Systolic and mean blood pressures and afferent arteriolar myogenic response dynamics: a modeling approach

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Submitted 6 July 2007; accepted in final form 1 August 2008

Williamson GA, Loutzenhiser R, Wang X, Griffin K, Bidani AK. Systolic and mean blood pressures and afferent arteriolar myogenic response dynamics: a modeling approach. Am J Physiol Regul Integr Comp Physiol 295: R1502–R1511, 2008. First published August 6, 2008; doi:10.1152/ajpregu.00490.2007.—The afferent arteriolar myogenic response contributes to the autoregulation of renal blood flow (RBF) and glomerular filtration rate (GFR), and plays an essential role in protecting the kidney against hypertensive injury. Systolic blood pressure (SBP) is most closely linked to renal injury, and a myogenic response coupled to this signal would facilitate renal protection, whereas mean blood pressure (MBP) influences RBF and GFR. The relative role of SBP vs. MBP as the primary determinant of myogenic tone is an area of current controversy. Here, we describe two mathematical models, Model-Avg and Model-Sys, that replicate the different delays and time constants of vasoconstrictor and vasodilator phases of the myogenic responses of the afferent arteriole. When oscillating pressures are applied, the MBP determines the magnitude of the myogenic response of Model-Avg, and the SBP determines the response of Model-Sys. Simulations evaluating the responses of both models to square-wave pressure oscillations and to narrow pressure pulses show decidedly better agreement between Model-Sys and afferent arteriolar responses observed in cortical nephrons in the in vitro hydronephrotic kidney model. Analysis of mean pressure, the regulatory function dictates that the response be primarily governed by the mean pressure.

Observations in the in vitro perfused hydronephrotic kidney (HNK) model have shown that the afferent arteriole myogenic response to oscillating pressures is primarily determined by the systolic or peak pressure (7). It was postulated that this response characteristic derived from the kinetic attributes of the afferent arteriolar myogenic response. The constriction and dilatation time constants (τ1 and τ2) differed, with τ1 < τ2, as did the time delays for the initiation of the constriction (Δ1) and dilatation (Δ2), with Δ1 < Δ2.

Of relevance to these observations in the HNK, Young and Marsh (16) observed a constriction delay and a constriction time constant in response to step pressure increases in vivo in the rat that are quantitatively similar to that of the afferent arteriole in the HNK. Similarly, in an investigation of the dynamics of step autoregulation, Just and Arendshorst (6) described quantitatively similar values for the delay and the time constant of the constriction response. They also noted a difference in the delays for the constriction and dilatation responses that was qualitatively similar to those observed in the HNK model with Δ1 < Δ2, although the magnitude of the difference was substantially smaller (150 vs. 700 ms). By contrast, the differences in time constants of the constriction and relaxation responses were directionally dissimilar in that τ1 > τ2. However, it is of note that, when afferent arteriolar constriction and relaxation are initiated in the absence of pressure changes through altering TGF activity (via changes in loop of Henle perfusion), dilation responses are noted to be substantially slower than the constriction responses, so that τ1 < τ2, similar to the observations in the HNK (1, 2).

To explore the influence of differences in the delays and time constants between constriction and dilatation, we developed two mathematical models for AR dynamics that replicate the delays and time constants associated with step changes in pressure. The models capture two possible means of eliciting these responses. We have named the first model “Model-Sys,” since its behavior is such that when presented with pulsatile pressures, its overall response is determined by the systolic pressure that it sees. We call the second model “Model-Avg” because its response is determined by the average of the pressure waveform. For comparison, a third model called “Model-Avg-Sens” provides a variation that also responds to average pressure, like Model-Avg, but dynamically is configured similarly to Model-Sys. Model-Avg-Sens, however, does of mean pressure.

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METHODS

Model-Sys. The myogenic mechanism is first modeled as shown in Fig. 1A. In this model, the vascular BP \( p(t) \) is sensed as \( p_s(t) \). This sensed BP is determined as the maximum of \( p(t) \) over an interval of time between \( t - \Delta_2 \) and \( t - \Delta_1 \). The values \( \Delta_1 \) and \( \Delta_2 \) correspond to delay times between an abrupt increase in BP and the onset of AR constriction (\( \Delta_1 \)) and between an abrupt decrease in BP and the onset of AR relaxation (\( \Delta_2 \)) of the afferent arterioles. Thus

\[
p_s(t) = \max_{n(-\Delta_2 < \tau < \Delta_1)} p(\tau)
\]

Equation 1 presumes \( \Delta_2 > \Delta_1 \), which corresponds to the kinetic features of the afferent arteriolar myogenic response that are observed in the HNK (7) and the renal AR response of anesthetized rats (6).

The sensed BP \( p_s(t) \) drives the myogenic response dynamics of the model. First, \( p_s(t) \) is converted to a target conductance \( c_T(t) \). The target conductance value for each value of BP is determined to conform to the AR curves of conductance \( c \) vs. arterial BP \( p \) and equivalently RBF \( q \) vs. arterial BP \( p \) shown in Fig. 2. This curve is similar to those described previously (9). With \( (p_0,q_0) \) and \( (p_1,q_1) \) denoting the pairs of BP and flow values where slope of the AR curve changes, as shown in Fig. 2, we determine the appropriate value of conductance according to

\[
c_T(t) = \begin{cases} 
\kappa \left( q_0/p_1 \right), & p_s(t) > p_1 \\
\kappa \left( p_s(t) - p_0 \right)/\left( p_1 - p_0 \right), & p_0 \leq p_s(t) \leq p_1 \\
\left( q_1/p_0 \right), & p_s(t) < p_0
\end{cases}
\]

Equation 2

In this expression, \( \kappa \) denotes the AR index (ARI; the relative fractional change in flow resulting from a change in pressure).

