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

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Short title: Structural adaptation in arterioles

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Abstract

Structural adaptation in arterioles is part of normal vascular physiology but is also seen in disease states such as hypertension.

Smooth muscle cell (SMC) activation has previously been shown to be central to microvascular remodeling. We hypothesize that in a remodeling process driven by SMC-activation, stress sensitivity of the vascular wall is a key element in the process of achieving a stable vascular structure. We address the question whether the adaptive changes seen in arterioles under different conditions can arise through a common mechanism: remodeling in a stress-sensitive wall, driven by a shift in SMC-activation.

We present a simple dynamic model and show that structural remodeling of vessel radius, by a rearrangement of the wall material around a lumen of a different diameter and driven by differences in SMC-activation, can lead to vascular structures similar to those observed experimentally under various conditions. The change in structure simultaneously leads to uniform levels of circumferential wall stress and wall strain despite differences in transmural pressure. A simulated vasoconstriction caused by increased SMC-activation leads to inward remodeling, whereas outward remodeling follows relaxation of the vascular wall. The results are independent of the specific myogenic properties of the vessel. The simulated results are robust to parameter changes and hence may be generalized to vessels from different vascular beds.
**Introduction**

Vessels of the microcirculation must continuously meet the changing demands of the tissues. On short time scales, vascular diameter and hence tissue perfusion is regulated by variation in smooth muscle (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).

It was noted already 6 decades ago by Folkow and coworkers (15) that 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; *inward eutrophic remodeling* (33). They 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, in analogy 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* (7) 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 have been revealed, which may explain the different manifestations of remodeling as originating through a common mechanism.

Through a series of vessel-culture studies, Bakker and co-workers (2; 5; 6) have shown that sustained contraction leads to structural inward remodeling in micro-vessels. These studies include the effect of myogenic vasoconstriction in vitro (4; 43), but the process in general appears to be independent of what causes the constriction (5; 6; 48). This led Bakker and co-workers (2; 5; 6) and vanBavel et al. (48) to hypothesize that structural remodeling depends on SMC-activation per se, hence 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 changes in pressure or tissue demand. To enable a qualitative analysis, a simplistic approach is used in which the myogenic response is modelled explicitly whereas influence from 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 result 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 decrease in activation. The simulated results are stable under changes in the parameters, and hence may be generalized to vessels from different vascular beds.
The model

**The 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, \( \sigma \), can be expressed as:

\[
\sigma = \sigma_e + \sigma_a. \tag{1}
\]

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

\[
\sigma_e = C_1(e^{\rho_1 \varepsilon} - 1) + C_2(e^{\rho_2 \varepsilon} - 1). \tag{2}
\]

To reproduce the mechanical properties of the passive elastic component as found in first order rat cremaster arterioles, connective tissue parameters were adjusted to fit passive pressure-radius curves from these vessels (please see appendix section A1).

The stress contribution from the active muscular component increases with increasing distension of the vessel until a certain point, after which contribution from active contraction will decline with a 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 (constants in Table 1):

\[
\sigma_a = be^{-(\varepsilon-m)^2/s^2}. \tag{3}
\]

Where \( b \) determines the maximum active stress the wall can develop and \( m \) and \( s \) determines 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 there are no residual stresses left in the wall (please 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. Due to incompressibility, and since the longitudinal strain is assumed to remain constant (please see discussion), the transsectional area of the vessel wall is conserved during distension and constriction. With \( r \) being the radius of a layer within the wall when transmural pressure and activation are both zero and \( r_i \) being the radius of the same layer at a certain level of pressure and activation, wall area conservation can be expressed as:

\[
\frac{r^2}{r_i^2} = \frac{\rho^2}{\rho_i^2}, \text{ where } i \text{ refer to the inner radius.}
\]

With \( o \) referring to outer radius the transmural pressure, \( P \), is given by Laplace's law:

\[
P = \int_{r_i}^{o} \frac{S}{r_i^2} dr = \int_{1}^{\eta} \frac{\sigma \varepsilon}{r_{\rho}^2} dz + \int_{1}^{\eta} \frac{\sigma_{\epsilon}}{r_{\rho}} \frac{\psi = 1}{dz} \tag{4}
\]

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

Finally, the expression for the average circumferential wall stress at a given SMC-activation and transmural pressure takes the form (21):
Fig. 1A shows the stress-distension characteristics of the model vascular wall. The relative distension, \( r_\rho \), shown on the x-axis is 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). The dashed lines show the theoretical contribution from the active muscular component at different levels of SMC-activation, \( \psi \), as indicated to the right (13). \( \psi \) 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 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 versus 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 A1).

