesize that structural remodeling depends on SMC activation per se, providing a link between short- and long-term flow regulation in the microcirculation.

The present in silico study, using a simple vessel model, investigates microvascular adaptation, which, in accordance with the above concept, is driven by SMC activation. We hypothesize that only if the vascular wall is sensitive to stress, can such activation-driven adaptation result in an adequate remodeling response to a change in pressure or tissue demand. To enable a qualitative analysis, we use a simplistic approach, in which the myogenic response is modeled explicitly, whereas the influence of other mechanisms is lumped into a single constant modifying SMC activation. Acute changes in activation alter active vessel size and are followed by a slow remodeling response that alters the vascular structure.

The simulated results are in qualitative agreement with results obtained from a variety of vessel culture studies and are consistent with the structural changes found in hypertension. They also show the emergence of a structure similar to that observed in rat cremaster arterioles, with increasing diameter along the vessel. The results do not depend on the specific myogenic properties of the vessel. The same pattern arises in...
vessels with positive and negative slopes on the steady-state pressure-diameter curves. If the vessel is subject to increased activation, the structural radius will decrease until a new steady state is reached. The opposite is seen during a sustained activation, the structural radius will decrease until a new steady state is reached. The opposite is seen during a sustained activation, the structural radius will decrease until a new steady state is reached.

**MODEL**

**Vessel Wall Model**

The vascular wall is modeled as a passive elastic component (e) arranged in parallel with an active muscular component (a) (13). It is assumed that the wall material is isotropic from the innermost to the outermost layer in the wall. It is further assumed that idealized circumferential wall stress (σ) can be expressed as

\[ \sigma = \sigma_e + \sigma_a \]  

(1)

The elastic part is modeled as consisting of two components (C₁ and C₂), both exhibiting an exponential increase in stress with extension (i.e., distension of the vessel). With strain \( \epsilon \) (where \( \epsilon = (L_0/L) - 1 \) (where \( L_0 \) is tissue length at zero transmural pressure), a stress-strain expression for \( \sigma_e \) is approximated by the form (see constants in Table 1)

\[ \sigma_e = C_1(\epsilon^{\alpha_1} - 1) + C_2(\epsilon^{\alpha_2} - 1) \]  

(2)

For reproduction of the mechanical properties of the passive elastic component as found in first-order rat cremaster arteries, connective tissue parameters were adjusted to fit passive pressure-radius curves from these vessels (see *Mechanics of the relaxed vessel wall* in APPENDIX).

The stress contribution from the active muscular component increases with increasing distension of the vessel to a certain point, after which contribution from active contraction will decline with further distension. This gives the overall stress-distension relation of this component a triangular shape (13), in the present model approximated by a Gaussian function of the form (see constants in Table 1)

\[ \sigma_a = b e^{-[(e-m)/s^2]} \]  

(3)

where \( b \) determines the maximum active stress the wall can develop and \( m \) and \( s \) determine the position and width, respectively, of the active stress-distension curves (Fig. 1A). It is assumed that, with no SMC activation and a transmural pressure of 0 kPa, no residual stresses remain in the wall (see DISCUSSION). It is further assumed that constants relating to passive elastic and active contractile properties of the wall material (Table 1) remain invariant under all circumstances.

Longitudinal (i.e., length) stress is not considered in the model. Because of incompressibility and since the longitudinal strain is assumed to remain constant (see DISCUSSION), the transsectional area of the vessel wall is conserved during distension and constriction. With \( p \) being the radius of a layer within the wall when transmural pressure and activation are zero and \( r \) being the radius of the same layer at a certain level of pressure and activation, wall area conservation can be expressed as \( r^2 - r_i^2 = p^2 - r_i^2 \), where \( r_i \) refers to the inner radius.

With \( a \) referring to the outer radius, the transmural pressure (P) is given by Laplace’s law

\[ P = \int_{r_i}^{r_a} \frac{S}{r} \, dr = \int_{r_i}^{r_a} \frac{\sigma_e}{r} \, dz + \psi \int_{r_i}^{r_a} \frac{\sigma_a}{r} \, dz = 1 \]  

(4)

where \( S = \sigma(1 + \epsilon) \) is the Cauchy stress, \( r_p = r/p_i \) is the normalized internal radius, \( \eta = r_i/p_i \) is the relative thickness of the relaxed wall, \( z = r/p_i \) is an integration variable, and where the strain has been expressed as \( \epsilon = (1/r) \sqrt{r^2 - 1 + z^2} - 1 \).

