A mathematical model of the myogenic response to systolic pressure in the afferent arteriole

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Chen J, Sgouralis I, Moore LC, Layton HE, Layton AT. A mathematical model of the myogenic response to systolic pressure in the afferent arteriole. Am J Physiol Renal Physiol 300: F669–F681, 2011. First published December 29, 2010; doi:10.1152/ajprenal.00382.2010.—Elevations in systolic blood pressure are believed to be closely linked to the pathogenesis and progression of renal diseases. It has been hypothesized that the afferent arteriole (AA) protects the glomerulus from the damaging effects of hypertension by sensing increases in systolic blood pressure and responding with a compensatory vasoconstriction (Loutzenhiser R, Bidani A, Chilton L. Circ Res 90: 1316–1324, 2002). To investigate this hypothesis, we developed a mathematical model of the myogenic response of an AA wall, based on an arteriole model (Gonzalez-Fernandez JM, Ermentrout B. Math Biosci 119: 127–167, 1994). The model incorporates ionic transport, cell membrane potential, contraction of the AA smooth muscle cell, and the mechanics of a thick-walled cylinder. The model represents a myogenic response based on a pressure-induced shift in the voltage dependence of calcium channel openings: with increasing transmural pressure, model vessel diameter decreases; and with decreasing pressure, vessel diameter increases. Furthermore, the model myogenic mechanism includes a rate-sensitive component that yields constriction and dilation kinetics similar to behaviors observed in vitro. A parameter set is identified based on physical dimensions of an AA in a rat kidney. Model results suggest that the interaction of Ca$^{2+}$ and K$^+$ fluxes mediated by voltage-gated and voltage-calcium-gated channels, respectively, gives rise to periodicity in the transport of the two ions. This results in a time-periodic cytoplasmic calcium concentration, myosin light chain phosphorylation, and cross-bridge formation with the attending muscle stress. Furthermore, the model predicts myogenic responses that agree with experimental observations, most notably those which demonstrate that the renal AA constricts in response to increases in both steady and systolic blood pressures. The myogenic model captures these essential functions of the renal AA, and it may prove useful as a fundamental component in a multiscale model of the renal microvasculature suitable for investigations of the pathogenesis of hypertensive renal diseases.

Renal microcirculation; smooth muscle mechanics; calcium transport; nonlinear system

The rates of blood flow and filtration in a nephron are regulated by two major mechanisms. One is the tubuloglomerular feedback (TGF) system, a feedback loop in which alterations in tubular fluid chloride concentration alongside the macula densa cells result in compensatory adjustments in the muscle tension of the afferent arteriole (AA). The second is the myogenic mechanism, which is an intrinsic property of the AA. This mechanism induces a compensatory vasoconstriction of the AA when the vessel is presented with an increase in transmural pressure. The relative contributions of these two mechanisms to the autoregulation of nephron blood flow and filtration rate depend on a number of factors, including genetic factors, hormonal status, and arterial blood pressure.

In the rat kidney, the myogenic response has been found to operate at 0.1–0.3 Hz (4, 19, 20, 39), whereas the TGF mechanism operates at much lower frequencies (<0.05 Hz). These findings have been interpreted to imply that renal autoregulatory compensation is limited by the upper bound of the myogenic frequency response and that pressure fluctuations with frequencies higher than ~0.3 Hz are transmitted passively through the renal vasculature.

However, in recent years evidence has emerged which demonstrates that the renal myogenic mechanism can respond to pulse pressure fluctuations in blood flow. Rather than fully responding to each pressure pulse, the AA exhibits a sustained vasoconstriction that is determined by the systolic pressure (28, 29). This surprising behavior arises from a marked asymmetry in the kinetics of vasoconstriction and relaxation. Loutzenhiser and coworkers (28, 29) developed a simple phenomenological model of AA kinetics which predicted changes in AA radius as a function of renal blood pressure; the predictions of the model agreed with their measurements. The modulation of baseline vascular resistance by systolic pressure is thought to protect the renal microvasculature from hypertension-induced injury, the incidence of which is correlated with both autoregulatory dysfunction and systolic pressure (2, 3).

The goal of the present study was to develop a detailed mathematical model of the myogenic response of a small segment of the AA wall, including the endothelium and the surrounding smooth muscle cell. The model, which is intended to be incorporated into models of integrative renal hemodynamic regulation, is used to examine the response of a segment of the AA to changes in mean and pulsatile pressure. The simulations reveal model behaviors that agree well with experimental data and that lend support to the hypothesis that the AA myogenic response plays an important role in protecting the glomerular capillary against elevated systolic pressures.

Mathematical Model

Our AA wall model represents the response of both the smooth muscle cell and the endothelium. The model is based on a model for cerebral arterioles in the cat that was developed by Gonzalez-Fernandez and Ermentrout (14). To account for the differences in physical dimensions and in dynamical behaviors between the cerebral arterioles and the renal afferent arteriole, we adjusted a number of the model parameters in the Gonzalez-Fernandez and Ermentrout model (see below). We also incorporated into the model a new myogenic response mechanism that is based on the hypothesis that the dependence of calcium channel openings on voltage is shifted by changes in...
transmural pressure, such that vessel diameter decreases with increasing pressure and vice versa.

Key model equations are summarized below; detailed derivations for the equations can be found in the APPENDIX and in Ref. 14. The model simulates the interactions among voltage-sensitive Ca\textsuperscript{2+} channels, Ca\textsuperscript{2+}-sensitive and voltage-sensitive K\textsuperscript{+} channels, and the membrane potential. The model AA wall undergoes contractions that are controlled by the free cytosolic calcium concentration, denoted C\textsubscript{ai}. The rate of change of C\textsubscript{ai} is given by

\[
\frac{dC_{ai}}{dt} = \left( -\alpha g_{Ca}m_{ref}(v - v_{Ca}) - k_{Ca}C_{ai} \right) \left( \frac{(K_d + C_{ai})^2}{(K_a + C_{ai})^2 + K_{BF}F_1} \right).
\]

where \(\alpha = 1/(Z_{Ca}\beta V_{cell}F)\), \(Z_{Ca} = 2\) is the valence of the calcium ion, \(\beta\) is the fraction of cell volume occupied the cytosol, \(V_{cell}\) is the cell volume, \(F\) is the Faraday constant, \(g_{Ca}\) is the maximum whole-cell membrane conductance for the calcium current, \(k_{Ca}\) is the first-order rate constant for cytosolic calcium extrusion, \(K_d\) is the ratio of the forward and backward reaction rates of the calcium-buffer system, and \(B_T\) is the total buffer concentration. The equilibrium distribution of open calcium channel states \(m_{ref}\) is described as a function of membrane potential \(v\) (13, 27)

\[
m_{ref}(v) = 0.5 \left( 1 + \text{tanh} \left( \frac{v - v_1}{v_2} \right) \right),
\]

where \(v_1\) is the voltage at which half of the channels are open, and \(v_2\) determines the spread of the distribution.