A first-order differential equation governs the myogenic response dynamics. A time constant \( \tau_1 \) determines the dynamic rate for constriction, and a time constant \( \tau_2 \) determines the dynamic rate for relaxation. With \( q(t) \) denoting the vascular conductance (at the whole kidney level), we have

\[
d(t) = 100 \left( \frac{c(t)}{q_0/p_0} \right)^{1/4}.
\]

Equation 3

The value of \( d(t) \) will be 100% when the conductance \( c \) is at its largest value. To display conductance, we will frequently use a normalized conductance

\[
\gamma(t) = 100 \left( \frac{c(t)}{q_0/p_0} \right).
\]

Equation 4

Finally, the equation

\[
c(t) = c_T(t)p(t)
\]

Equation 5

determines the RBF rate produced by the model.

If we represent the kidney as a single vessel, we may convert conductance values to an (normalized) effective vascular diameter, expressed in percent, via the expression

\[
d(t) = 100 \left( \frac{c(t)}{q_0/p_0} \right)^{1/4}.
\]

Equation 6

not exactly produce the desired response to step changes in pressure. We evaluated the validity of the models by comparing their responses with cortical afferent arteriolar responses observed in the HNK preparation when presented with squarewave pressure waveforms of varying frequency, duty cycle, and duration. We also investigated the impact of variations and differences in delays and time constants in constriction and dilatation via the predictive behavior of the models.
Note also that passive distension as a function of BP is not reflected in the model and therefore will not manifest itself in the model response. Furthermore, TGF is not represented in the model, since the time constants of the dynamics are commensurate with those associated with the myogenic response, but are too short to be associated with TGF.

Model-Avg. Our second model, Model-Avg, is depicted in Fig. 1B. In this model, the target conductance $c_T(t)$ is determined directly from the instantaneous pressure $p(t)$ without any sensing delays. We use Eq. 2 to evaluate $c_T(t)$ but with $p(t)$ substituted for $p_i(t)$ in that expression. If $c_T(t) > c_T(i)$, then relaxation of vascular tone is needed to achieve the target conductance, in which case relaxation dynamics are initiated. If $c_T(t) < c_T(i)$, constriction dynamics are instead excited. Only one or the other of these two dynamic pathways is stimulated at any one time, although future responses may be “in the pipeline” simultaneously in both pathways. The constriction dynamics determines a rate of change in conductance $\delta_s(t)dt$, and the relaxation dynamics determines a rate of change $\delta_r(t)dt$. Each dynamic pathway has associated with it a different delay time; these delays are effected by updating $c_T(t)$ according to

$$ c_T(t) = \delta_s(t - \Delta_s) + \delta_r(t - \Delta_r). \tag{7} $$

Therefore, any constriction change initiated at time $t$ is affected at time $t + \Delta_s$, and relaxation changes take place at time $t + \Delta_r$.

The incremental conductance changes are computed by discretizing the governing differential equations in Eq. 3 with a sampling period of $T$ and assuming that $c_T(t)$ is constant over each sampling period. We have

$$ \delta_s(t + T) = [1 - \exp(-T\tau_s)][(c_T(t) - c_T) - c_T(t)] \tag{8} $$

$$ \delta_r(t + T) = [1 - \exp(-T\tau_r)]c_T(t) - c_T(t) \tag{9} $$

and

$$ c_T(t + T) = c_T(t) + \delta_s(t - \Delta_s) + \delta_r(t - \Delta_r) \tag{10} $$

where $\tau_1$ and $\tau_2$ are the constriction and relaxation time constants, respectively.

Model-Avg-Sens. A third model, Model-Avg-Sens, provides an alternative approach to representing a dynamic response driven by average pressure. Model-Avg-Sens is configured in the fashion shown in Fig. 1A, just as was Model-Sys. However, whereas the “pressure-sensing” block of Model-Sys followed the relation of Eq. 1, in Model-Avg-Sens this is replaced with

$$ p_i(t) = \frac{\text{avg}}{\pi(t - \Delta_s - \Delta_i)} p(t) \tag{11} $$

Otherwise, Model-Avg-Sens and Model-Sys are identical, so that Model-Avg-Sens provides a comparison to Model-Sys that differs only in the pressure quantity that is sensed. However, Model-Avg-Sens does not produce the same responses to step changes in pressure that arise from Model-Sys and Model-Avg. Its response differs in that the onset of the response following a step decrease in pressure remains $\Delta_1$ rather than $\Delta_2$, and the responses themselves are not exactly represented as exponential with a given time constant. These differences arise because of the additional dynamics stemming from the averaging in the sensor. Nonetheless, the step responses are not too dissimilar from those of Model-Sys and Model-Avg, and they provide an alternative dynamic response that is driven by average pressure.