Finally, the expression for the average circumferential wall stress at a given SMC activation and transmural pressure takes the form (21)

\[ S = \frac{Pr_i}{r_o} = \frac{r_p}{\sqrt{\eta^2 - 1} + r_p} - r_p \]

\[ \times \left( \int_{r_i}^{r_a} \frac{\sigma_e}{r_p} \, dz + \psi \int_{r_i}^{r_a} \frac{\sigma_a}{r_p} \, dz = 1 \right) \]

(5)

Figure 1A shows the stress-distension characteristics of the model vascular wall. The relative distension (\( r_p \)) shown on the x-axis is the radius relative to the relaxed radius at 0 kPa transmural pressure. The thick curve is the stress contribution from the passive elastic component using the adjusted parameters (please see DISCUSSION). Dashed lines show the theoretical contribution from the active muscular component at different levels of SMC-activation, (\( \psi \)) as indicated to the right (13). SMC-activation is normalized to lie between 0 (complete relaxation) and 1 (full activation). The positions of the active curves were adjusted to correspond to the estimated maximum stress at different activation levels.

**Table 1. Standard parameter values used in the model**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_1 )</td>
<td>Factor in stiff connective tissue element</td>
<td>13.5 \times 10^3 Pa</td>
<td>2.7 \times 10^3 Pa</td>
<td>13, adjusted to fit (7, 12)</td>
</tr>
<tr>
<td>( \alpha_1 )</td>
<td>Exponential factor in stiff connective tissue element</td>
<td>1.9</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>( C_2 )</td>
<td>Factor in soft connective tissue element</td>
<td>40 kPa</td>
<td>250 kPa</td>
<td></td>
</tr>
<tr>
<td>( \alpha_2 )</td>
<td>Exponential factor in soft connective tissue element</td>
<td>6.7</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>( b )</td>
<td>Factor determining maximum active stress development</td>
<td>182.8 \times 10^3 Pa</td>
<td>100 \times 10^3 Pa</td>
<td>13, adjusted to fit (12)</td>
</tr>
<tr>
<td>( m )</td>
<td>Position of top point of active stress-distension curves</td>
<td>0.5</td>
<td>0.25</td>
<td>13</td>
</tr>
<tr>
<td>( s )</td>
<td>Width of active stress-distension curves</td>
<td>0.7</td>
<td>0.5</td>
<td>13</td>
</tr>
<tr>
<td>( t_{activation} )</td>
<td>Time constant for development of activation</td>
<td>75 s</td>
<td>75 s</td>
<td>Present model</td>
</tr>
<tr>
<td>( t_{remodeling} )</td>
<td>Time constant for remodeling process</td>
<td>7,500 s</td>
<td>7,500 s</td>
<td>Present model</td>
</tr>
<tr>
<td>( \Delta t )</td>
<td>Integration time step</td>
<td>10^{-3} s</td>
<td>10</td>
<td>Present model</td>
</tr>
<tr>
<td>Layers</td>
<td>Radial discretization of wall</td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AJP-Regul Integr Comp Physiol • VOL 294 • APRIL 2008 • www.ajpregu.org
stress developed by the wall during a myogenic response in a first-order rat cremaster arteriole (12). Thin black lines show the sum of passive and active contributions. At low distension, wall stress is dominated by the contribution from active contraction, whereas the passive elastic component dominates at high distension. The grey line shows the circumferential wall stress vs. relative distension (13) at different levels of pressure during a myogenic response in a first-order rat cremaster arteriole in vitro (12) (please see APPENDIX).

Figure 1B shows the relation between the steady-state activation ($\psi$) of the contractile component and the average circumferential wall stress.

Vascular Responses

In the present model, two kinds of vascular responses, operating on separate time scales, are considered.

Myogenic response. The myogenic response represents an acute activation-regulating mechanism. The myogenic response operates on a time scale that is on the order of seconds or minutes (12). Short-duration myogenic contraction involves a change in activation but no (measurable) structural change in the vessel and, hence, no change in the position of its passive pressure-radius curve (30).

In the present model, a simple first-order expression for the change in activation is integrated forward in time to determine the actual activation at a given moment. The rate of change depends on the difference between the actual activation ($\psi$) and $\bar{\psi}$ at the same pressure (see constants in Table 1)

$$\frac{d\psi}{dt} = \frac{1}{\tau_{\text{activation}}} (\bar{\psi} - \psi) \quad (6)$$

where the value of $\bar{\psi}$ is determined from the fit in Fig. 1B. The time constant for the process ($\tau_{\text{activation}}$) is chosen such that the time from a step change in pressure to a new steady-state radius is similar to that reported for first-order rat cremaster arterioles in vitro (≈1 min; Table 1) (12); however, the exact value is not important for the conclusions of the model.

To obtain a steady-state pressure-radius curve, the pressure is increased in small steps. At each pressure level, the internal radius is recorded when the simulated vessel has settled at a constant radius. The resulting curve is shown in Fig. 2. The experimental data points (reproduced from Ref. 12) are those used to estimate the stress-activation characteristic of Fig. 1B; hence, the curve coincides with these points.