Oscillations in C\textsubscript{ai} vary the phosphorylation rate of the 20-kDa myosin light chains (MLC), which are involved in the formation of cross bridges between overlapping myosin and actin filaments. The formation of cross bridges causes smooth muscle contraction. Because the kinetics of that phosphorylation, which is calcium dependent, is much faster than other vasomotion processes considered here, we assume that the fraction of phosphorylated MLC to total MLC, denoted by \(\psi\), is given by (34)

\[
\psi = \frac{C_{ai}^3}{C_{ai}^3 + C_{ai}^{-1}},
\]

where \(C_{ai,m}\) is a constant. The phosphorylated myosin interacts with actin to form cross bridges and develop stress (25). Let \(\omega\) denote the fraction of cross bridges formed; then we describe the net formation of cross bridges by means of the ordinary differential equation given by

\[
\frac{d\omega}{dt} = k_{\phi} \left( \psi - \frac{\psi_m}{\psi_m + \psi} - \omega \right).
\]

Variations in the number of cross bridges induce variations in a contractile force, which in turn gives rise to variations in AA diameter. To simulate the resulting vasomotion, we consider the blood vessel to be a thick-walled cylinder. The motion of the vessel wall is driven, in part, by the transmural pressure, muscle activity, and wall deformation, which give rise to forces described below and in the APPENDIX. Let \(r_1\) and \(r_o\) denote the inner and outer vessel radius, respectively. Let \(\Delta p\) denote the transmural pressure, and let \(x\) denote the average circumferential length, i.e., \(x = \pi (r_1 + r_0)\). The transmural pressure causes the vessel to relax or contract, which then gives rise to a tension force in the angular (\(\theta\)) direction. That force, which we denote by \(f_{3\theta}\), is given by

\[
f_{3\theta} = \frac{1}{2} \Delta p \left( \frac{x^2 - A}{x} \right),
\]

where \(A\), the wall cross-sectional area, is given by \(A = \pi (r_1^2 - r_0^2)\) (14). A schematic diagram of the model AA wall is shown in Fig. 1.

Wall deformation gives rise to additional stresses along the \(\theta\) direction of the wall. Let \(y\) and \(u\) be the circumferential lengths associated with the contractile and series elastic components, respectively. We assume that these stresses consist of the following components: a contractile component of length \(y\), in series with an elastic component of length \(u\); these two components are in parallel with an elastic component of length \(x = y + u\) (recall that \(x\) is the average circumference). We consider the resulting hoop forces on a surface \(S\), which is bounded by the inner and outer radii of the vessel; \(S\) is assumed to be perpendicular to the angular (\(\theta\)) direction, and to have unit length along the axial (\(z\)) direction. Then, given the stresses \(\sigma_x\), \(\sigma_y\), and \(\sigma_u\) (given in the APPENDIX), the hoop forces on \(S\) are

\[
f_x = w_x \sigma_x, \quad f_y = w_y \sigma_y, \quad f_u = w_u \sigma_u,
\]

where \(w_x\) and \(w_u\) are weights representing the contribution by the elastic and muscular components of the hoop forces. The rate of change of the parallel elastic component’s length is given by

\[
\frac{d\theta}{dt} = \frac{1}{\tau} (f_{3\theta} - f_x - f_u),
\]

where \(\tau\) is a pseudo-time constant associated with the wall internal friction.

For a given number of cross bridges, the velocity of the contractile component (\(y\)) is assumed to depend on the balance between the muscle load experienced by the contractile component, given by the elastic stress \(\sigma_x\) and the contractile stress \(\sigma_y\). For \(\sigma_y > \sigma_x\), the velocity is also proportional to phosphorylation level (7, 8, 33). Thus, following Ref. 14, we have

\[
\frac{dy}{dt} = -av_{cel} \frac{\psi}{\psi(C_{ai,m})} \left( 1 - \frac{\sigma_x / \sigma_y}{\alpha + \sigma_u / \sigma_y} \right);
\]

for \(\sigma_u > \sigma_y\), the contractile component lengths:

\[
\frac{dy}{dt} = c \left( \exp \left( b \frac{\sigma_x}{\sigma_y} - d \right) - \exp \left( b (1 - d) \right) \right).
\]
**Myogenic Response**

A notable feature of the AA myogenic mechanism is the asymmetry in its response times for vasconstriction and vasodilation. Loutzenhiser and coworkers (28, 29) observed that the initial delay in the activation of a pressure-dependent vasoconstriction was ~0.3 s, with the time-profile of the response approximated by an exponential having a time constant of 4 s. In contrast, vasodilation exhibited an initial delay of ~1 s, with a response approximated by two exponentials having time constants of 1 and 14 s, respectively.

Based on the hypothesis that the dependence of calcium channel openings on voltage is shifted by changes in transmural pressure, Gonzalez-Fernandez and Ermentrout (14) described the voltage associated with the opening of half of the calcium channels (denoted \( v_1 \)) as a decreasing function of transmural pressure \( \Delta p \) (see Fig. 6 in Ref. 14). However, our implementation of their model fails to predict the aforementioned asymmetry in the kinetics of the AA vasomotion (see discussion). To attain that asymmetry (28, 29), we hypothesize that, as transmural pressure \( \Delta p \) changes from \( \Delta p_1 \) to \( \Delta p_2 \), \( v_1 \) undergoes transient changes (see below), with the final \( v_1 \) value, denoted \( v_1^* \), representing a decreasing function (in units of mV) of \( \Delta p_2 \) (in units of mmHg); thus we hypothesize that \( v_1^* \) is given by

\[
\begin{align*}
\dot{v}_1^* &= c_1^* (\Delta p_2 - \Delta p^*) + c_2^* (\Delta p_2 - \Delta p^*)^2 + c_3^* (\Delta p_2 - \Delta p^*) + c_4^*,
\end{align*}
\]

where the parameters \( c_1^* \), \( c_2^* \), \( c_3^* \), \( c_4^* \), and \( \Delta p^* \) are given in Table 6. Figure 3 shows \( v_1^* \) as a function of \( \Delta p \). For a given transmural pressure, Eq. 10 yields an AA radius that is in general agreement with experimental measurements by Loutzenhiser and coworkers (28).

To obtain response times that are consistent with experiments, the rate of change of \( v_1^* \) depends not only on the \( \Delta p \) values, but also on the rate of change of \( \Delta p \). We further assume that as \( \Delta p \) changes, the response in \( v_1 \) consists of a fast component and a slow component, i.e.,

\[
\frac{\text{d}v_1}{\text{d}t} = R_{\text{fast}} + R_{\text{slow}},
\]

where \( R_{\text{fast}} \) and \( R_{\text{slow}} \) are determined by \( \Delta p \) and its rate of change.