Fig. 1B shows the relation between the steady-state activation, \( \bar{\psi} \), of the contractile component and the average circumferential wall stress. The data-points are those shown on the grey line of Fig. 1A and the black line is a simple exponential expression fitted to the points.

\[
\bar{S} = \frac{P r_i}{r_0 - r_i} = \frac{r_\rho}{(\sqrt{\eta^2 - 1} + r_\rho^2)^{\frac{1}{2}}} \left( \int_1^\eta \frac{\sigma_z}{r_\rho} dz + \psi \int_1^\eta \frac{\sigma_a}{r_\rho} \bigg|_{\psi = 1} dz \right).
\]
**Vascular responses:** In the present model two kinds of vascular responses, operating on separate timescales, are considered.

The myogenic response represents an acute activation-regulating mechanism. The myogenic response operates on a time-scale which is of the order of seconds or minutes (12). Short lasting 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, \( \varphi \), and the steady-state activation, \( \bar{\varphi} \), at the same pressure (constants in Table 1):

\[
\frac{d\varphi}{dt} = \frac{1}{\tau_{\text{activation}}} (\bar{\varphi} - \varphi)
\]  

(6)

where the value of \( \bar{\varphi} \) is determined from the fit in Fig. 1B. \( \tau_{\text{activation}} \) is the time constant for the process. The value of \( \tau_{\text{activation}} \) (Table 1) is chosen such that the time elapsed from a step change in pressure and until a new steady-state radius is reached, is similar to that reported for first order rat cremaster arterioles *in vitro* (about one min, (12)), however, the exact value does not matter 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 (12)) are those used to estimate the stress-activation characteristic of Fig. 1B, and 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 it takes to change the level of activation.

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

**Eutrophic remodeling.** A structural change in luminal radius without a change in the wall transsectional area is the second type of vascular response considered. 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 a process in which vascular smooth muscle cells of the media migrate 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 smooth muscle cell 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
smooth muscle cell in short term flow-regulation is optimal. Due to remodeling the habitual level of activation is restored. This process is slow compared to 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 wall transsectional area being preserved, is therefore modeled as (constants in Table 1):

\[
\frac{d \rho_i}{dt} = \frac{1}{\tau_{\text{remodelling}}} (\psi^* - \psi) \rho_i
\]  

(7)

where \( \psi^* \) is the habitual level of activation. \( \tau_{\text{remodelling}} \) is the time constant for the process (table 1) and it was chosen arbitrarily to be 100 times larger than \( \tau_{\text{activation}} \) to effectively separate the two processes. The magnitude of \( \tau_{\text{remodelling}} \) only affects the time it takes to reach a new stable structure, not the final structure itself (please Discussion and Fig. S2).

The rate of remodeling thus depends on \( \tau_{\text{remodelling}} \) and on 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 \textit{vice versa}.

\textit{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 radii. Using the final vessel morphology, the
active and passive pressure-radius curves were simulated. For details of program
structure, please see section A3.

The program source code was written in C (ANSI C standard) by the authors,
using Microsoft Developer Studio (Visual C++ 6.0, professional ed, Microsoft, Seattle,
WA). To differentiate the right hand side of Eq. 4 for Newton-Raphson iteration,
Mathematica® (Wolfram Research, Champaign, IL) was used. 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 Supplementary Material.
Results

Fig. 3 shows the acute effect on a vascular segment of a step change in pressure (initial values given in Table 2, column 4). The traces are from two different simulations in which the pressure (Fig. 3A) is either increased (full lines) or reduced (dashed lines) to arrive at the average up and down-stream pressures reported by Bakker et al. (7) for cremaster arterioles.

Fig. 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 (dashed line). Remodeling is not evident on the short time-scale shown in the figure.

If the pressure change is applied instead as a linear pressure ramp (up or down) over a period of $2-3 \times \tau_{activation}$ (a few 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 is 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 the subsequent myogenic adjustment of radius. As the new equilibrium state is reached, wall stress remains increased in the high-pressure segment and reduced in the low-pressure segment.

As shown in Fig. 3D activation mirrors the shift in circumferential wall stress (cf. Fig. 2A). However, a change in activation, takes time (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. This is shown in Figs. 4 and 5 in which influences from additional vasomotor mechanisms are assumed to outbalance each other; hence $\psi_{\text{add}} = 0$.