The hydronephrotic kidney. The in vitro hydronephrotic rat kidney model was used to examine cortical afferent arteriolar responses to renal arterial pressure signals (described in detail in Ref. 7). Unilateral hydrenephrosis was induced in male Sprague Dawley rats by ligating the left ureter under halothane anesthesia. Kidneys were harvested after 6–8 wk, when tubular atrophy had advanced to a stage allowing direct visualization of the in situ afferent arteriole in cortical nephrons. The renal artery was cannulated, and the kidney was excised with continuous perfusion and transferred to a heated microscopic stage for in vitro perfusion. Pressure was monitored within the renal artery by a swaged stainless steel catheter placed at the lumen of the renal arterial cannula. Kidneys were perfused with a modified Dulbecco’s minimum Eagle’s medium (Sigma-Aldrich, St. Louis, MO) at 37°C, equilibrated with 5% CO₂, and containing (in mmol/l) 1.6 Ca²⁺, 30 bicarbonate, 5 glucose, 1 pyruvate, and 5 HEPES, using a system that has two pressurized reservoirs that are independently controlled by back-pressure-type regulators (7). A solenoid valve, used to switch between perfusion reservoirs, was activated at varying frequencies or duty cycles using a function generator (Instek, Melrose, MA). Pressure transients were generated using a pulse generator (Directed Energy, Fort Collins, CO) to activate the valve. Changes in diameter in response to changes in renal perfusion pressure were determined by online image processing. Use of animals in the study was in accordance with the guidelines of the National Institutes of Health and the Canadian Council on Animal Care, and the specific protocols were approved by the University of Calgary Animal Care Committee and the Institutional Animal Care and Use Committee of Loyola University and Hines Veterans Administration Hospital.

RESULTS

Response to step changes in pressure. We first consider Model-Sys’s and Model-Avg’s responses to step increases and step decreases in BP. These responses illustrate the differential delays and time constants associated with AR constriction and relaxation. By design, both models produce the same response to (single) step changes in pressure. With a sufficiently long time between successive step changes, the responses of both models are essentially identical.

We excite the model with a BP waveform that rests at 90 mmHg with an increase to 160 mmHg at time 0 s and then a decrease back to 90 mmHg at time 30 s. The model parameters are $\Delta_1 = 0.2$, $\Delta_2 = 1$, $\tau_1 = 4$, and $\tau_2 = 10$ (all times are in s). The ARI is set to $\kappa = 0.1$. We show in Fig. 3A the profile of the models’ responses in terms of normalized conductance $\gamma(t)$ (see Eq. 6), with details at the times of BP change shown in Fig. 3B.

Note that the delay in onset of the vascular response corresponds to $\Delta_1 = 0.2$ for the BP increase and to $\Delta_2 = 1$ for the BP decrease. Note also the differences in dynamic rate between constriction and relaxation due to the disparity in time constants $\tau_1$ and $\tau_2$. This response is quite similar to that seen in the afferent arteriole of the HNK (see Fig. 7B in Ref. 7).

Model-Avg-Sens produces a response to step changes in pressure that differs from that shown in Fig. 3 in two ways. First, the response to a step decrease in pressure commences after a delay of only $\Delta_1$, and not $\Delta_2$ as desired. Second, because of the dynamics present in the averaging of pressure at the pressure sensor, the response is not a pure, single exponential.

Response to a narrow pulse increase in pressure. The diameter of an afferent arteriole in the HNK was measured at a sample rate of 50 Hz when the pressure waveform shown in Fig. 4A was applied at the renal artery. This pressure waveform consists of a sequence of five narrow pulse increases in pressure, with base pressure of ~80 mmHg increased to ~160 mmHg with pulse durations of 300, 200, 100, 50, and then 500 ms. Subsequently, a pulse pressure increase lasting ~10 s is applied. Note that the small notches in pressure seen in Fig. 4A represent the increase in pressure resulting from the reservoir being refilled in the experimental apparatus. A pump controlled by a level sensor refills the reservoir as it empties, and it overshoots the set point. The responses of Model-Sys, Model-
Avg, and Model-Avg-Sens were determined using the measured pressure waveform as the input to the two models. The ARI used in the models was set to $\kappa = 0.1$. Delay values (in s) for the models were set to $\Delta_1 = 0.1233$ and $\Delta_2 = 1.2783$; these delays are the averages of the measured delays in the observed afferent arteriolar responses to each of the six pulses. The time constants were set to $\tau_1 = 3.85$ and $\tau_2 = 3.70$ (in s). The value $\tau_1$ was determined by fitting a single exponential of the form $A + Be^{-\tau t}$ to the observed afferent arteriolar constriction in response to the wide pulse using a least-squares criterion for the fit. The value of $\tau_2$ was determined by averaging the time constants of a single exponential fit to each of the relaxation responses from the first, fourth, and fifth pulses.

The three models' responses are shown in Fig. 4B together with the measured afferent arteriolar diameter in the HNK. Responses are displayed in terms of normalized diameter as a percentage of full constriction. For the simulated models, the diameter associated by each model with the baseline pressure of 80 mmHg is considered to be 0% of full constriction, and the diameter associated with pressure of 160 mmHg is 100% of full constriction. For the afferent arteriolar data, the 0% constriction value was measured from the initial diameter before the pressure pulses, and the 100% constriction value was estimated by extending the exponential fit to the constriction following the wide pressure pulse. Both Model-Sys and Model-Avg produce a response similar to that of the afferent arteriole in the HNK preparation for the wide pulse because that pulse acts effectively like a step change.