Consider first an increase in \( \Delta p \) (i.e., \( \Delta p_2 > \Delta p_1 \)); the response in \( v_1 \) begins after an initial delay of 0.3 s. The fast component of the response, \( R_{\text{fast}} \), which lasts for the same time interval as the increase in \( \Delta p \), yields a rapid increase in \( v_1 \), which first overshoots beyond \( v_1^* \) and then decreases exponentially to \( v_1^* \). The slow component, \( R_{\text{slow}} \), begins after an initial delay of 1 s and which lasts for the same time interval as the decrease in \( \Delta p \), increases \( v_1 \) rapidly to \( v_\text{void} \) which lies between \( v_1^* \) and \( v_1^* \).

\[
R_{\text{fast}} = c_1^* \left( \frac{\text{d}\Delta p}{\text{d}t} \right) + c_2^* \left( \frac{\text{d}\Delta p}{\text{d}t} \right)^2 + c_3^* \left( \frac{\text{d}\Delta p}{\text{d}t} \right),
\]

where \( c_1^* \), \( c_2^* \), and \( c_3^* \) are given in Table 6. The overshoot generated by \( R_{\text{fast}} \) is necessary for the model to generate a sufficiently rapid vasoconstriction response. The slow component, \( R_{\text{slow}} \), exponentially increases to \( v_1^* \), if we let

\[
R_{\text{slow}} = -k_1 (v_1 - v_1^*),
\]

where \( k_1 \) is given in Table 6. The slow component elevates \( v_1 \) exponentially to \( v_1^* \):

\[
R_{\text{slow}} = -k_2 (v_1 - v_1^*),
\]

where we set \( k_2 = \ln(2)/10 \text{ s}^{-1} \) to yield an exponential decay with a half-life of 0.2 s. Unlike the fast component which lasts for the same time interval as the pressure increase, the slow component continues after the pressure increase has ended.

To illustrate the response of \( v_1 \) to changes in \( \Delta p \), we display in Fig. 4, A and B, the time course of \( v_1 \) as \( \Delta p \) changes rapidly from 80 to 120 mmHg during an interval of 0.1 s, then, after 70 s, decreases rapidly back to 80 mmHg over 0.1 s. This simulation will be discussed further in RESULTS.

**Parameters**

A large number of parameters are used in this model to describe the AA wall’s geometrical dimensions, membrane transport properties, and muscle mechanical properties. The values of these parameters are given in Tables 1–5. Myogenic mechanism parameters are given in Table 6. Most of these parameters are taken from Ref. 14 and the references therein. A selected subset of parameters in Ref. 14 has been modified to account for the differences in physical dimensions and in dynamic behaviors between the cerebral arterioles modeled in Ref. 14 and the renal AA of this study; modified parameters are marked with asterisks in Tables 1–5.
MODEL RESULTS

Using the base-case parameter set given in Tables 1–5, we investigated the dynamic behaviors of the model AA wall. In this study, we set the baseline transmural pressure, $\Delta p$, to 100 mmHg, a value consistent with a AA wall segment located at the proximal portion of the vessel. The $\Delta p$ for a wall segment in the distal AA would be smaller owing to the pressure drop along the AA. We first considered the dynamics of the model’s ionic transport and membrane potential. Figure 5, A and B, depicts the oscillations of electrical current across the membrane by $\text{Ca}^{2+}$ and by $\text{K}^+$ (i.e., $I_{\text{Ca}}$ and $I_K$, respectively, given by Eq. 26) and the corresponding transmembrane potential $\nu$. The asynchrony between the ionic currents $I_{\text{Ca}}$ and $I_K$ gives rise to the oscillations of the action potential. The inward-directed $\text{Ca}^{2+}$ current depolarizes the cell, which results in an increase in the membrane potential. The outward-directed $\text{K}^+$ current then follows and repolarizes the cell, resulting in a decrease in the membrane potential. Because

![Diagram](image_url)

Table 1. Afferent arteriole geometric dimensions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
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<tbody>
<tr>
<td>$S^*$</td>
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<td>cm$^2$</td>
</tr>
<tr>
<td>$A^*$</td>
<td>$1.38 \times 10^{-6}$</td>
<td>cm$^2$</td>
</tr>
<tr>
<td>$r_e^*$</td>
<td>$12.0 \times 10^{-4}$</td>
<td>cm</td>
</tr>
<tr>
<td>$r_i^*$</td>
<td>$10^{-3}$</td>
<td>cm</td>
</tr>
<tr>
<td>$w_e$</td>
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</tr>
<tr>
<td>$w_m$</td>
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<tr>
<td>$\tau$</td>
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<td>dyn$\cdot$s$\cdot$cm$^{-1}$</td>
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</table>

*aParameters that differ from those in Ref. 14.

![Diagram](image_url)

Table 2. Arteriolar membrane parameters

<table>
<thead>
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<th>Parameter</th>
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<tbody>
<tr>
<td>$\nu_2$</td>
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<td>mV</td>
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<tr>
<td>$\nu_4$</td>
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<td>mV</td>
</tr>
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<td>$\nu_5$</td>
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<td>mV</td>
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<tr>
<td>$\nu_6$</td>
<td>$-15.0$</td>
<td>mV</td>
</tr>
<tr>
<td>$\nu_L$</td>
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<td>mV</td>
</tr>
<tr>
<td>$\nu_K$</td>
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<td>mV</td>
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<td>$\nu_{\text{Ca}}$</td>
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<tr>
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<td>nM</td>
</tr>
<tr>
<td>$\phi_n^*$</td>
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*aParameter that differs from that in Ref. 14.

![Diagram](image_url)
Table 3. Arteriolar cell parameters

<table>
<thead>
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<td>C( \text{M}^{-1})mV(^{-1})</td>
</tr>
<tr>
<td>( g_k )</td>
<td>( 3.14 \times 10^{-13} )</td>
<td>C( \text{M}^{-1})mV(^{-1})</td>
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<td>C( \text{M}^{-1})mV(^{-1})</td>
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<td>( C^* )</td>
<td>( 7.85 \times 10^{-14} )</td>
<td>C\text{mM}^{-1}</td>
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<td>( K_d )</td>
<td>( 10^3 )</td>
<td>nM</td>
</tr>
<tr>
<td>( B_f )</td>
<td>( 10^5 )</td>
<td>nM</td>
</tr>
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<td>( \alpha )</td>
<td>( 8.00 \times 10^{15} )</td>
<td>nM\text{C}^{-1}</td>
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<tr>
<td>( \kappa_{C^*} )</td>
<td>190</td>
<td>s(^{-1})</td>
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*Parameters that differ from those in Ref. 14.