The radius adjusts instantly to the given level of activation and transmural pressure. Thus the delay related to myogenic movement of the wall is assumed to be due to the time required to change the level of activation.

Besides myogenic activation, a lumped contribution from all additional (add) vasomotor mechanisms ($\psi_{\text{add}}$) is assumed. This term modifies the myogenic activation; hence, $\psi_{\text{add}}$ can attain positive (activating) and negative (deactivating) values. If no value is stated, $\psi_{\text{add}}$ is zero; hence, activating and deactivating contributions are assumed to outbalance each other (see DISCUSSION).

Fig. 1. A: stress-distension curves of the vessel wall model. Thick black curve, stress contribution due to passive elastic components; dashed curves, stress contribution from the active contractile component at different levels of activation ($\psi$); solid curves, sum of active and passive contributions; gray curves, estimated average circumferential wall stress during a myogenic response based on Ref. 12 (see Table S1 in the online version of this article). After the curve for $\psi = 1$ is reached, vessel dilates following the characteristics of that curve (last data point). B: steady-state activation ($\bar{\psi}$) vs. average circumferential wall stress. Data points (●) are identical to those in A. A fit of the form $\psi(S) = ae^{bS} + c$ (where $a = 0.01$, $b = 0.0534$, and $c = 0.055$) was made to the data points (curve).

Fig. 2. Simulated steady-state myogenic response. Curve shows myogenic contraction of the vessel with increasing transmural pressure. Experimental data points (●) are reproduced from Ref. 12.
**Eutrophic remodeling.** Eutrophic remodeling is a structural change in luminal radius without a change in wall transsectional area. The basis of the present formulation is the previously outlined hypothesis by Bakker and co-workers (2, 5, 6) and vanBavel et al. (48) that activation per se is central in structural remodeling. Furthermore, as shown by Martinez-Lemus et al. (30), vasoconstriction may lead to migration of vascular SMCs relative to each other, leading to encroachment of the lumen and increased wall thickness. Such migration also leads to a normalization of the length of the individual SMC in the contracted state of the vessel, a process that has been termed “length autoregulation” (30). At the same time, there appears to be remodeling of the extracellular matrix dependent on tissue transglutaminases (1, 11, 35) and, most likely, involving new cross-link formation between matrix proteins (48). These processes lead to a downward shift in the passive pressure-radius curve of the vessel.

Collectively, the following assumption is made in the model: a vessel remodels when the level of activation deviates from the habitual level at which the function of the SMC in short-term flow regulation is optimal. Because of remodeling, the habitual level of activation is restored. This process is slow compared with the acute regulation of activation, which includes the myogenic mechanism, and remodeling is evident only when the deviation has been present for a certain period. The structural change in the internal radius of the vessel, with preservation of wall transsectional area, is therefore modeled as (see constants in Table 1)

$$\frac{dp_i}{dr} = \frac{1}{\tau_{\text{remodeling}}} (\psi^* - \psi) \rho_i \quad (7)$$

where $\psi^*$ is the habitual level of activation and $\tau_{\text{remodeling}}$, the time constant for the process (Table 1), was chosen arbitrarily to be 100 times larger than $\tau_{\text{activation}}$ to effectively separate the two processes. The magnitude of $\tau_{\text{remodeling}}$ affects only the time required to reach a new stable structure, not the final structure itself [see supplemental data (Fig. S2 and discussion) for this article online at the American Journal of Physiology-Regulatory, Integrative, and Comparative Physiology website].

The rate of remodeling thus depends on $\tau_{\text{remodeling}}$ and the input stimulus, i.e., the deviation from the habitual activation level, and is scaled to the size of the vessel through $\rho_i$. At the same time, $\psi^* - \psi$ determines the direction of remodeling, so that if $\psi > \psi^*$, the vessel will display inward remodeling and vice versa.

**Computational Methods**

Initial conditions are given in Table 2. The simulated setup corresponds to a cannulated arteriolar segment in a vessel culture chamber. The transmural pressure of the vessel can be controlled and is uniform throughout the vessel. Initially, the vessel equilibrates at the starting pressure (8.13 kPa) until there is no further change in diameter. At $t = t_{\text{intervention}}$, a pressure change is imposed on the system. Forward integration in time continues until convergence to a new steady state, as identified from the curves for active and relaxed internal radius. The final vessel morphology was used to simulate the active and passive pressure-radius curves (see Program structure in Appendix).

The program source code was written in C (ANSI C standard) by the authors using Microsoft Developer Studio (Visual C++ 6.0, professional edition, Microsoft, Seattle, WA). Mathematica (Wolfram Research, Champaign, IL) was used to differentiate the right-hand side of Eq. 4 for Newton-Raphson iteration. Simulations were performed on ordinary Pentium III, dual-core personal computers.

**Parameter Sensitivity**

Sensitivity of the results to changes in the model parameters is shown in the online version of this article.