In Fig. 4 grey lines indicate the state at the onset of the simulation with the segment in equilibrium at 8.13 kPa. Again pressure is changed in a step (Fig. 4A) and full and dashed lines refer to high and low-pressure segments respectively.

Fig. 4B shows how 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 (c.f. Fig. 3B) is not discernable. Initially the myogenic response adjusts radius to the new pressure level (vertical parts of the curves). In the course of the following 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. 3E), corresponds to a “length auto-regulation” of both contractile and passive elastic wall components. Hence the eutrophic remodeling response enables a vessel to remain within 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 $\eta$ (relative wall thickness), are unaffected by the myogenic response, but change due to remodeling. This is shown in Fig. 5 (same simulation as in Fig. 4). The
high-pressure segment ends up having a low diameter and a thicker wall whereas the low-pressure segment ends up with a large diameter and a thinner wall.

Fig. 6 shows the passive (Fig. 6A) and active (Fig. 6B) pressure-radius curves for the segments before (grey lines) and after structural adaptation to high pressure (full lines) or low pressure (dashed lines). On the passive curves experimental data points from Bakker et al (7) has been reproduced for comparison (open stars: downstream position, closed stars: upstream position). 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 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 (please 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 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 response (shape 3). Vessel morphology is given in data-set III of table 2.

Fig. 8 shows simulations using the different myogenic shapes of Fig. 7. Pressure is changed as before. When the segments are in equilibrium at 8.13 kPa (grey lines), their
level of activation, i.e. the habitual activation, differ (Fig. 8C), and consequently, also the radii are different in the pressurized state (Fig. 8A). Following the pressure change each segment adapts so as to restore the habitual activation level. Due to remodeling, 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 towards 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 position. Also circumferential wall stress (Fig. 8B) and relative distension (not shown) normalizes 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 \( \psi_{add} > 0 \) or deactivating \( \psi_{add} < 0 \) stimulus, acting in concert with the myogenic mechanism. Initial values are 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 subject to the maintained stimulus, \( \psi_{add} \) (sign and magnitude shown to the right in the figure) starting at \( t = 0 \). Following 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 following 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). Note that, despite activation returning to normal levels, wall stress in this case cannot be normalized by eutrophic remodeling alone (Please 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).

Remodeling depends in the present formulation on rearrangement of both active and passive wall components. Following 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 smooth muscle cell to remain in a homeostatic state, and hence, to operate continuously under optimal conditions. Although the individual SMC was not explicitly modelled, a parallel can be drawn to the in vitro observation by Martinez-Lemus et al (30) of normalization of smooth muscle cell length, “length autoregulation” during sustained vessel constriction.

In contrast to the characteristic inward eutrophic remodeling found in human hypertensive resistance arteries and arterioles (< 300 µm in diameter (33)), the qualitative response to hypertension in large conduit arteries is different with medial hypertrophy and preserved luminal radius (41). This response has been subject to detailed modelling both with (16) and without (40) inclusion of smooth muscle cell tone and the results shows 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. Modelling complex systems such as vessels necessitates simplifications. Some possible consequences of these will be addressed in the following.
Relaxed microvessels in the no-load state are not strain-free. A compressive strain residual is present in the inner layers of the wall, whereas in the outer layers this residual is tensile (17). In the model however, the relaxed no-load state possesses 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 in comparison, be higher in the inner layers and lower in the outer layers. This difference will be more pronounced for the stress (c.f. Eq. 2). The model however, is concerned only with the average wall stress which, for the reason of the symmetric over and underestimation of the stress in the different layers, is likely to be a reasonable approximation to the in vivo situation. Not considering 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 (WTA) is invariant under changes in pressure. Real vessels do show longitudinal extension with pressure (18) and therefore assuming constant WTA (see model description) is reasonable only if pressure changes are small. Compared to the initial value, pressure increases or decreases less than 1 kPa (7 mmHg) in the simulations of remodeling.

Bakker et al. (7) found different passive pressure-radius curves when measuring on vessel segments from the up and downstream positions on the 1st order cremaster arteriole. As shown in Fig. S1, the vessel morphology (i.e. radius and wall thickness) may per se explain reasonably well this difference. It cannot be excluded however, that there can be differences in the elastic properties of the wall material at the up and downstream positions, although along a single vessels such differences are likely to be small. Even if
there were differences however, the simulated results would only be minimally
influenced since in the presence of active tone, the passive elastic component carries only
a minor part of the total wall stress (c.f. Fig. 1A).