Table 5. Arteriolar smooth muscle parameters

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<td>( C_{a,m} )</td>
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<td>nM</td>
</tr>
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<td>( a )</td>
<td>( 3.00 )</td>
<td>Dimensionless</td>
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<tr>
<td>( C_{a, \text{ref}} )</td>
<td>( 400 )</td>
<td>nM</td>
</tr>
<tr>
<td>( a^{\text{fast}} )</td>
<td>( 1.46 \times 10^7 )</td>
<td>dyn\cdot cm(^{-2})</td>
</tr>
<tr>
<td>( a^{\text{slow}} )</td>
<td>( 1.69 \times 10^7 )</td>
<td>dyn\cdot cm(^{-2})</td>
</tr>
<tr>
<td>( \psi_{\text{m}} )</td>
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<tr>
<td>( k_d )</td>
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<td>( \sigma )</td>
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<tr>
<td>( b )</td>
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</tr>
<tr>
<td>( c )</td>
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</tr>
<tr>
<td>( d )</td>
<td>1.30</td>
<td>Dimensionless</td>
</tr>
</tbody>
</table>

*Parameters that differ from those in Ref. 14.

both the Ca\(^{2+}\) and K\(^+\) channels are voltage dependent, variations in membrane electrical potential \( v \) affect those currents. As \( v \) decreases, the equilibrium distributions of open Ca\(^{2+}\) and K\(^+\) channel states (denoted \( m_v \) and \( n_v \); see Eqs. 2 and 24) both decrease. Consequently, the magnitudes of currents \( I_{Ca} \) and \( I_K \) decrease, which result in periodic oscillations in the transmembrane potential and the ionic currents.

Oscillations in \( I_{Ca} \) result in oscillations in the intracellular free calcium concentration, \( C_{a,i} \), which give rise to cross-bridge formation and smooth muscle contractions. Figure 5, \( C \) and \( D \), shows the time courses of the intracellular free calcium concentration \( C_{a,i} \) and the vessel’s inner diameter, respectively. The calcium concentration oscillations (Fig. 5C) lag behind those of the membrane potential (Fig. 5A), whereas the peaks and troughs of the membrane potential correspond in time to those of the vessel diameter (Fig. 5D). The frequency of these oscillations is \( \sim 175 \) mHz, and the amplitude of the vessel diameter oscillations is \( \sim 1 \) μm. These predictions are consistent with experimental measurements (28).

Responses to Different Steady-State Transmural Pressure Values

We examined the model AA wall’s behaviors for differing steady-state transmural pressure values. For the first set of simulations, we neglected the myogenic response. That is, we assumed that the voltage-dependence of calcium channel openings is unaffected by changes in transmural pressure. In all simulations, we set \( v_1 \) to \(-22.5 \) mV, the value that corresponds to \( \Delta p = 100 \) mmHg. The dynamic behaviors of the model vessels were computed for a range of transmural pressure \( \Delta p \) values. The vessel’s time-averaged inner diameters for differing \( \Delta p \) are shown in Fig. 6. As transmural pressure is elevated, the tension force due to pressure (i.e., \( f_{\text{press}} \), Eq. 5) increases. Thus, in the absence of the myogenic response, the model vessel reacts passively to changes in transmural pressure, expanding from an average inner diameter of \( \sim 17.3 \) μm at \( \Delta p = 60 \) mmHg to \( \sim 24.2 \) μm at \( \Delta p = 160 \) mmHg.

In the next set of simulations, we incorporated the myogenic response by allowing dependence of calcium channel openings on membrane potential to be shifted by changes in transmural pressure (see Eq. 10). We computed the time-averaged vascular diameters for differing transmural pressure values; see Fig. 6. As \( \Delta p \) increases from 60 to 160 mmHg, \( v_1 \) decreases from \(-20.6 \) to \(-26.6 \) mV. The more negative \( v_1 \) values obtained for larger \( \Delta p \) generated larger inward-directed calcium currents and thus higher calcium concentrations, which resulted in the formation of cross bridges and muscle contraction. The increased pressure-induced tension force (i.e., increased \( f_{\text{act}} \)) and the increased contractile force competed, with the net result being a vasoconstriction. In contrast to the previous case, which neglected the myogenic response, the model predicts a vasodilation when \( \Delta p \) is reduced to 60 mmHg: the vessel’s average inner diameter increases from the base-case value of 19.95 μm at \( \Delta p = 100 \) mmHg to 26.8 μm at \( \Delta p = 60 \) mmHg; when \( \Delta p \) is increased to 160 mmHg, the vessel’s average inner diameter decreases by 28.0% from base case (19.95 μm) to 14.4 μm. For sufficiently low or sufficiently high transmural pressure (\( \Delta p < 40 \) mmHg or \( \Delta p > 160 \) mmHg), no oscillations occurred.

Table 4. Arteriolar vessel mechanical parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
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<td>( x_0^* )</td>
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<td>cm</td>
</tr>
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</tr>
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<td>( x_2 )</td>
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<td>Dimensionless</td>
</tr>
<tr>
<td>( x_3 )</td>
<td>2.22</td>
<td>Dimensionless</td>
</tr>
<tr>
<td>( x_4 )</td>
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<td>Dimensionless</td>
</tr>
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<td>( x_5 )</td>
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</tr>
<tr>
<td>( x_7 )</td>
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<td>Dimensionless</td>
</tr>
<tr>
<td>( x_8 )</td>
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</tr>
<tr>
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<tr>
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<tr>
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<td>( y_3 )</td>
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</tr>
<tr>
<td>( y_4 )</td>
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*Parameter that differs from that in Ref. (14).

Table 6. Myogenic mechanism parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
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<tr>
<td>( c_f )</td>
<td>( 3.81 \times 10^{-4} )</td>
<td>mV\cdot mmHg(^{-3})</td>
</tr>
<tr>
<td>( c_2 )</td>
<td>( -2.71 \times 10^{-1} )</td>
<td>mV\cdot mmHg(^{-1})</td>
</tr>
<tr>
<td>( c_3 )</td>
<td>( -6.53 \times 10^{-2} )</td>
<td>mV\cdot mmHg(^{-1})</td>
</tr>
<tr>
<td>( c_4 )</td>
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<td>mV</td>
</tr>
<tr>
<td>( \Delta p^* )</td>
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<td>mmHg</td>
</tr>
<tr>
<td>( c_{\text{ref}} )</td>
<td>(-2.79 \times 10^{-7} )</td>
<td>mV\cdot mmHg(^{-3})\cdot s(^2)</td>
</tr>
<tr>
<td>( c_{\text{fast}} )</td>
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<td>mV\cdot mmHg(^{-2})\cdot s(^{-1})</td>
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<td>( c_{\text{slow}} )</td>
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<td>( c_{\text{fast}} )</td>
<td>(-2.53 \times 10^{-2} )</td>
<td>mV\cdot mmHg(^{-1})</td>
</tr>
</tbody>
</table>

*Parameters that differ from those in Ref. 14.
of significant amplitude were obtained in the vascular diameter.