Figure 4B shows clearly that Model-Sys’s response is a much better qualitative fit to the observed behavior of the afferent arteriole than is either Model-Avg’s or Model-Avg-Sens’s response. The response of Model-Sys to the narrow pulse pressures is sustained for an amount of time $\Delta_2 - \Delta_1$, which achieves approximately the same constriction as seen in the HNK. Because the other two models respond to the average pressure, the narrow pulse pressures do not cause a substantial constriction.

Response to square-wave pressure of varying frequency. Square-wave pressure patterns of constant 50% duty cycle but with varying frequency were applied at the renal artery, with the afferent arteriolar diameter in response measured at a sampling rate of 50 Hz. A representative pressure pattern that illustrates the character of the models’ responses is shown in

Fig. 3. A: model response to step changes in pressure. B: detail at pressure changes.
Fig. 5A. (Again, the small notches in pressure in Fig. 5A represent refilling of the experimental apparatus’s reservoir.)

The responses of the simulated models were determined when using the measured pressure waveform of Fig. 5A as the input. Parameter values for the models were set to \( \Delta_1 = 0.3, \Delta_2 = 1.0, \tau_1 = 4.0, \) and \( \tau_2 = 5.3 \) (all values in s), with the ARI value set to 0.1. The values of \( \Delta_1 \) and \( \Delta_2 \) are those reported for the afferent arteriole of the HNK (7). The value of \( \tau_1 \) was also obtained from Ref. 7. Because the relaxation was modeled as a double exponential in Ref. 7, we did not have a \( \tau_2 \) value to put directly into the model. Instead, we determined the time constant of a single exponential that best matched the double exponential described in Ref. 7, yielding \( \tau_2 = 5.3 \).

The models’ responses and the measured afferent arteriolar diameter in the HNK are shown in Fig. 5B. Responses are again displayed in terms of normalized diameter as a percentage of full constriction. Diameters corresponding to 0% and 100% constriction for the models were adjusted so that the responses matched the afferent arteriole’s initial diameter (for the low pressure) and the HNK diameter in response to the pressure held at the high value (~160 mmHg).

Notice that the constriction in Model-Sys is at 100% (matching the step pressure increase response) for square-wave pressures oscillating at 6, 4, 2, and 1 Hz. Only for the pressure oscillations at the lowest frequencies of 0.5 and 0.25 Hz does the constriction lessen. Thus, at the higher frequencies, Model-Sys is responding to the systolic pressure. Only when the duration of the low-pressure portion of the cycle exceeds \( \Delta_2 - \Delta_1 = 0.7 \) s is there any relaxation response to that lower pressure. This effect arises because, if the duration of the low pressure is less than \( \Delta_2 - \Delta_1 \) for a square-wave pressure, then the maximum pressure over any time interval of width \( \Delta_2 - \Delta_1 \) is always the high pressure. Therefore, the sensed pressure \( p_s(t) \) always equals the high pressure. At 1 Hz, half the full cycle is 0.5 s, still <0.7, while at 0.5 Hz, half the full cycle is 1 s, which exceeds 0.7. The critical frequency at which half the full cycle equals \( \Delta_2 - \Delta_1 = 0.7 \) s is \( f = \frac{1}{1.4} = 0.7143 \) Hz. For Model-Avg and Model-Avg-Sens, on the other hand, the response level is basically unaffected by pressure frequency and is close to 50% constriction for a pressure waveform whose average value is halfway between the low and high pressures regardless of the frequency. As seen in Fig. 5B, Model-Sys provides a better match to the afferent arteriolar response as assessed in the HNK preparation.

We also measured the average percentage of arteriolar constriction achieved in the HNK preparation for 50% duty cycle square-wave BP waveforms over a range of frequency from 0.2 to 6 Hz. The full-diameter change in response to a step increase of pressure from 80 to 160 mmHg was measured, and the average diameter in response to the 50% duty cycle was measured as a percentage of this full change. Thus 100% constriction corresponds to vascular diameter for 160 mmHg constant BP, and 0% constriction corresponds to 80 mmHg constant BP. This average afferent arteriolar response was measured for a number of trials that varied between \( N = 5 \) and \( N = 19 \) for each frequency. The resulting average constriction values as a function of frequency are shown in Fig. 5C. Also shown are the average percentages of constriction measured in the responses of the two models for the same BP waveforms, using the model parameters given above.

Notice in Fig. 5C that Model-Avg’s and Model-Avg-Sens’s responses remain at ~50% constriction, as expected, since the average pressure is constant and does not vary with frequency. In Model-Sys, only when the frequency falls below 0.7 Hz does the vascular constriction drop below 100%, as predicted.
The general character of the afferent arteriolar response observed in the HNK is much better predicted by Model-Sys than it is by Model-Avg or by Model-Avg-Sens.