**RESULTS**

Figure 3 shows the acute effect on a vascular segment of a step change in pressure (see Table 2 for initial values). The traces are from two different simulations in which the pressure (Fig. 3A) is increased or reduced to arrive at the average up- and downstream pressures reported by Bakker et al. (7) for cremaster arterioles.

Figure 3B shows the traces of the active internal radius. When pressure is increased in a step, the vessel segment dilates abruptly, since the inwardly directed force generated by the wall does not match the increased transmural pressure. As activation increases, the vessel constricts and arrives at a new reduced steady-state radius. The opposite is seen under a sudden reduction in pressure. Remodeling is not evident on the short time scale shown in Fig. 3B.

If the pressure change is applied instead as a linear pressure ramp (up or down) over a period of $2\times10^5$ ms (10 minutes), the vessel follows the steady-state pressure-radius curve closely, to arrive at the same final radius (not shown). Thus, in the model, as observed experimentally in rat cremaster arterioles (24), the initial radius transient is not required for steady-state myogenic contraction.

The shift in circumferential wall stress (Fig. 3C) induced by the pressure change is only partly normalized by subsequent myogenic adjustment of the radius. As the new equilibrium state is reached, wall stress remains increased in the high-pressure segment and reduced in the low-pressure segment.

<table>
<thead>
<tr>
<th>Parameter values of data sets I–III</th>
<th>Data Set I (upstream)</th>
<th>Data Set II (downstream)</th>
<th>Avg of Data Sets I and II</th>
<th>Data Set III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radius, length of IEL, μm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp.</td>
<td>42.81 ± 1.43</td>
<td>44.56 ± 1.43</td>
<td>43.5</td>
<td>39.0 (with holds)</td>
</tr>
<tr>
<td>Model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WTA, μm²</td>
<td>1.739 ± 0.89</td>
<td>1.810 ± 0.81</td>
<td></td>
<td>1.629</td>
</tr>
<tr>
<td>Exp.</td>
<td>1.749</td>
<td>1.735</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\eta$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp.</td>
<td>1.141</td>
<td>1.136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model</td>
<td>1.151</td>
<td>1.125</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure, kPa</td>
<td>9.06</td>
<td>7.20</td>
<td></td>
<td>9.06</td>
</tr>
<tr>
<td>Exp.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model</td>
<td></td>
<td></td>
<td></td>
<td>8.13</td>
</tr>
<tr>
<td>Wall stress, kPa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp.</td>
<td>266 ± 16</td>
<td>260 ± 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model (relaxed)</td>
<td>267.5</td>
<td>251.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data sets I and II are from Bakker et al. (7); data set III is from Falcone et al. (12). IEL, internal elastic lamina; WTA, wall transsectional area; $\eta$, relative wall thickness $\eta = \sqrt{\text{WTA}/\text{WTA}_{\text{ref}}}$, where $\rho$ is internal radius at 0 kPa transmural pressure. Relaxed wall stress is average circumferential wall stress calculated using model parameters and pressure of the same column.
period, the high-pressure segment remolds inwardly and the low-pressure segment remolds outwardly.

Remodeling causes differences in wall stress (Fig. 4C) and relative distension (Fig. 4E) to vanish under normalization of the activation (Fig. 4D). This is due to rearrangement of the wall material around a smaller lumen in the high-pressure segment and vice versa. Normalization of the relative distension (a measure of the wall strain, Fig. 4E), corresponds to a length autoregulation of contractile and passive elastic wall components. Hence, the eutrophic remodeling response allows a vessel to remain in a state where wall stress, strain, and activation are independent of the prevailing pressure.

The structural parameters of the relaxed vessel wall at 0 kPa, \( \rho_i \) (internal radius) and \( \eta_i \) (relative wall thickness), are unaffected by the myogenic response but change as a result of remodeling, as shown in Fig. 5 (same simulation as in Fig. 4). The high-pressure segment ends up with a small diameter and a thicker wall, whereas the low-pressure segment ends up with a larger diameter and a thinner wall.

Figure 6 shows the passive and active pressure-radius curves for the segments before and after structural adaptation to high or low pressure. On the passive curves, experimental data points from Bakker et al. (7) have been reproduced for comparison. After remodeling, the high-pressure segment, with its smaller radius (Fig. 6A) and thicker wall, can operate across a wider range of pressures (Fig. 6B). In the low-pressure segment, where the radius has become larger and the wall thinner, the dynamic range is narrower, but the gain is stronger, as reflected in the more negative slope of the curve (Fig. 6B).

Since, in vivo, the average pressure and the pressure fluctuations will decrease along the vessel (7), the structure emanating from the simulation would enable efficient damping of pressure fluctuations around the normal pressure level for a given part of the vessel.