The shifting of calcium channel openings by transmural pressure results in changes in calcium current and membrane potential. We computed the time-averaged membrane potential for differing transmural pressure; see Fig. 7. As $P$ increases, $v_1$ decreases and the inward-directed calcium current increases, which depolarizes the membrane. This result is consistent with experimental observations (17, 37) that report the depolarization of vascular muscle cells when transmural pressure is elevated. When the membrane calcium conductance, $g_{Ca}$, is reduced by a factor of 10, membrane potential becomes nearly insensitive to transmural pressure; see Fig. 7.

Responses to Step Perturbations in Transmural Pressure

We examined the model’s vasoconstriction kinetics by simulating a rapid increase in transmural pressure from 80 to 160 mmHg. A true step change in pressure was approximated by a smooth rise having a duration of 0.1 s. The vasodilation kinetics were then assessed when transmural pressure was reduced from 160 to 80 mmHg. We computed the model AA wall’s vasodilation response, which we defined by

$$\frac{r_i(t) - \bar{r}_0}{\bar{r}_{max} - \bar{r}_0} \times 100\%,$$

where $r(t)$ denotes the inner radius at time $t$, $\bar{r}_0$ denotes the time-averaged inner radius before the pressure change, and $\bar{r}_{max}$ denotes the maximum response, i.e., the time-averaged inner radius value that the model AA wall approaches after the pressure change. The time courses for the responses, expressed as the percentage of the maximum response, are exhibited as solid curves in Fig. 8. To facilitate the interpretation of these responses, we also provide (as dashed curves) in Fig. 8, A and B.

![Fig. 5. Base-case oscillation profiles. A: oscillations in Ca$^{2+}$ and K$^+$ currents (denoted $I_{Ca}$ and $I_K$, respectively) and membrane potential $v$. B: oscillations in equilibrium distribution of open Ca$^{2+}$ and K$^+$ channel states (denoted $m_o$ and $n_o$, respectively). C and D: oscillations in intracellular free Ca$^{2+}$ concentration and AA inner diameter, respectively.](image)

![Fig. 6. Average vessel inner diameter as a function of steady-state transmural pressure, with and without a myogenic response.](image)

![Fig. 7. Average membrane potential as a function of steady-state transmural pressure, obtained for base-case membrane Ca$^{2+}$ conductance $g_{Ca}$ and for $g_{Ca}$ reduced by a factor of 10.](image)
the sensitivity studies at the end of results, the amplitude of the vasomotion decreases with increasing pressure, as shown in Fig. 8B, the time courses of the spontaneous vasomotion corresponding to steady-state pressures of 80 and 160 mmHg, respectively.

Note that the maximum responses approached 100% in both simulations, but the response did not start at 0% in Fig. 8A, the case where pressure was increased from 80 to 160 mmHg. Instead, at $t = 0$, both the spontaneous vasomotion and the vasoconstrictive response were determined to be at $-13.5\%$ of the maximum contractile response (see Fig. 8A). That is because the model AA wall undergoes spontaneous vasomotion even in the absence of pressure changes. In this simulation, the AA radius was below its average radius, corresponding to 80 mmHg at $t = 0$. Immediately after the pressure increase, the AA wall underwent a passive dilatation, inasmuch as the myogenic response did not begin until 0.3 s after the pressure change. That delay was followed by an almost monotonic contractile response, with the AA radius reaching $90\%$ of the maximum contractile response in $\sim 11.3$ s. As shown in Fig. 8B, the vasodilation response exhibited a longer initial delay ($\sim 1$ s), and a generally slower response time: $90\%$ of maximal dilation was attained in $\sim 45.2$ s. Because the amplitude of the vasomotion decreases with increasing pressure, as shown in the sensitivity studies at the end of results, the amplitude of the oscillations at $\Delta p = 160$ mmHg is insignificant.

We then simulated the vessel’s responses to a rapid, steplike increase or decrease in transmural pressure. In this simulation, $\Delta p$ began to increase from 80 to 120 mmHg at $t = 50$ s, remained constant at 120 mmHg for $\sim 70$ s, and then began to decrease from 120 to 80 mmHg at $t = 120$ s. Figure 4 shows the time course of the transmural pressure, and the resultant $v_1$, Ca$^{2+}$ current, intracellular free calcium concentration, membrane potential, and vascular inner diameter.

As $\Delta p$ increased from 80 to 120 mmHg, $v_1$ exhibited an overshoot response (after an initial delay of 0.3 s), in which it decreased rapidly from $-21.3$ to $-28.0$ mV (see Fig. 4B). As $v_1$ decreased, a larger Ca$^{2+}$ current was induced, depolarizing the cell. After the overshoot response, $v_1$ returned to the target value $-23.9$ mV, which corresponds to $\Delta p = 120$ mmHg. Compared with the response at 80 mmHg, the magnitude of the average calcium current, and thus the average calcium concentration, is higher at $\Delta p = 120$ mmHg; consequently, the magnitude of the average membrane potential ($v$) is reduced (see Fig. 4, C–E). As a result of the higher calcium concentration, a higher fraction of cross bridges is formed, which gives rise to smooth muscle contractions, exhibited in a decrease in vascular diameter from an average of $-23.1$ to 17.5 $\mu$m (see Fig. 4F).

As $\Delta p$ decreased from 120 to 80 mmHg, $v_1$ increased, after an initial delay of 1 s, from $-23.9$ to $-22.5$ mV, in a first-phase response of duration 0.1 s. That was then followed by a longer second-phase response, during which $v_1$ further increased to $-21.3$ mV, the target value that corresponds to $\Delta p = 80$ mmHg. The elevation in $v_1$ gave rise to a smaller Ca$^{2+}$ current, a lower calcium concentration, and a smaller fraction of cross bridges formed. A vasodilation thus resulted, with average $v_1$ increases from $\sim 8.76$ to 11.5 $\mu$m. Compared with vasoconstriction, vasodilation occurred over a substantially longer time interval. These results demonstrate the asymmetry in response times for vasoconstriction and vasodilation, in agreement with measurements by Loutzenhiser et al. (28, 29).

**Responses to Pressure Pulses**

We then assessed the model vessel’s response to pressure oscillations having differing frequencies. We first considered steplike pressure pulses, having a frequency of 1 Hz, with transmural pressure varying between 100 and 120 mmHg. The period of those oscillations is substantially shorter than the response times of the vessel’s myogenic mechanism; in that sense, the frequency of these pressure signals can be considered high. The time course of the transmural pressure and the changes in the vessel’s inner diameter are shown in Fig. 9, A1 and B1. The response to a single pressure pulse of 20-s duration is included for comparison. That response is qualitatively similar to that shown in Fig. 4.