**Effect of duty cycle on the extent of constrictive response.** To further test the predictions of the model, we applied a square-wave BP waveform at 0.5 Hz while varying the duty cycle. The duty cycle is the percentage of the square-wave period that the BP is at its larger value. As before, the BP oscillates between 80 and 160 mmHg. In keeping with the above discussion, Model-Sys predicts that full constriction will occur when  $p(t)$ is at 80 mmHg for no longer than $\Delta_2 - \Delta_1$. In the model simulations, we again used the values $\Delta_1 = 0.3$, $\Delta_2 = 1.0$, $\tau_1 = 4.0$, and $\tau_2 = 5.3$. With a difference of $\Delta_2 - \Delta_1 = 0.7$ at a frequency of 0.5 Hz, the critical duty cycle for which $\Delta_2 - \Delta_1$ equals the duration of the low-pressure segment of the pressure is 65%. We expect, then, that, when the duty cycle exceeds 65%, the vascular response of Model-Sys will remain constant at full constriction. Only when the duty cycle falls below 65% should Model-Sys yield a response less than full constriction. On the other hand, we expect Model-Avg and Model-Avg-Sens to respond to the average pressure value, which is determined as the low pressure plus the fraction of the difference between the low and high pressure equal to the duty cycle.

This effect is illustrated when we apply the pressure waveform in Fig. 6A to the three models and to the afferent arteriole of the HNK. This pressure profile starts with a step increase to $\sim 160$ mmHg pressure, allowing complete constriction. The pressure profile then includes three sections in which the pressure undergoes square-wave oscillations with a 50%, then a 30%, and finally a 70% duty cycle. Figure 6B shows the three models’ responses and the response measured in the afferent arteriole. Notice that Model-Avg’s and Model-Avg-Sens’s responses vary approximately proportional to the duty cycle, as one would expect. Model-Sys’s response maintains full constriction for the 70% duty cycle square wave, as expected, and drops for the 30 and 50% duty cycles, but not in a proportionate fashion. The observed response in the HNK shows nearly full constriction for the 70% duty cycle and constriction closer to that of Model-Sys for the lower values of duty cycle. All models match well the response of the afferent arteriole to the step increase of pressure.

We computed for the models the average amount of constriction as duty cycle for the 0.5-Hz square wave was varied between 10 and 90%. These results are shown in Fig. 6C, with the average measured afferent arteriolar responses from a set of seven trials conducted in the HNK. In Fig. 6C, we can observe the proportionate response of Model-Avg and Model-Avg-Sens, and the 100% constriction for Model-Sys for duty cycles >65% as predicted. The observed response matches that of Model-Sys but is dissimilar to that of Model-Avg or Model-Avg-Sens.

**Effect of differences in delay and time constant values.** The above trials used model parameter values of $\Delta_1 = 0.3$, $\Delta_2 = 1.0$, $\tau_1 = 4.0$, and $\tau_2 = 5.3$. These parameter values were derived from afferent arteriolar responses measured in the HNK. However, in Ref. 6, values of $\Delta_1 = 0.39$, $\Delta_2 = 0.53$, $\tau_1 = 5.1$, and $\tau_2 = 2.6$ were reported from in vivo measurements. In the values from Ref. 6, the difference between $\Delta_1$ and $\Delta_2$ is smaller, but in a similar direction, whereas the difference between $\tau_1$ and $\tau_2$ is directionally opposite. Below we investigate the consequences in the differences between these measured parameters.

**Differences in delay.** In Model-Avg and Model-Avg-Sens, differences in the delay values $\Delta_1$ and $\Delta_2$ are expected to have little impact on the response to repeated pressure patterns, such
as those in naturally occurring BP waveforms. To verify this predicted behavior of the models, we applied square-wave pressure oscillations at 6 Hz while the difference $\Delta_2 - \Delta_1$ was varied (with $\Delta_1 = 0.3 \text{ s}$), while keeping other parameter values constant. To suppress differences from disparate time constants, we set $\tau_1 = \tau_2 = 4.0 \text{ s}$.

We measured the percent of full-diameter change observed in the respective models. These results are shown in Fig. 7 as a function of $\Delta_2 - \Delta_1$. Notice that Model-Avg’s response shows no dependence on $\Delta_2 - \Delta_1$. The percentage of vascular constriction remains just slightly below 50%. For small $\Delta_2 - \Delta_1$ values, Model-Sys’s response is much like that of the average, but, as $\Delta_2 - \Delta_1$ approaches the critical value of half the period of the oscillation (which here is $\Delta_2 - \Delta_1 = 0.0833 \text{ s}$), the response becomes determined solely by the systolic pressure of the oscillation. Model-Avg-Sens’s response changes with $\Delta_2 - \Delta_1$ in a fashion similar to that of Model-Sys, but the constriction is only $\sim 60\%$.

**Differences in time constant.** The effect of variation in time constants and the effect of differences between $\tau_1$ and $\tau_2$ are more difficult to ascertain by inspection of the equations that define the models. To see the effects, we ran the models with no difference in constriction and relaxation delay ($\Delta_1 = \Delta_2 = 0.3$) while varying $\tau_2$ between 0.4 and 20 with $\tau_1 = 4.0 \text{ a fixed constant}$. The pressure waveform applied is a square-wave pressure oscillating at 6 Hz. The results in terms of the percent of full-diameter change are shown in Fig. 8.