*In vivo* most arterioles possess a certain basal activation, normally attributed to
the myogenic mechanism (23). This activation provides for efficient modification of
radius by pressure changes and by a variety vasomotor mechanisms including
perivascular nerves, conducted responses, metabolites and endothelial 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 studies (19; 26; 38) 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 vasodilatation 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, $\psi_{add}$, was held constant throughout each simulation. There is no way of
knowing in detail the simultaneous influence from each individual mechanism and this
simplistic approach was applied to avoid invoking numerous assumptions. Fig. 9 should
hence be taken only as a qualitative indication of the early remodeling response under
sustained vasoconstriction or dilatation. $\psi_{add}$ is here treated as an independent variable,
but in vivo, as remodeling progresses, it will influence $\psi_{add}$ as part of a negative feedback loop. In periods of sustained downstream vasodilatation signaling a chronic need for increased perfusion, upstream vessels will, among other vaso-dilating signals, experience an increase in wall shear stress. This will contribute negatively to $\psi_{add}$ 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 $\psi_{add}$ will return towards its neutral value ($\psi_{add} = 0$). Hence, $\psi_{add}$ can be viewed as an error signal in structural remodeling. Note that $\psi_{add}$ being 0 is not the same as lack of additional vasomotor mechanisms. Rather it means that at a given moment their influence 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, in which influence from various vasomotor mechanisms may be determined under closely controlled conditions.

It remains a hypothesis that a tapering vessel has a uniform level of activation along its length. Indeed, Bakker et al (7) and others (39) have found a downstream decrease in wall shear stress, which may be associated with an inverse increase in activation, if not compensated for by other mechanisms. 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. 7-8), 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 \textit{in vitro} (6) and, most likely, also \textit{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, duration of each training period etc. \textit{In vitro} morphological changes may appear within hours (30), proceed through days (4; 5) and may \textit{in vivo} (renal hypertension), complete within 1-2 weeks (29). Information about the total time-course cannot at present be obtained from vessel culture studies due to limited viability of vessels beyond 4-5 days, within which the remodeling process is unlikely to complete. As shown in Fig. S2 however, final structure is, in the present formulation, independent of the value of $\tau_{\text{remodeling}}$.

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 generating the basal activation (10). At the same time, 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 \textit{in vivo} and \textit{in vitro} preparations of the same vessel, including those of 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 of the 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. when $\nu_{add} \neq 0$, 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, although 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 prior to any substantial change in the amount of wall material. However it reproduces the very common structural changes (inward eutrophic remodeling (33; 34)) seen under an isolated increase in pressure in essential hypertension.

Regarding the reverse process, i.e. that vasodilatation may lead to a structural increase in diameter, there are several indications that such a mechanism exists. Outward remodeling was found in vitro by Sorop et al (43), who induced chronic vasodilatation in pressurized vessels using calcium channel blockade. 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, regarding 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 towards 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. Due to remodeling the vascular wall can return to a homeostatic state regarding stress, strain and activation, following a sustained change in pressure. The results are invariant under changes in model parameters, including the specific myogenic reactivity, and hence, the model may represent a general mechanism in the microcirculation.
Acknowledgments

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 the BioSim Network of Excellence, Contract No. LHSB-CT-2004-005137.

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

A1. 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-set I & II from Bakker et al (7), represent measurements from upstream and downstream positions respectively on 1st order Wistar rat cremaster arterioles. Data-set III, from Falcone et al (12), are 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 all three data-sets simultaneously. These fits and the experimental data-points reproduced from reference (7) and (12) are shown in Fig. S1 of the Supplementary material.

The radii reported by Bakker et al (7), which are close to those used in the model (please see Table 2), are based on measurements of the length of the (folded) internal elastic lamina. Relative wall thickness, \( \eta \), was adjusted to give the experimentally measured wall transsectional area. For data-set III we assumed the same approximate vessel size as of data-set I (the upstream position) and approximately the same wall transsectional area, since relaxed vessel-size (skipping the folds) does not differ much (31\( \mu \)m versus 34.5 \( \mu \)m) between these two data-sets. This gives a passive pressure-radius curve that fits the experimental curve well in the physiological pressure range (Fig. S1, bottom curve). Furthermore, it gives a wall stress similar to that of data-set I & II.
As shown in Table 2 and Fig. S1, with the present simple connective tissue model it was possible to satisfy simultaneously the constraints set by the three experimental data-sets. 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 (around 8 kPa), in which simulations of wall remodeling were subsequently run.