Instead of responding to the high-frequency pressure variations passively without attenuation, the model vessel exhibited a sustained vasoconstriction. Vasoconstriction occurred because the response to the pressure stimulus continues during the 1-s delay in vasodilatation. Thus, when presented with a train of such pulses, the contractile responses are additive. Also, results in Fig. 9B1 show that similar sustained vasoconstriction responses were obtained for both the single-step perturbation and the high-frequency pressure signals, even though the average pressure increase in the high-frequency signals was only half of that of the single-step perturbation. (If we consider pressure increases $>100$ mmHg, then the average pressure increase in the high-frequency signals was $10$ mmHg, because the pressure was $100$ mmHg for half of the interval over which the signal was applied, and the pressure was $120$ mmHg for the...
other half of the time, whereas the pressure increase corresponding to the single-step perturbation was 20 mmHg, because the pressure was set to 120 mmHg for the entire 100-s interval.

In contrast, when presented with a train of pressure pulses of a lower frequency of 0.05 Hz, the inner vessel diameter exhibited clearly distinguishable oscillations instead of a sustained vasoconstriction; see Fig. 9, A2 and B2.

To further examine the hypothesis that myogenic tone is determined, in large part, by systolic pressure rather than mean pressure, we conducted a simulation in which the transmural pressure was perturbed by high-frequency (0.5 Hz) oscillations, of increasing amplitude but constant mean pressure. Specifically, transmural pressure first oscillated for 60 s between 60 and 100 mmHg, then for 60 s between 40 and 120 mmHg, then for another 60 s between 20 and 140 mmHg. The model response is shown in Fig. 10. An increase in systolic pressure elicited AA vasoconstriction, which occurred progressively with increasing range in pressure oscillations, and which occurred despite a constant mean pressure of 80 mmHg, owing to a corresponding decrease in diastolic pressure.

Model Sensitivities to Parameters

The values used for some models parameters are substantially uncertain. Therefore, in a set of parameter sensitivity studies, we studied the effects of varying selected parameters on model behaviors. The parameters that we considered were the following: $v_1$, the voltage associated with the opening of half the population of the calcium channels (see Eq. 2); $v_6$, which determines the voltage associated with the opening of half the population of the potassium channels (see Eq. 25); $\Phi_p$, which determines the rate at which the potassium channels open (see Eq. 23); $k_{Ca}$, the rate constant for cytosolic calcium extrusion (see Eq. 21); $k_\psi$, which determines the rate of formation of cross bridges (see Eq. 4); $C$, the cell capacitance (see Eq. 26); and $g_{K}$ and $g_{Ca}$, which are the whole-cell membrane conductances associated with the potassium and calcium currents (see Eq. 26). We varied these parameters individually, over wide ranges, with transmural pressure set to 100 mmHg. We determined the amplitude and frequency of the vasomotion, average AA inner radius, average membrane voltage potential, and average cytosolic calcium concentration. The results of this sensitivity study are summarized in Table 7. We conducted simulations for 20 sets of parameters, labeled A1, A2, ..., B1, B2, etc. in Table 7 under column “Case.” Cases labeled with the same letter (e.g., A1, A2, and A3) correspond to simulations in which the same parameter was varied; the number distinguishes cases in which different values were assigned to that parameter.

The model’s oscillatory behavior is caused by the interactions between cytosolic calcium and potassium currents, with the depolarization of the cell membrane by the calcium current, followed by hyperpolarization by the potassium calcium. Thus variations in model parameters that determine the rate of oscillations in these currents may affect the dynamics of the model. Results in Table 7 show that, in case C2, the large $\varphi_p$ value accelerated the kinetics of potassium channel opening, with the effect that oscillations persist but at a frequency 1.33 times of that found in the base case. Oscillation frequency is also increased by decreasing the cell capacitance $C$ (F1), or vice versa.

When calcium extrusion rate $k_{Ca}$ is increased (D2), cytosolic calcium concentration decreases, and vascular radius increases. Similarly, when cross-bridge formation rate constant $k_\psi$ increases, vasodilation is predicted. This is because the model predicts that, for model parameters considered, the time-averaged values of cross-bridge formation rate, given by $k_\psi/(\varphi_{m} + \psi)$, is lower than cross-bridge degeneration rate, $k_{b,60}$. Thus Eq. 4 yields...
a smaller $\omega$ for a larger first-order rate constant $k_b$ and vasodilation results.

With $v_1$ set to a large negative value ($-30.0$ mV) in case A1, the equilibrium distribution of open calcium channel states is shifted so that cytosolic calcium concentration increases, the calcium transport overrides the potassium transport, cell membrane is depolarized, and oscillations vanish. An opposite effect was obtained when the magnitude of $v_1$ was reduced to $-19.0$ mV (case A4), or when the whole-cell membrane conductances associated with the calcium current ($g_{Ca}$) were reduced (case H3). In both cases, oscillations again vanish, but with cell-membrane hyperpolarization and vasodilation. When $v_6$, which is associated with the equilibrium distribution of open potassium channel states, is set to a large negative value (B2), the outward-directed potassium current increases, which hyperpolarizes the cell. The same effect is achieved by increasing $g_K$, the whole-cell membrane capacitances associated with the potassium current ($G_1$).

**DISCUSSION**

We have identified a set of parameters that are consistent with the physical properties and dynamics of the AA in the rat kidney and applied those parameters to the model of arteriolar smooth muscle cell vasomotion by Gonzalez-Fernandez and Ermentrout (14). Using base-case parameters, the resultant model predicts that, given a transmural pressure of 100 mmHg at the entrance to the AA, the time-averaged inner diameter of the AA is $20 \mu$m, consistent with experimental measurements (28). The model also predicts that the interactions among the calcium and potassium cell membrane transports spontaneously generate periodic membrane voltage oscillations and vasomotion, with an amplitude of $1 \mu$m and a frequency of $175$ mHz. Model simulations suggest that, owing to the asymmetry in vasoconstriction and vasodilation response times, the AA may be able to sense systolic pressure at heartbeat frequency and respond with a sustained vasoconstriction when systolic pressure is elevated.

Comparison with Previous Models

Our AA model is based on the vascular muscle cell model of Gonzalez-Fernandez and Ermentrout (14) (which we refer to as the “GE model”). The GE model was formulated for cerebral...
arterioles of the cat, which are substantially larger than the renal AA and which exhibit quantitatively different dynamic behaviors. The model cerebral arteriole has an average diameter of ∼540 μm, and the frequency of the vasomotion is ∼450 mHz. In contrast, the average diameter of the AA is ∼20 μm; and the frequency of the vasomotion is ∼175 mHz.