With $\Delta_1 = \Delta_2$ and $\tau_1 = \tau_2$ (which corresponds to $\tau_2 = 4.0$ in Fig. 8), we see that Model-Sys’s response is 50% of the total. For smaller $\tau_2$ values, relaxation is faster than constriction, and the total response favors relaxation, with less of a percentage of full constriction. When $\tau_2 > \tau_1$, constriction is favored, and the response is closer to full constriction. However, rather long relaxation time constants are needed to approach a response determined by systolic pressure in this case. Indeed, $\tau_2 > 20$ is required. With $\Delta_1 = \Delta_2$, Model-Avg’s and Model-Avg-Sens’s responses remain close to Model-Sys’s, with no appreciable difference. The amount of full constriction is between 40 and 60% for $\tau_2$ values within 50% of $\tau_1$ for these parameter settings. This holds true for all three models. For Model-Sys, the effect that causes systolic pressure to trigger the response is much more sensitive to differences in delay than to differences in time constant.

**Model behavior when driven by normal BP waveforms.** For naturally occurring pressure waveforms, we have pulsatile pressures whose fundamental frequency is at the heart rate. In the rat, this is 4 to 6 Hz. For such pulsatile waveforms, we expect Model-Sys to respond to the systolic pressure as long as $\Delta_2 - \Delta_1$ is sufficiently long so that the maximum pressure, or a pressure close to the maximum, persists within each sensing window. Clearly if $\Delta_2 - \Delta_1$ exceeds the pulse period, this will happen. Because the peak of each pulse does not persist for a full half-cycle (as with a square-wave pressure), the critical value for $\Delta_2 - \Delta_1$ will be something longer than half the fundamental period.

\[ \frac{1}{2f_{hr}} < \delta_c < \frac{1}{f_{hr}} \]  

(12)

with $f_{hr}$ denoting the heart rate frequency, Model-Sys will be triggered entirely by systolic pressure. Equivalently, the critical frequency $f_{cr}$ above which Model-Sys shows complete systolic triggering lies in the range

\[ \frac{1}{2(\Delta_2 - \Delta_1)} < f_{cr} < \frac{1}{(\Delta_2 - \Delta_1)}. \]

(13)

To examine the impact that different parameter values have on vascular response when the models are presented with natural pressure waveforms, we constructed the following pressure profile. A 40-s segment of BP measured in the rat was selected as a template pressure waveform. This pressure waveform was rescaled and shifted to change its average and its systolic pressure independently. Six segments of these scaled and shifted pressures were concatenated into a 240-s waveform such that for the first 120 s the systolic pressure remains constant while the average pressure changes, and such that for the last 120 s the average pressure remains constant while the systolic pressure changes. This pressure profile was applied to the models for two sets of parameters. The first set has $\Delta_1 = 0.3, \Delta_2 = 1.0, \tau_1 = 4.0$, and $\tau_2 = 5.3$, which are derived as noted before from afferent arteriolar responses measured in the HNK. The second set of simulations uses values of $\Delta_1 = 0.39, \Delta_2 = 0.53, \tau_1 = 5.1$, and $\tau_2 = 2.6$ as reported previously (6). The pressure waveform is presented in Fig. 9A, and the corresponding vascular response (in normalized conductance) is presented in Fig. 9B for the first set and in Fig. 9C for the second.
One can see in Fig. 9 that Model-Sys maintains relatively constant response when systolic pressure is constant (even when average pressure is changing) but changes in response to shifts in systolic pressure (even when average pressure is constant). The other two models, as expected, respond to the average pressure, independent of changes in systolic pressure, and it shows relatively little variation in its response when systolic pressure changes but average pressure remains constant. These effects occur for both parameter sets. Although heart rate frequency in this pressure waveform fluctuates modestly, it remains in the range of 5–6 Hz. The critical value for systolic triggering in Model-Sys at these frequencies would be somewhere in the range of 0.08–0.2 s. For the in vitro perfused HNK (the first model set), 0.7, which is much longer than this range. For the in vivo parameters from Ref. 6, 0.14. This value lies within the range in which the critical delay difference is expected, and indeed we see a response triggered by systolic pressure in the simulation of Model-Sys.

DISCUSSION

Our models form two possible ways to generate mathematically a response to step changes in pressure that matches those observed in vivo and in vitro. Tests of the behavior of these models in response to other pressure waveforms show that the behavior of Model-Sys, the model in which autoregulation is triggered by systolic pressure, is close to the behavior of the cortical afferent arterioles, as assessed in the HNK preparation, in a variety of circumstances. The behaviors of Model-Avg and Model-Avg-Sens, which respond to average pressure, are unlike that seen in these different arterioles. Although we did not construct these models based upon underlying physical principles of the biochemistry and biophysics in the kidney, each model provides a description of the aggregate behavior of the myogenic AR response. Therefore, the stronger predictive capabilities of Model-Sys support the hypothesis discussed in Ref. 8 that systolic pressure determines the extent of the myogenic response, rather than average pressure, at least for response rates commensurate with time constants on the order of 1–10 s.