Since myogenic reactivity varies between vessels (see discussion), the manner in which this vessel-specific property may influence remodeling was tested. Different (arbitrarily chosen) stress-activation characteristics are shown in Fig. 7A. The steeper the slope, the stronger is the activation response to a given change in pressure. The steady-state myogenic response curves resulting from these characteristics are shown in Fig. 7B. They include a very weak (shape 1) and a very strong (shape 3) response. Vessel morphology is given in data set III of Table 2.

Figure 8 shows simulations using the different myogenic shapes of Fig. 7. Pressure is changed as described above. When the segments are in equilibrium at 8.13 kPa, their levels of activation, i.e., the habitual activation, differ (Fig. 8C) and, consequently, also the radii are different in the pressurized state (Fig. 8A). After the pressure change, each segment adapts so as to restore the habitual activation level. Because of remodeling, the radius decreases in the high-pressure segment and increases in the low-pressure segment in all cases (Fig. 8A). The final differences in radius between the three cases (Fig. 8A) are due to different levels of myogenic activation (Fig. 8C). The structural changes in radius, although progressing at different speeds, are similar in all three cases (Fig. 8D).

Thus, under adaptation toward the habitual activation level, the simulated remodeling response is independent of the vessel-specific myogenic properties. The adapted passive pressure-radius curves will therefore end up at approximately the same

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**Fig. 3.** Simulated dynamic myogenic response. Traces from 2 simulations are shown. In both cases, vessel morphology (\( \rho_i \) and \( \eta_i \)) and initial pressure are averages of data sets I and II (Table 2). A: at \( \tau_{\text{activation}} = 0.5 \tau_{\text{activation}} (\tau_{\text{activation}} = 75 \text{ s}) \), pressure is increased [to the upstream pressure (7), solid line] or decreased [to the downstream pressure (7), dashed line]. B: step change in pressure is followed by a radius transient due to the time required to adjust the activation. C: after the initial transient, circumferential wall stress is only partially normalized because of myogenic adjustment of radius. D: as the myogenic response develops, the difference in activation between high- and low-pressure segments increases.

As shown in Fig. 3D, activation mirrors the shift in circumferential wall stress (cf. Fig. 2A). However, time is required for a change in activation (cf. Eq. 6), leading to the transients in radius shown in Fig. 3B. As radius reaches a new steady state, activation remains increased in the high-pressure segment and reduced in the low-pressure segment.

On longer time scales, the remodeling response becomes significant, as shown in Figs. 4 and 5, in which influences from additional vasomotor mechanisms are assumed to outbalance each other; hence, \( \psi_{\text{add}} = 0 \).

Figure 4A shows pressure changed in a step. Figure 4B shows how the radius develops in the segments. Since the time scale is now in units of \( \tau_{\text{remodeling}} \), the fast transient phase of the myogenic response (cf. Fig. 3B) is not discernable. Initially, the myogenic response adjusts the radius to the new pressure level (vertical parts of the curves). In the course of the following...
position. Also, circumferential wall stress (Fig. 8B) and relative distension (not shown) normalize in the course of the remodeling process. Again, this happens independently of the specific myogenic properties of the vessels.

Finally, Fig. 9 shows the effect on vessel structure of an activating ($\psi_{\text{add}} > 0$) or a deactivating ($\psi_{\text{add}} < 0$) stimulus, acting in concert with the myogenic mechanism. Initial values are shown in data set III of Table 2. Pressure is 8.13 kPa and is not changed in the course of the simulation. Instead, the vessel segment is subjected to the maintained stimulus, $\psi_{\text{add}}$ starting at $t = 0$. After an activating stimulus leading to an increase in total activation, the vessel constricts and wall stress decreases (Fig. 9B). The segment then remodels inwardly (Fig. 9A), resulting in a further reduction in wall stress (Fig. 9B), until the habitual level of activation is restored (Fig. 9C). The opposite is seen after a deactivating stimulus. Thus the simulated remodeling response is similar to the responses observed in constricted or dilated vessels in a vessel culture bath (6, 43). Despite return of activation to normal levels, wall stress in this case cannot be normalized by eutrophic remodeling alone (see DISCUSSION).

**DISCUSSION**

Our main finding is that, in vessels with a stress-sensitive wall, activation-driven remodeling may normalize strain and average wall stress and result in the structure found in cremaster arterioles (7), in cultured vessels (2, 6), and in hypertension (33). In the present formulation, remodeling depends on rearrangement of active and passive wall components. After a change in pressure, the vessel settles at a new structure, with concomitant normalization of activation, strain, and wall stress. Hence, the system has returned to its original position on the stress-distension curve (Fig. 1A). An adequate remodeling response would therefore enable the individual SMC to remain in a homeostatic state and, hence, to operate continuously under optimal conditions. Although the individual SMC was not explicitly modeled, a parallel can be drawn to the in vitro...
observation by Martinez-Lemus et al. (30) of normalization of SMC length, i.e., length autoregulation, during sustained vessel constriction.