In the GE model, the myogenic response is incorporated by assuming that the voltage associated with the opening of half of the calcium channels (denoted \( \nu_1 \)) is a decreasing function of transmural pressure \( \Delta p \) (see Fig. 6 in Ref. 14). Reference 14 exhibits the model arteriole’s responses to differing steady-state transmural pressure values, but it does not include the model’s dynamic responses to variations in pressure. Our implementation of the GE model generates approximately the same vasocnstriction and vasodilatation response times, which is inconsistent with experimental observations by Loutzenhiser and coworkers (28, 29). To obtain the appropriate asymmetry in response times, rate sensitivity was introduced into the model equations. We hypothesize that, during vasocnstriction, \( \nu_1 \) first undergoes a transient overshoot response before returning to the target value. This overshoot response shortens the response time and produces the desired rapid vasocnstriction. Rate sensitivity has been observed in many vascular beds (15, 23). In the renal microvasculature, spectral analysis of renal blood flow (RBF) dynamics reveals features characteristic of rate sensitivity, namely, a rise in gain and an increase in phase that are accentuated by inhibition of nitric oxide synthesis (38, 39). Although the rapid RBF response to a step change in pressure predicted by rate sensitivity is often not seen in barbiturate-anesthetized rats, responses consistent with a rate-sensitive component emerge after inhibition of nitric oxide synthesis (24). During vasodilatation, we have assumed that \( \nu_1 \) undergoes a slow, two-phase response, which gives rise to a slow vasodilatation. This behavior is consistent with observations in renal vessels (28) and with data from isolated hamster cheek pouch arterioles, which exhibit unidirectional rate sensitivity such that the responses to rapid decreases in pressure show much less rate dependency than responses to step increases in pressure (5). Nevertheless, further direct studies of rate sensitivity of renal arterioles will need to be conducted to evaluate our assumption of unidirectional rate sensitivity. Furthermore, the origin of the rate sensitivity has yet to be determined. One possibility is that rapid changes in wall tension following a rapid rise in intravascular pressure may open the sodium or calcium channels, which are tethered to the cytoskeleton and extracellular matrix; subsequent remodeling of the cytoskeleton or relaxation of the viscoelastic elements in the vessel wall may reduce the tension, thereby resulting in rate sensitivity.

Marsh and coworkers (30) adopted the smooth muscle cell model of Gonzalez-Fernandez and Ermentrout (14) to study the interactions between AA myogenic response and TGF. However, some of the model parameters used in Ref. 30 are not appropriate for the dimensions of the rat AA, which is at least an order of magnitude smaller than the arterial vessel considered by Gonzalez-Fernandez and Ermentrout. For example, the length of the parallel elastic component associated with a reference stress (denoted by a parameter \( \nu_0 \)) should be on the same order of magnitude as the circumference of the AA. However, \( \nu_0 \) was taken to be 1,500 μm in Ref. 30. In contrast, \( \nu_0 \) was set to 150 μm in our model. Also, in Ref. 30 myogenic responses were generated only in response to oscillatory transmural pressure, whereas it has long been observed that changes in mean pressure also induce myogenic responses (28). In contrast, our model exhibits myogenic responses as a function of both pressure and its rate of change.

Based on the kinetic attributes of the AA myogenic response and the steady-state pressure and AA diameters, Loutzenhiser et al. (28) developed a mathematical model of renal autoregulation. Both that model and the present model predict vascular responses that appear to be consistent with the dynamic features of renal autoregulation observed in the intact kidney. However, the model in Ref. 28 is a phenomenological model that predicts only AA diameters. In a follow-up study, Williamson et al. (41) developed a more extensive systems model to examine the impact of systolic-pressure sensitivity on renal autoregulation. Their results show that the asymmetry in time delays in the myogenic response is more important than differences in the time constants of vasocnstriction vs. vasodilatation in accounting for the sensitivity to systolic pressure in the hydronephrotic kidney. The present model extends those efforts in that it incorporates ionic transport, cell membrane potential, muscle contraction of AA smooth muscle cells, and the mechanics of a thick-walled cylinder, while still capturing the important behaviors identified by Loutzenhiser and his colleagues (28).

Implications of Model Results

When presented with pressure oscillations of sufficiently high frequency (>1 Hz), our model generates a sustained vasocnstriction, the magnitude of which is determined by the peak pressure rather than the mean pressure. These results support the hypothesis that baseline myogenic tone is strongly influenced by systolic pressure (28, 29). This observation broadens the concept that the myogenic response functions to maintain an approximately constant RBF and glomerular filtration rate (GFR) as blood pressure is varied. Under physiological conditions, where mean and systolic blood pressures vary in tandem, a myogenic response determined by systolic pressure would also regulate RBF and GFR, which are determined primarily by mean perfusion pressure, not peak pressure. However, under some pathophysiologic conditions, where changes in systolic and mean blood pressures can be decoupled, an elevation in systolic pressure would result in a myogenic vasocnstriction, even if mean perfusion pressure is unchanged or decreased. Thus the myogenic response serves not only to maintain an approximately constant RBF, but it also protects the glomerulus from systolic pressure peaks. This behavior is of potential importance because studies have identified strong correlations between systolic pressure and renal injury (18).
Model Limitations and Potential Extensions

Because, as previously noted, this AA wall model is intended to be incorporated into future multiscale models of integrated renal hemodynamic control, we sought to develop a model that is computationally efficient. Thus some degree of simplification was necessary, and certain details, such as the possible involvement of epithelial sodium channels (ENaC) in the initiation of the myogenic response, signaling pathways underlying the vascular smooth muscle constriction, or signaling mechanisms that modulate the myogenic response, while important, were neglected or represented phenomenologically to keep computational costs low.

In the present model, the initiating event of the myogenic response is based on the assumption that the voltage associated with the opening of half of the calcium channels (denoted \( v_1 \)) is a decreasing function of transmural pressure \( \Delta p \) (see Fig. 6 in Ref. 14). Although this assumption is adequate for our purposes here, a number of other factors have been shown to be essential elements in the myogenic response, including TRPC cation channels (1, 36) and cytochrome \( P-450 \) metabolites (35). However, it has been difficult to determine to what extent these factors are involved in the sensory event that initiates the myogenic response, or whether they are essential downstream mediators. One intriguing explanation of the origin of the myogenic response is the involvement of a stretch- or tension-induced membrane depolarization mediated by ENaC that may be part of a complex membrane mechanotransducer (12). It has been proposed that ENaC play a role in mechanotransduction events in a variety of organisms (12) and are essential elements in the renal myogenic response (16, 21, 22), although the available data for involvement in renal autoregulation are by no means conclusive (40). As new data emerge, the present model could be modified to include this alternative mechanism, which would replace the assumption of a pressure-dependent shift in the voltage dependency of calcium channels with a pressure-dependent membrane depolarization driven by an increase in membrane sodium conductance.