**A2. Activation of the vascular smooth muscle cell.** Smooth muscle cell 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) points to a change in wall tension or circumferential wall stress, as input stimulus to the myogenic mechanism. Both of these 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 (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, based on the vessel morphology that fits the passive curve (Fig. S1, lower curve), we estimated the relative distension, $r_\rho = r_i / \rho_i$, and the corresponding average circumferential wall stress during the active myogenic response. The average circumferential wall stress was estimated as: $P \times r_i / h$ where $P$ is the transmural pressure, $r_i$ is the internal radius and $h$ is the wall thickness (full data-set is shown in Table S1,
Supplementary material). We assumed that the data-point with maximum active contraction (at 14.73 kPa in Fig. 2) represents full activation ($\psi = 1$).

Subsequently, using Eq. 5, curves for the average circumferential wall stress as a function of relative distension were calculated at different levels of activation. At specific levels of activation these curves pass through the data-points (diamonds on grey curve on Fig. 1A) and hence activation as a function of average circumferential wall stress could be determined (Fig. 1B).

**A3. Program structure.** In the radial direction, the vessel wall was partitioned into a number of layers (Table 1). Based on current (or initial) values of $\rho_i, \eta, \psi$ and on the transmural pressure, $r_i$ was determined from Eq. 4 using Newton-Raphson iteration. Eq. 5 was then used to calculate $\bar{S}$ whereby a new value of $\bar{\psi}$ could be determined. The system was hereafter integrated forward in time (Eqs. 6 and 7) with calculation of new values of $\psi$ and $\rho_i$. The cycle was then re-initiated.
Supplementary Material

Sensitivity to parameter changes. To test the sensitivity to parameter changes, the structural internal radius, \( r_i \), and the active internal radius, \( r_f \), were chosen as target variables. The effect of parameter changes were compared to simulations in which the values of Table 1 were used. Simulations were performed using the structural parameters of data-set III, initiated at 8.13 kPa and subject to a step increase in pressure to 9.06 kPa.

Numerical methods. Eqs. 6 and 7 were integrated forward in time using the explicit Euler scheme. This scheme is simple to implement and precise for sufficiently small time steps. In the present model, the traces of \( \rho_i \) and \( \psi \) are very smooth adding to the precision.

The effect of changing the time step \( \Delta t \) and the radial discretization of the wall (Layers) was evaluated after \( 0.48 \times \tau_{\text{remodeling}} \) (one hour) of simulated time. Results were invariant until the 5th significant figure under the changes shown in Table S2.

Time constants. Changing the time constants \( \tau_{\text{activation}} \) and \( \tau_{\text{remodeling}} \) has, in the present model, no influence on the final values of \( \rho_i \) and \( r_f \). Variation in these parameters only changes the time it takes to reach steady state. This is illustrated in Fig. S2, Supplementary material.

Stress-distension curves. The stress-distension curves shown in Fig. 1A are invariant under a change in the value of \( \rho_i \). A change in the relative wall thickness, \( \eta \), during
remodeling influences the position of the curves, but the effect is small if $\eta$ is not changed excessively. Fig. S3, Supplementary material, shows the position of the curves for $\psi = 1$ (upper two curves) and for $\psi = 0.1$ (lower two curves) for a relative wall thickness of 1.1 (full lines) and 1.2 (dashed lines). Values of $\eta$ encountered in the simulations of Figs. 4-9 are within these limits. As seen from the curves, if the remodeling process does not lead to large changes in $\eta$, the difference in wall stress at a given level of distension is small.

**Mechanical vessel properties.** To test if a change in tissue properties would influence the general results of the simulations, we implemented the characteristics of a rat kidney afferent arteriole (13). This vessel has mechanical properties very different from those used in the present model. The connective tissue is stiffer, but also the contractile properties differs, as reflected by the constants shown in Table 1, column 4. We used a stress-activation characteristic specific for this vessel (13):

$$\psi(S) = 0.0145e^{0.127S} + 0.0145.$$

Initial values of $\rho_i$ and $\eta$ were 9 $\mu$m and 1.3 respectively. Fig. S4, Supplementary material, displays the same variables after the same pressure change as shown in Figs. 7 and 8. Using these different vessel characteristics does not change the general results of the simulations.
**Figure legend**

**Figure 1**

**Fig. 1A:** Stress-distension curves of the vessel wall model. Thick black line is the stress contribution due to passive elastic components. Dashed lines represent the stress contribution from the active contractile component at different levels of activation, $\psi$. Full lines represent the sum of these contributions. Grey line with black diamonds: estimated average circumferential wall stress during a myogenic response based on (12) (details in Table S1, Supplementary material). After the curve for $\psi = 1$ is reached, the vessel dilates following the characteristics of that curve (last data-point).