In contrast to the characteristic inward eutrophic remodeling found in resistance arteries and arterioles (H11021 H9262 m diameter) (33) in human hypertension, the qualitative response to hypertension in large conduit arteries is different, with medial hypertrophy and preserved luminal radius (41). This response has been subjected to detailed modeling with (16) and without (40) SMC tone, and the results show that also this mode of remodeling can result in normalization of several key parameters, including wall shear stress, total wall stress, and stress distribution within the wall.

Critique of the Model

Modeling complex systems such as vessels necessitates simplifications.

Relaxed microvessels in the no-load state are not strain free. A compressive strain residual is present in the inner layers of the wall; in the outer layers, this residual is tensile (17). In the model, however, the relaxed no-load state has no residual strain. Consequently, at physiological distending pressure, where the transmural strain distribution may be rather uniform in real vessels (17), the strain in the model will be higher in the inner layers and lower in the outer layers. This difference will be more pronounced for the stress (cf. Eq. 2). The model, however, is concerned only with the average wall stress, which, for the reason of the symmetrical over- and underestimation of the stress in the different layers, is likely to be a reasonable approximation to the in vivo situation. Failure to
consider residual strain is therefore unlikely to affect the conclusions.

As an approximation, the axial stretch of the model vessel is assumed to remain constant; hence, wall transsectional area is invariant under changes in pressure. Real vessels do show longitudinal extension with pressure (18) and therefore assuming constant local wall transsectional area (see model description) is reasonable only if pressure changes are small. Compared with the initial value, pressure increases or decreases /H11021 kPa (7 mmHg) in the simulations of remodeling.

When measuring on vessel segments from the up- and downstream positions on the first-order cremaster arteriole, Bakker et al. (7) found different passive pressure-radius curves. The vessel morphology (i.e., radius and wall thickness) may explain this difference reasonably well (see Fig. S1 in the online version of this article). However, differences in the elastic properties of the wall material at the up- and downstream positions cannot be excluded, although along a single vessel such differences are likely to be small. Even if there were differences, however, the simulated results would be minimally influenced, since in the presence of active tone the passive elastic component carries only a minor part of the total wall stress (cf. Fig. 1A).

In vivo, most arterioles have a certain basal activation, normally attributed to the myogenic mechanism (23). This activation provides for efficient modification of the radius by pressure changes and by a variety of vasomotor mechanisms, including perivascular nerves, conducted responses, metabolites, and endothelial perfusion factors (23, 25). In vivo, a delicate balance between these stimuli, integrated through SMC activation, governs local perfusion. As indicated by the present simulations and by in vitro (36, 43), as well as in vivo (11, 19, 37, 44, 45) and model (19, 26, 38), studies, a more protracted disturbance of this balance may lead to vascular remodeling. One possible advantage of SMC activation being a long-term regulated variable would be that in vivo deviation from the habitual level of activation may provide the vascular wall with an unambiguous signal guiding the direction of the remodeling to arrive at a structure where blood flow can match a changed tissue demand. Thus, increasing the periods of vasodilation as a consequence of an increased need for perfusion will lead to structural outward remodeling and vice versa.

In the present model, the summarized influence from additional mechanisms, $\psi_{\text{add}}$, was held constant throughout each simulation. There is no way to know in detail the simultaneous influence from each individual mechanism, and this simplistic approach was applied to avoid invoking numerous assump-

![Fig. 8. Remodeling under varying myogenic reactivity. Simulations are performed using stress-activation characteristics shown in Fig. 7A. Solid and dashed lines, high- and low-pressure segments, respectively. All segments adapt toward the individual level of myogenic activation present at 8.13 kPa. A: final active radii of segments differ among shapes 1, 2, and 3. B: normalization of circumferential wall stress in the course of the remodeling process. C: normalization of activation over the course of the remodeling process. D: final structural radius is similar for shapes 1, 2, and 3.](http://ajpregu.physiology.org/)