To enable the myogenic mechanism to respond to systolic pressure, we incorporated measured asymmetrical time delays and constructed an asymmetrical multicomponent dynamic pattern of calcium channel activation based on unilateral rate sensitivity. Although this description yields behaviors consistent with the observations of Loutzenhiser et al. (28, 29), it must be viewed as an emergent hypothesis that needs experimental verification. Furthermore, if the initiating event in the myogenic response does, in fact, involve ENaC that respond to systolic pressure, then the dynamics of the response of the ENaC to an abrupt increase in tension would have to exhibit unilateral rate sensitivity and time delays similar to those we have assumed for calcium channel activation.

The present model only represents the myogenic response of an isolated segment of the AA near its origin. The transmural pressure is specified a priori, the AA responds with a change in diameter, and the rise in segmental resistance is assumed to alter downstream pressure. Thus, at present, the model does not account for the interactions between the AA myogenic response and the fluid dynamics of the blood flowing through the segment.

Despite its limitations, the present model of a small segment of the AA wall can be used as an essential component in models of integrated renal hemodynamic regulation. For example, a model of the entire AA can be constructed by connecting instances of the AA wall segment model in series. Each segment model can be coupled to its neighbors through gap junctions, which allows representation of the electrotonic conduction along the AA, a phenomenon that is central to coordination of the responses of the individual cells. An appropriate fluid dynamics model would need to be included to relate fluid pressure, fluid flow, and tubular resistance. Also, many of the parameters of the present AA wall segment model will depend upon the location within the AA because of the decrease in intravascular pressure along the vessel. Using an approach similar to Ref. 30, the AA tubular model could then be combined with a model of glomerular filtration (e.g., Ref. 6) and a model of the TGF mechanism (e.g., Ref. 26) to study the interactions between the myogenic and TGF mechanisms in the context of renal autoregulation.

APPENDIX

Model Equations

Ion transport and membrane potential. The smooth muscle cells of the AA can undergo contractions that are determined by the free cytosolic calcium concentration \( C_{ai} \). The sum of \( C_{ai} \) and bound buffer \( C_{aB} \) gives the total calcium concentration \( C_{aT} \), i.e.,

\[
C_{aT} = C_{ai} + C_{aB}
\]

(17)

The free cytosolic calcium and the unbound buffer \( B \) combine to yield \( C_{aB} \) in a reversible reaction that can be represented by

\[
C_{ai} + B \rightleftharpoons C_{aB}.
\]

(18)

Because the kinetics of the calcium-buffer system is substantially faster than other relevant membrane transporters, the above reaction is assumed to be at equilibrium. Thus

\[
C_{aB} = \frac{C_{ai}B}{K_d + C_{ai}}.
\]

(19)

By differentiating Eq. 17 with respect to time and using Eq. 19, one obtains

\[
\frac{dC_{aT}}{dt} = \frac{dC_{ai}}{dt} \left( 1 + \frac{B_pK_d}{(K_d + C_{ai})^2} \right).
\]

(20)

The rate of change of \( C_{aT} \) can be described by the following first-order kinetics

\[
\frac{dC_{aT}}{dt} = -\frac{1}{z_{Ca}FV_{cell}} \frac{g_{Ca}m_{n}(v - v_{Ca}) - k_{Ca}C_{ai}}{k}.
\]

(21)

where \( V_{cell} \) is the cell volume; \( \beta \) is the fraction of cell volume occupied by the cytosol; \( F \) is the Faraday constant; \( z_{Ca} = 2 \) is the valence of the calcium ion; and \( k_{Ca} \) is the first-order rate constant for cytosolic calcium extrusion. Equation 1 is obtained by equating the right-hand sides of Eqs. 21 and 20.

The opening of potassium channels induces a transmembrane \( K^+ \) efflux, which polarizes the cell membrane. To represent the \( K^+ \) flux, we describe the rate of change of the fraction of \( K^+ \) channel open states, denoted \( n \), by first-order kinetics

\[
\frac{dn}{dt} = \lambda_n(n_e(n, C_{ai}) - n),
\]

(22)

where \( n_e \) denotes the equilibrium distribution of open \( K^+ \) channel states. The rate constant \( \lambda_n \) is given by

\[
\lambda_n.
\]
\[ \lambda_n = D \cosh \left( \frac{v - v_3}{2v_4} \right), \]  
(23)

where \( \varphi_n \) determines the rate at which the potassium channels open. This distribution depends on the membrane voltage \( v \) and the free cytoplasmic calcium concentration \( C_{a_4} \).

\[ n_v(v, C_{a_4}) = 0.5 \left( 1 + \tanh \left( \frac{v - v_3}{v_4} \right) \right), \]  
(24)

where

\[ v_3 = - \frac{v_5}{2} \tanh \left( \frac{C_{a_4} - C_{a_3}}{C_{a_4}} \right) + v_6. \]  
(25)

The potential \( v_3 \), which determines the voltage at which half of the potassium channels are open, is a function of \( C_{a_4} \); \( v_4 \) and \( C_{a_4} \) are measures of the spread of the distributions of \( n_v \) and \( v_3 \), respectively.

The rate of change of the membrane potential \( v \) is the sum of transmembrane currents

\[ \frac{dv}{dt} = -I_L - I_K - I_C, \]  
(26)

where \( C \) denotes the cell capacitance. The transmembrane leak, potassium, and calcium currents, denoted \( I_L, I_K, \) and \( I_C \), respectively, are given by

\[ I_L = g_L(v - V_L), \]
\[ I_K = g_K n(v - V_K), \]
\[ I_C = g_C m(u)(v - V_C), \]
respectively, where \( g_L, g_K, \) and \( g_C \) are associated with the respective whole-cell membrane conductances, and \( V_L, V_K, \) and \( V_C \) denote the respective Nernst reversal potentials.

**Hoop stresses.** To approximate experimental measurements (8–11, 32), the hoop stresses associated with the parallel elastic, contractile, and series elastic components, denoted by \( \sigma_x, \sigma_y, \) and \( \sigma_z \), respectively, are given in Ref. 14 by

\[ \sigma_x = \sigma_0 \left( 1 + \tanh \left( \frac{x - x_1}{x_5} \right) \right) + x_a(x - x_3) - x_4 \left( \frac{x_6}{x - x_7} \right)^2 - x_9, \]  
(27)

\[ \sigma_y = \sigma_0 \left( \frac{\exp \left( - \frac{(y - y_0)^2}{2(y_1/(y + y_0)^2)} \right) - y_3}{1 - y_3} \right), \]  
(28)

\[ \sigma_z = u_2 \exp(u_1 u) - u_3, \]  
(29)

where \( \sigma_0 \) is the reference stress that depends on the fraction of cross bridges formed, \( \sigma_0 \).

On the right-hand side of Eq. 27, the first term represents the stiff collagen fibers that come into play for large expansions; the second term represents the compliant elastin fibers that play a role in smaller deformations; the third term represents the large stiffness that arises when the vessel radius is substantially reduced; and the fourth term serves to fit \( \sigma_0 \) to experimental data (32).

**REFERENCES**