**Fig. 1B:** Steady-state activation versus average circumferential wall stress. Data-points (diamonds) are identical to those of Fig. 1A. A fit of the form: $\psi(S) = ae^{bs} + c$ was made to the data-points (black line). The constants are $a = 0.01$, $b = 0.0534$ and $c = 0.055$.

**Figure 2**

Simulated steady-state myogenic response. Black line shows the myogenic contraction of the vessel with increasing transmural pressure. The experimental data points are reproduced from (12).

**Figure 3**

Simulated dynamic myogenic response. The figure shows traces from two simulations. In both cases, vessel morphology ($\rho$ and $\eta$) and initial pressure, is the average of data-set I and II (Table 2, column 4). **Fig. 3A:** At $t_{\text{intervention}} = 0.5 \tau_{\text{activation}}$ ($\tau_{\text{activation}} = 75$ s) pressure is either increased (to the upstream pressure (7)) or decreased (to the downstream...
pressure (7)). **Fig. 3B**: The step change in pressure is followed by a radius transient due to the time it takes to adjust the activation. **Fig. 3C**: Following the initial transient circumferential wall stress is only partially normalized due to myogenic adjustment of radius. **Fig. 3D**: As the myogenic response develops, the difference in activation between high and low-pressure segments increases.

**Figure 4**
The dynamic remodeling response. Note that the time-scale is in units of $\tau_{\text{remodeling}}$ ($\tau_{\text{remodeling}} = 7500 \text{ s}$). The simulation is started at $t_{\text{intervention}} = 0$. Thin grey lines indicate the initial equilibrium state of the vessel segments. Full and dashed black lines refer to high and low-pressure segments respectively. **Fig. 4A**: The step change in pressure imposed on the system at $t = 0$. **Fig. 4B**: The pressure change gives rise to an initial myogenic adjustment of radius (transients not shown). Afterwards a slow remodeling response causes a further decrease in radius in the high-pressure segment and a ditto increase in the low-pressure segment. **Figs. 4C, 4D and 4E**: Circumferential wall stress, activation and relative distension of the vessel is normalized due to the remodeling response.

**Figure 5**
Change in structural internal radius and relative wall thickness due to remodeling. Full and dashed lines refer to high and low-pressure segments respectively. **Fig. 5A**: structural internal radius is unaffected by the initial myogenic response but changes slowly due to remodeling. **Fig. 5B**: The structural relative wall-thickness is unaffected by the initial myogenic response but changes slowly due to remodeling.
Figure 6
Passive and active properties before and after remodeling. **Fig. 6A:** Passive pressure-radius curves for the un-remodeled segment (grey line) and for segments remodeled under high pressure (full black line) and low pressure (dashed line). For comparison experimental data points from Bakker *et al* (7) for the passive pressure-radius curves are reproduced (★ = upstream position, ☆ = downstream position). **Fig. 6B:** Myogenic responses of the un-remodeled segment (grey) and for the remodeled thick-walled high-pressure segment (full black line) and the thin-walled low-pressure segment (dashed line).

Figure 7
Varying myogenic responsiveness. Vessel morphology is shown in *data-set III* (Table 2).

**Fig. 7A:** different stress-activation characteristics. With $S$ in kPa activation is:

Shape 1: $\varphi(S) = 5 \times 10^{-6} S^2 + 5 \times 10^{-4} S + 0.08$

Shape 2: $\varphi(S) = 6 \times 10^{-3} S + 0.03$

Shape 3: $\varphi(S) = 0.0003 e^{0.2S} + 0.02$

**Fig. 7B:** steady-state pressure-radius curves for the stress-activation characteristics of Fig. 7A. Shape 1: a weak myogenic response. Shape 2: the segment shows a stronger myogenic response but is unable to reduce diameter in response to increasing pressure. Shape 3: very strong myogenic response with a steeper negative slope than that of Fig. 2.
**Figure 8**

Remodeling under varying myogenic reactivity. Simulations using the stress-activation characteristics of Fig. 7A. Full and dashed lines refer to high and low-pressure segments respectively. All segments adapt towards the individual level of myogenic activation present at 8.13 kPa. **Fig. 8A:** Final active radii of the segments differ in the three cases. **Fig. 8B:** Normalization of circumferential wall stress in the course of the remodeling process. **Fig. 8C:** Normalization of the activation in the course of the remodeling process. **Fig. 8D:** Final structural radius is similar in all three cases.