Certainly the direct empirical observations that we report here are limited to myogenic response behaviors seen in the cortical afferent arterioles in the HNK preparation. Afferent arterioles in other sections of the kidney and also interlobular arteries exhibit myogenic response as well, and the kinetics of this response in other portions of the kidney’s vascular tree may differ from that seen in the cortical afferent arterioles. The overall effect for autoregulation that combines the relative contributions of the various segments of the vasculature may be more complicated than what is predicted by our models. However, it is rather interesting that Model-Sys, which was developed to mimic the response to a single step change in pressure, provides such a strong qualitative match to the type of behavior exhibited in the HNK’s cortical afferent arterioles in response to successive step changes in pressure at different rates and duty cycles.

Fig. 8. Percentage of vascular constriction as $\tau_2$ is varied for 6-Hz square-wave pressure; 100% constriction corresponds to the vascular diameter for 160 mmHg constant blood pressure (BP), and 0% constriction corresponds to 80 mmHg constant BP. Solid line: Model-Sys; broken line: Model-Avg; dash-dot line: Model-Avg-Sens.

Fig. 9. Model’s normalized conductance response to scaled and shifted natural pressure. A: pressure waveform vs. time (in s). B: response using first parameter set (from the HNK). C: response using second parameter set (measured in vivo).
One could further ask whether there are other models that replicate the observed behavior yet still achieve autoregulation in response to average pressure, ask what type of physical mechanism could cause the observed behavior, and ask whether the behavior we have observed is supported by observations made in vivo.

First, consider the possibility of other models for the AR behavior, different from Model-Avg, that are triggered by average pressure and have step responses that display the proper delays and time constants, and yet have behavior that matched the afferent arteriolar responses observed in the HNK to narrow pulse and square-wave pressure waveforms. We believe that such models cannot exist. Any AR mechanism that is fundamentally driven by the average input value will of necessity have a response that depends on all portions of the input waveform, since the average itself depends on all portions. The various experiments reported herein reiterate, as was shown previously (7), that the afferent arteriolar response does not depend on the entire input waveform. Although there are likely other average-responding models, different from our Model-Avg, that may have appropriate step responses, these should all behave qualitatively similarly to Model-Avg in the face of the narrow pulse and square-wave pressures by responding to the average value. Such a response would be inherently different from that of the afferent arteriole, as observed in the HNK.

Thus, Model-Sys remains a viable candidate to describe the myogenic AR behavior that we observed in the afferent arteriole of the HNK, whereas Model-Avg has been eliminated by these tests. As yet unknown, however, are what physical aspects of the myogenic mechanism in these arterioles enable it to respond in the way that is replicated by Model-Sys, and whether or not the effects can be replicated in vivo. For the dynamics of Model-Sys to be a direct reflection of the myogenic response, there would need to be some physical process in the microcirculation that produces a sensed pressure that depends only on the systolic pressure in pulsatile waveforms. One possible means to achieve a response of this character is a process that “latches” sensed increases in pressure for a time given by $\Delta_2 - \Delta_1$, with an overall throughput delay of $\Delta_1$ in the response. Such a sensory mechanism has not yet been demonstrated.

Nonetheless, several prior studies, some in vivo, are supportive of the existence of sensory mechanisms that are sensitive to systolic pressure. In a study undertaken in the isolated perfused kidney, Nobiling et al. (12) observed increases in renal vascular resistance in response to pulse pressure increases while average pressure was held constant. Although this study primarily considered effects on renin release caused by pulse pressure, it also noted that the myogenic response was evoked by pulsation, with an increased vascular resistance under pulsation (with average pressure constant) that was absent after administration of calcium channel blockers. Also, Naftz et al. (11, 13) observed effects on renin release and urine flow that depended on pulse pressure via a study in conscious dogs in which average pressure was held constant, suggesting a sensing mechanism triggered by variations in peak or pulse pressure and confirming in vivo the observations of Nobiling et al. in the isolated perfused kidney. Note too that the same sensing mechanism is thought to drive both renin secretion and the myogenic response (3, 4). Such studies provide a precedent for the sensing of pressure peaks in oscillations, and not only average pressure, within the context of renal hemodynamics.

Model-Sys also predicts that, for pulsatile pressure waveforms, the critical parameter that enables a response to systolic pressure is the difference in delays $\Delta_2 - \Delta_1$ and how it relates to heart rate. The difference between time constants $\tau_1$ and $\tau_2$ has much less impact on whether or not systolic pressure controls the extent of response, as was conjectured previously (7). In the rat, the average difference $\Delta_2 - \Delta_1$ was reported to be $\sim 0.7 \text{ s}$ in Ref. 7 and 0.14 s in Ref. 6. These values correspond to critical frequencies in the range between 0.71 and 1.42 Hz (for $\Delta_2 - \Delta_1 = 0.7$) and between 3.57 and 7.14 Hz (for $\Delta_2 - \Delta_1 = 0.7$), using the Eq. 13. The normal heart rate for the rat lies in the range of 5–8 Hz, so that in most cases these values for $\Delta_2 - \Delta_1$ would result in a myogenic response triggered by systolic pressure. However, the $\Delta_2 - \Delta_1$ value from Ref. 6 is close to the lower limit that would cause full systolic triggering. Nonetheless, we saw in simulations of Model-Sys that its vascular response was triggered by systolic pressure for these parameter values when driven by a natural pressure waveform measured in the rat.