![Fig. 9. Remodeling under external activation ($\psi_{\text{add}} > 0$) or deactivation ($\psi_{\text{add}} < 0$) of vessel segments maintained at 8.13 kPa. At $t_{\text{intervention}}$, a maintained stimulus, $\psi_{\text{add}}$, is imposed on the segment. A: changes in structural radius. Response to positive and negative values of $\psi_{\text{add}}$ is not symmetrical. Outward remodeling requires a stronger stimulus. B: under external stimulation, normalization of circumferential wall stress by eutrophic remodeling alone is not possible. C: normalization of activation by remodeling under a maintained external stimulus.](http://ajpregu.physiology.org/)
tions. Therefore, Fig. 9 should be taken only as a qualitative indication of the early remodeling response under sustained vasoconstriction or dilatation. Here, $\psi_{\text{add}}$ is treated as an independent variable, but in vivo, as remodeling progresses, remodeling will influence $\psi_{\text{add}}$ as part of a negative-feedback loop. In periods of sustained downstream vasodilatation signaling a chronic need for increased perfusion, upstream vessels will experience, among other vasodilating signals, an increase in wall shear stress. This will contribute negatively to $\psi_{\text{add}}$ and, hence, induce outward remodeling, but as the structural dimensions of the network are adjusted to match the actual need, the downstream stimulus will decline and $\psi_{\text{add}}$ will return toward its neutral value ($\psi_{\text{add}} = 0$). Hence, $\psi_{\text{add}}$ can be viewed as an error signal in structural remodeling. Note that $\psi_{\text{add}} = 0$ is not the same as lack of additional vasomotor mechanisms. Rather, it means that at a given moment, the influence from these mechanisms is balanced and, hence, they provide no net drive for remodeling. A key to a better understanding of the dynamics and cellular processes underlying microvascular remodeling lies in future vessel culture studies, from which the influence of various vasomotor mechanisms may be determined under closely controlled conditions.

We remain with the hypothesis that a tapering vessel has a uniform level of activation along its length. Indeed, Bakker et al. (7) and others (39) found a downstream decrease in wall shear stress, which may be associated with an inverse increase in activation if other mechanisms do not compensate for it. Differential habitual activation along the vessel is, however, not in conflict with the general conclusions of the model, since the vascular structure can be stable at different levels of habitual activation (cf. Figs. 7 and 8), and with a decline in pressure, the observed difference in structure can still arise.

The dynamic remodeling process is governed by Eq. 7, and this particular functional form was chosen for simplicity. The temporal behavior of the remodeling process in vitro (6) and, most likely, also in vivo (20) is more complex. For instance, the speed of outward remodeling during long-term training may be influenced by the training pattern itself, such as peak intensity and duration of each training period. In vitro, morphological changes may appear within hours (30), may proceed over days (4, 5), and may, in vivo (renal hypertension), be complete within 1–2 wk (29). Information about the total time course cannot be obtained from vessel culture studies because of limited viability of vessels beyond 4–5 days, which is probably not sufficient for completion of the remodeling process. However, the final structure is, in the present formulation, independent of the value of $\tau_{\text{remodeling}}$ (see Fig. S2 in the online version of this article).

Myogenic reactivity varies between vascular beds and between arterioles of different dimensions, with a tendency for larger vessels to be less reactive (9). Such differences may be reflected in the level of basal (habitual) tone, since myogenic contraction to the intravascular pressure head is a central component in generation of the basal activation (10). At the same time, the tonic influence from other vasomotor mechanisms (e.g., those dependent on shear stress) may modify myogenic activation (22) differentially. The latter could, to some extent, explain differences in activation between in vivo and in vitro preparations of the same vessel, including cremaster arterioles (2, 3, 7, 12, 24, 31). As shown in Fig. 8, however, the general results are independent of the specific myogenic reactivity and habitual activation level. As long as the vessel wall remains sensitive to stress, it is possible to rearrange the wall material so that the wall remains in homeostasis (Fig. 4).

In the present model, we have considered only a eutrophic remodeling response. Therefore, wall stress cannot be normalized concomitantly with activation during a sustained activating or deactivating stimulus (i.e., $\psi_{\text{add}} \neq 0$; cf. Fig. 9B). There is, however, evidence that circumferential wall stress is a controlled parameter in microvascular biology (7) and that long-standing deviations in wall stress are normalized through growth or atrophy of the vascular wall (37, 44). These processes are probably slower than eutrophic remodeling, since they involve extensive synthesis and breakdown of extracellular material in addition to changes in the number of cells. Thus, as previously suggested (48), it seems likely that acute flow regulation, eutrophic remodeling, and vascular wall growth or atrophy, despite being continuous and interdependent processes, are separated by the time scales on which these processes proceed. Therefore, the present model is only representative of the situation before any substantial change in the amount of wall material. However, it reproduces the very common structural changes [inward eutrophic remodeling (33, 34)] under an isolated increase in pressure in essential hypertension.

There are several indications for the existence of the reverse process, i.e., that vasodilatation may lead to a structural increase in diameter. Outward remodeling was found in vitro by Sorop et al. (43), who used Ca$^{2+}$ channel block to induce chronic vasodilatation in pressurized vessels. Recently, similar outward remodeling has been observed in vivo (11). Increased wall shear stress, known to cause acute vasodilatation in many vascular beds (27, 28), was shown by Pistea et al. (36) to prevent inward remodeling in pressurized vessels in vitro and has been shown in a number of studies to cause outward remodeling in vivo (45, 46). Finally, in human essential hypertension, there are indications that pharmacological normalization of the structural hypertensive changes in microvessels depend on vasodilatation (32).