**Figure 9.** Remodeling under external activation \( \psi_{\text{add}} > 0 \) or de-activation \( \psi_{\text{add}} < 0 \) of vessel segments kept continuously at 8.13 kPa. At \( t_{\text{intervention}} = 0 \) a maintained stimulus, \( \psi_{\text{add}} \), is imposed on the segment. **Fig. 9A:** Changes in structural radius. Note that the response to positive and negative values of \( \psi_{\text{add}} \) is not symmetrical. Outward remodeling requires a stronger stimulus. **Fig. 9B:** Under external stimulation it is not possible to normalize circumferential wall stress through eutrophic remodeling alone. **Fig. 9C:** Activation is normalized due to remodeling under a maintained external stimulus.
Figure legend of Supplementary Material

Figure S1
Passive elastic properties of first order rat cremaster arterioles. Experimental data-points are reproduced from Bakker et al (7) (two upper curves: • = downstream position, × = upstream position, identical to data points in Fig. 6) and from Falcone et al (12) (lower curve: ▲ = no specified position along vessel). Lines represent the simulated increase in radius with pressure for relaxed vessels with dimensions shown in data-set I-III (Table 2). Constants related to the connective tissue stiffness (Table 1) were adjusted to give the best fit to the experimental data points for all three curves simultaneously.

Figure S2.
Variation in target parameter values ($r_i$ and $\rho_i$) with variation in $\tau_{activation}$ and $\tau_{remodelling}$.
Grey lines are for simulations using the standard values of Table 1. Fine dashed lines: $\tau_{activation}$ changed to 750 s. Coarse dashed lines: $\tau_{remodelling}$ changed to 750 s. The results show that in the present model $\tau_{activation}$ and $\tau_{remodelling}$ determine how fast the simulation settles to the new steady-state values, but that they have no influence on the final values of $r_i$ and $\rho_i$.

Figure S3
Variation in the position of the stress-distension curves with variation in relative wall thickness. Full lines are for thin-walled vessels ($\eta = 1.1$) and dashed lines are for vessels with a thicker wall ($\eta = 1.2$). In both cases curves are shown for full activation ($\psi = 1$, upper two curves) and low activation ($\psi = 0.1$, lower two curves). Values of $\eta$ encountered in the simulations of Figs. 4-9 are between 1.1 and 1.2.

**Figure S4**

Simulation of a renal afferent arteriole. Compared to the first order cremaster arteriole, the connective tissue of this vessel is stiff. In addition the active contractile properties are different (Table 1, column 4). The figure displays the same curves as in Fig. 4 and 5 and shows that the general results of the model are independent of the specific mechanical properties of the vessel used in the simulations.
Table caption

Table 1. Standard parameter values used in the model.

Table 2. Parameter values of Data-set I and II (7) and III (12). Grey font indicate values used in the present model. The last line is the average circumferential wall stress calculated using the model parameters (grey font) and pressure of the same column.

Table caption of Supplementary Material

Table S1. Wall thickness, relative distension and circumferential wall stress during a myogenic response. Based on experimental data from (12). Vessel morphology is given in Data-set III of Table 2.

Table S2. Sensitivity to changes in time-step and radial discretization of the vessel wall.
### Table 1.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value in present model</th>
<th>Value in reference</th>
<th>Reference</th>
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<td>(C_1)</td>
<td>Factor in stiff connective tissue element</td>
<td>(1.3 \times 10^3\ Pa)</td>
<td>(2.7 \times 10^3\ Pa)</td>
<td>(13) Adjusted to fit (7; 12)</td>
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<td>(\alpha_1)</td>
<td>Exponential factor in stiff connective tissue element</td>
<td>1.9</td>
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<td>(C_2)</td>
<td>Factor in soft connective tissue element</td>
<td>40 (Pa)</td>
<td>250 (Pa)</td>
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<td>12</td>
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<td>(b)</td>
<td>Factor determining maximum active stress development</td>
<td>(1.8 \times 10^3\ Pa)</td>
<td>(1.0 \times 10^3\ Pa)</td>
<td>(13) Adjusted to fit (12)</td>
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<td>(m)</td>
<td>Position of top point of active stress-distension curves</td>
<td>0.5</td>
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<td>(13)</td>
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<td>(s)</td>
<td>Width of active stress-distension curves</td>
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<td>0.5</td>
<td>(13)</td>
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<td>(\tau_{activation})</td>
<td>Time constant for the development of activation</td>
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<td>(\tau_{remodeling})</td>
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<td>(\Delta t)</td>
<td>Integration time-step</td>
<td>(10^{-3}\ s)</td>
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<td>Layers</td>
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Table 2