For the dynamics of Model-Sys to guarantee triggering of the myogenic response by systolic pressure in pressures at heart beat frequency $f_{hb}$, the delay difference $\Delta_2 - \Delta_1$ should be at least as large as $1/f_{hb}$. To avoid compromising the ability of the vasculature to adjust to lowered pressures, $\Delta_2 - \Delta_1$ should not exceed this value by a large amount. This reasoning predicts a value for the difference in delays given approximately by

$$\Delta_2 - \Delta_1 \approx \frac{1}{f_{hb}} \quad (14)$$

In the rat, $f_{hb}$ is $\sim 6 \text{ Hz}$, corresponding to a value of $\Delta_2 - \Delta_1 = 0.17 \text{ s}$. The values of $\Delta_1$ and $\Delta_2$ reported in Ref. 6 yield $\Delta_2 - \Delta_1 = 0.14$, close to this number. The value $\Delta_2 - \Delta_1 = 0.7$ for the rat afferent arteriole in the HNK, as reported in Ref. 7, is, however, several times greater. The threshold value for $\Delta_2 - \Delta_1$ associated with Model-Sys responding to systolic pressure changes with $f_{hb}$. For instance, for $f_{hb} = 10 \text{ Hz}$, the approximate heart rate of the mouse, $\Delta_2 - \Delta_1 > 0.1 \text{ s}$ is needed for Model-Sys to respond to systolic pressure, whereas one needs $\Delta_2 - \Delta_1 > 0.5 \text{ s}$ for $f_{hb} = 2 \text{ Hz}$ (the heart rate of the dog) and $\Delta_2 - \Delta_1 > 1 \text{ s}$ for $f_{hb} = 1 \text{ Hz}$ (the human heart rate). To our knowledge, these delay values and their differences have not been measured directly, nor inferred from other measurements, in animals other than the rat. Were such values available, it would be interesting to see if they change with heart rate in the manner that Model-Sys suggests.

The models presented in this paper include first-order linear dynamic responses to pressure changes. Often, representations of autoregulation dynamics, both for myogenic responses and TGF responses, are expressed as second-order linear dynamic systems to admit damped oscillations in the response waveforms. Such is the case, for instance, in Ref. 15. Indeed, one can observe oscillations in the relaxation response of the afferent arteriole in Fig. 4B while the model responses do not show these oscillations. If a higher-order dynamic response is incorporated into Model-Sys to manifest such oscillations, the triggering by systolic pressure will persist, since this property stems from the pressure “sensing” portion of the model and not
the dynamic character. To implement such a model, dilatory and constrictive responses have to be properly coordinated in switchings between the two modes.

Physiologically based mathematical models that combine myogenic and TGF dynamics include those presented in Refs. 5 and 10. Our preliminary assessment of the model in Ref. 5 suggests that the pressure-sensing portion of Model-Sys may be incorporated into this physiologically based model, which would then include a myogenic mechanism triggered by systolic pressure. Investigations of model response, which combines the slower TGF mechanism with the systolic triggered myogenic response, would suggest whether the response of the two mechanisms operating in tandem would be determined primarily by systolic or average pressure, or perhaps by both. Such studies are left as future work.

**Perspectives and Significance**

The pressure within the glomerular capillaries, and therefore the pressure within the preglomerular vasculature, is oscillatory in character (2a). Because RBF and GFR exhibit autoregulation, we know that the preglomerular afferent arteriole responds with a graded vasoconstriction to increases in this oscillating pressure signal. This myogenic response plays an essential role not only in autoregulation, but also in protecting the glomerulus from the damaging effects of high pressure. Accordingly, an understanding of how the afferent arteriole responds to oscillating pressure signals is of significant interest and of physiologic importance. Elevations in the peak or systolic BP signal are most closely correlated with hypertensive renal injury (1a, 13a). We have previously shown that the afferent arteriole of the in vitro perfused HNK preparation responds exclusively to this signal (7) and have suggested that this is an important property contributing to renal protection against hypertensive injury (8). In the present study, the determinants of this capability are investigated using a mathematical modeling approach. A key finding is that the difference in the delays in the initiation of the vasoconstrictor and vasodilator responses is critical (Fig. 7), whereas differences in the time constants have almost no effect (Fig. 8). Assuming that physiological or pathophysiologic conditions may impact on the nature of these two delays, mechanisms may exist to alter the afferent arteriolar response to elevations in systolic vs. mean BP. Thus, marked increases in the delay in vasoconstriction or decreases in the delay in vasodilation might be anticipated to result in an increased transmission of the systolic BP transient to the glomerulus. Because the vasculature would still respond to pressure changes, autoregulation may still be observed, although renal protection against elevations in the systolic pressure would be impaired.

Our suggestion that myogenic tone of the afferent arteriole is normally set to the level of the systolic BP signal is based primarily on observations in the in vitro perfused HNK model. The responses of the Model-Sys to a wide range of pressure signals correspond closely to those of the HNK preparation. Future studies applying this model to in vivo data will provide a unique way of evaluating the applicability of these concepts to the intact kidney (e.g., Fig. 9). When combined with in vivo assessments of the kinetic parameters subtending pressure-induced renal vascular responses, this approach may provide further insights into how the renal vasculature responds to oscillating pressure signals and how such responses might be altered in health and disease.

**REFERENCES**