In conclusion, the present model shows that, in a stress-sensitive vessel, eutrophic remodeling toward a certain level of activation may explain the morphology of rat cremaster arterioles. The model is compatible with the structural changes seen in human essential hypertension and during organ culture experiments. Because of remodeling, the vascular wall can return to a homeostatic state of stress, strain, and activation after a sustained change in pressure. The results are invariant under changes in model parameters, including the specific myogenic reactivity; hence, the model may represent a general mechanism in the microcirculation.

**APPENDIX**

**Mechanics of the relaxed vessel wall.** Model constants relating to connective tissue properties, myogenic contractility, and vessel morphology were adjusted to fit experimental data from rat cremaster arterioles. These data and the corresponding values used in the model are displayed in Table 2. *Data sets I and II* from Bakker et al. (7) represent measurements from up- and downstream positions, respectively, on first-order Wistar rat cremaster arterioles. *Data set III*, from Falcone et al. (12), is from the same vessels in Sprague-Dawley rats of similar body weight, with no specification of the position along the
vessel. Connective tissue constants were varied to give the best fit to the shape and position of the passive pressure-radius curves for data sets I–III simultaneously. (These fits and the experimental data points reproduced from Refs. 7 and 12 are shown in Fig. S1 in the online version of this article.)

The radii reported by Bakker et al. (7), which are close to those used in the model (Table 2), are based on measurements of the length of the (folded) internal elastic lamina. Relative wall thickness (\( h \)) was adjusted to give the experimentally measured wall transsectional area. For data set III, we assumed approximately the same vessel size as \( data \ set \ I \) (the upstream position) and approximately the same wall transsectional area, since there is little difference in relaxed vessel size (without the folds) between \( data \ set \ I \) and \( III \) (31 vs. 34.5 \( \mu m \)). This gives a passive pressure-radius curve that fits the experimental curve well in the physiological pressure range (see Fig. S1, bottom curve, in the online version of this article). Furthermore, it gives a wall stress similar to that of \( data \ set \ I \) and \( II \).

With the present simple connective tissue model, it was possible to satisfy simultaneously the constraints set by \( data \ set \ I-III \) (Table 2; see Fig. S1 in the online version of this article). Since it is a simple two-component connective tissue model, a perfect fit for the pressure-radius curve across the whole pressure range is not possible. We therefore focused on obtaining good fits in the physiological pressure range (~8 kPa), in which simulations of wall remodeling were subsequently run.

**Activation of the vascular SMC.** SMC activation (\( \psi \)) is assumed to be a graded function (13), here normalized to lie between 0 (no activation) and 1 (maximal activation). Experimental data (42, 49), as well as modeling (8, 47), point to a change in wall tension or circumferential wall stress as input stimulus to the myogenic mechanism. Wall tension and circumferential wall stress are proportional to the product of transmural pressure and radius, but, as a measure, circumferential wall stress takes into account differences in wall thickness between vessels. We fitted the model constants to match the experimental data from Falcone et al. (12) (data set \( III \) in Table 2) to obtain an expression for myogenic activation as a function of average circumferential wall stress in first-order rat cremaster arterioles (cf. Fig. 1B).

Initially, on the basis of the vessel morphology that fits the passive curve (see Fig. S1, bottom curve, in the online version of this article), we estimated the relative distension \( (r_i = r/p_i) \) and the corresponding average circumferential wall stress during the active myogenic response. The average circumferential wall stress was estimated as follows: \( P \times r/h \), where \( P \) is transmural pressure, \( r_i \) is internal radius, and \( h \) is wall thickness (see Table S1 in the online version of this article). We assumed that the data point with maximum active contraction (at 14.73 kPa in Fig. 2) represents full activation (\( \psi = 1 \)).

Subsequently, Eq. 5 was used to calculate curves for the average circumferential wall stress as a function of relative distension at different levels of activation. At specific levels of activation, these curves pass through the data points (Fig. 1A), and activation as a function of average circumferential wall stress could be determined (Fig. 1B).

**Program structure.** In the radial direction, the vessel wall was partitioned into a number of layers (Table 1). On the basis of current (or initial) values of \( \rho_i, \eta_i, \psi_i \) and transmural pressure, \( r_i \) was determined from Eq. 4 using Newton-Raphson iteration. Equation 5 was then used to calculate \( S \), from which a new value of \( \psi \) could be determined. The system was then integrated forward in time (Eqs. 6 and 7) with calculation of new values of \( \psi \) and \( \rho_i \), and the cycle was reimplemented.

**Acknowledgments**

The authors are grateful to Drs. Lars Jørn Jensen and Morten Colding-Jørgensen for comments on the manuscript.

**Grants**

This work was supported by grants from the Danish Heart Foundation, the Novo-Nordisk Foundation, the Danish Medical Research Council and the European Union through BioSim Network of Excellence Contract LHSH-CT-2004-005137.

**References**