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<td>Radius, length of int. elastic lamina, µm</td>
<td>42.81 ± 1.43 (41.4)</td>
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<td>Wall transsectional area (wta), µm²</td>
<td>1739 ± 89 (1749)</td>
<td>1810 ± 81 (1735)</td>
<td>1754</td>
<td>(1629)</td>
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<td>Rel. wall thickness</td>
<td>1.141 (1.151)</td>
<td>1.136 (1.125)</td>
<td>(1.138)</td>
<td>(1.158)</td>
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<td>Pressure, kPa</td>
<td>9.06 266 ± 16 (267.5)</td>
<td>7.20 260 ± 14 (251.0)</td>
<td>(8.13)</td>
<td>9.06 (253.0)</td>
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Table S1

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<th>Pressure (kPa)</th>
<th>Active radius (µm)</th>
<th>Active wall thickness (µm)</th>
<th>Relative distension</th>
<th>Wall-stress (kPa)</th>
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### Table S2

| Symbol | Test value | Relative deviation $|1 - r_i / r_{i, \text{standard}}|$ | Relative deviation $|1 - \rho_i / \rho_{i, \text{standard}}|$ |
|--------|------------|---------------------------------|---------------------------------|
| $\Delta t$ | $1 \times 10^{-4}$ s | $3.6 \times 10^{-5}$ | $4.7 \times 10^{-6}$ |
| | $1 \times 10^{-3}$ s (standard) | 0 | 0 |
| | $1 \times 10^{-2}$ s | $2.8 \times 10^{-8}$ | $7.0 \times 10^{-8}$ |
| | $1 \times 10^{-1}$ s | $4.7 \times 10^{-7}$ | $1.2 \times 10^{-7}$ |
| $\text{Layers}$ | 2 | $2.5 \times 10^{-5}$ | $4.2 \times 10^{-5}$ |
| | 5 | $3.1 \times 10^{-6}$ | $5.3 \times 10^{-6}$ |
| | 10 (standard) | 0 | 0 |
| | 20 | $7.8 \times 10^{-7}$ | $1.3 \times 10^{-6}$ |
| | 100 | $1.0 \times 10^{-6}$ | $1.8 \times 10^{-6}$ |


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Fig. 1

A

Circumferential wall stress, kPa

relative distension, $r_p$

B

Steady-state activation, $\psi$

Circumferential wall-stress, kPa
Fig. 2

Steady-state radius, μm vs. Pressure, kPa

- The graph shows the relationship between steady-state radius and pressure.
- The steady-state radius increases with pressure up to a certain point and then decreases.
- The maximum steady-state radius occurs at approximately 8 kPa.
Fig. 3

A. Pressure, kPa

B. Radius, μm

C. Wall stress, kPa

D. Activation

Time, $\tau_{activation}$
Fig. 4

A) Pressure, kPa

B) Radius, μm

C) Wall stress, kPa

D) Activation

E) Rel. distens., r_p

Time, t_{remodeling}
Fig. 5

A

\[ \rho_i, \mu \text{m} \]

B

\[ \varpi \]

Time, \( \tau_{\text{remodeling}} \)
Fig. 6

A

Passive radius, μm

B

Active radius, μm

Pressure, kPa
Fig. 7

A
Steady-state activation

Circumferential wall stress, kPa

B
Steady-state radius, μm

Pressure, kPa

Shape 1
Shape 2
Shape 3

Shape 1
Shape 2
Shape 3
Fig. 8

A

Radius, μm

Wall stress, kPa

B

Activation

C

Time, $\tau_{\text{remodeling}}$

D

$\rho$, μm

Time, $\tau_{\text{remodeling}}$
Fig. 9

A

$\rho_i, \mu_m$

B

Wall stress, kPa

C

Activation

Time, $\tau_{\text{remodeling}}$

ψ_{add}

-0.4
-0.25
-0.1
0.1
0.2
0.25

Activation

De-activation