Renal Myogenic Response
Kinetic Attributes and Physiological Role

Rodger Loutzenhiser, Anil Bidani, Lisa Chilton

Abstract—The kinetic attributes of the afferent arteriole myogenic response were investigated using the in vitro perfused hydronephrotic rat kidney. Equations describing the time course for pressure-dependent vasoconstriction and vasodilation, and steady-state changes in diameter were combined to develop a mathematical model of autoregulation. Transfer functions were constructed by passing sinusoidal pressure waves through the model. These findings were compared with results derived using data from chronically instrumented conscious rats. In each case, a reduction in gain and increase in phase were observed at frequencies of 0.2 to 0.3 Hz. We then examined the impact of oscillating pressure signals. The model predicted that pressure signals oscillating at frequencies above the myogenic operating range would elicit a sustained vasoconstriction the magnitude of which was dependent on peak pressure. These predictions were directly confirmed in the hydronephrotic kidney. Pressure oscillations presented at frequencies of 1 to 6 Hz elicited sustained afferent vasoconstrictions and the magnitude of the response depended exclusively on the peak pressure. Elevated systolic pressure elicited vasoconstriction even if mean pressure was reduced. These findings challenge the view that the renal myogenic response exists to maintain glomerular capillary pressure constant, but rather imply a primary role in protecting against elevated systolic pressures. Thus, the kinetic features of the afferent arteriole allow this vessel to adjust tone in response to changes in systolic pressures presented at the pulse rate. We suggest that the primary function of this mechanism is to protect the glomerulus from the blood pressure power that is normally present at the pulse frequency. (Circ Res. 2002;90:666–677.)

Key Words: renal hemodynamics ▪ myogenic vasoconstriction ▪ frequency domain analysis ▪ renal autoregulation ▪ mathematical modeling

Fluctuations in renal perfusion pressure over a range of 80 to 200 mm Hg result in proportional alterations in renal vascular resistance (RVR) such that renal blood flow (RBF) remains constant. The site of this autoregulatory RVR response is confined to the preglomerular microvasculature.1 As a consequence, glomerular capillary pressure (Pgc) and glomerular filtration rate (GFR) exhibit parallel autoregulation. Thus, renal autoregulation is believed to simultaneously insulate renal function from variations in blood pressure (BP) and to protect glomerular capillaries from potential barotrauma. Indeed, impaired renal autoregulation2,3 and the resultant elevation in Pgc4,5 are thought to play a predominant role in the pathogenesis of the progressive glomerular injury and sclerosis that is observed in most chronic renal disease states, including diabetic nephropathy.

Renal autoregulation is mediated by two intrinsic mechanisms, a slow component involving a signal derived from the early distal tubule, tubuloglomerular feedback (TGF), and a rapid component thought to be due to myogenic vasoconstriction. Transfer function analysis of the relationship between RBF (output) and BP (input) has been used to characterize the dynamic properties of renal autoregulation in the intact kidney.6 Frequency domain analysis has additionally allowed a characterization of the dynamic operating characteristics of the two control mechanisms. The fast, myogenic component operates at 0.1 to 0.3 Hz and is seen in models lacking TGF.7,8 The slower component, operating at frequencies less than 0.05 Hz, is furosemide-sensitive and is blocked by acute ureteral occlusion, properties consistent with its identification as TGF.9,10 Thus, the operating range of the myogenic component is believed to represent the upper limit at which the renal vasculature can compensate for BP fluctuations and maintain a constant RBF. Below the heart rate, the BP power spectrum exhibits a 1/f relationship, with more power at slow frequencies (f).11,12 The autoregulatory mechanisms are sufficiently fast to buffer BP power below 0.1 Hz. Thus, according to the current interpretations, pressure oscillations occurring faster than 0.3 Hz are handled passively by the preglomerular vasculature and would be transmitted to the downstream glomerular capillaries. Of interest in this regard,
the heart beat itself is responsible for the major oscillation in the BP at frequencies above 0.1 Hz and the pulse contributes a substantially greater fraction of the total BP power than that derived from lower frequency signals. The heart rate of the rat (4 to 6 Hz) is more than an order of magnitude faster than the myogenic operating frequency. How can a system operating at a maximal rate of 0.3 Hz protect the glomerulus from the BP power that is normally present at the pulse rate? Current concepts regarding dynamic renal autoregulation do not address this important question.

We used the in vitro perfused hydronephrotic kidney model to investigate these issues. Previous studies, applying frequency domain analysis, demonstrated that the operating frequency of the fast component of autoregulation of this preparation is identical to that of the normal kidney. In the present study, we sought to determine if the kinetic features of myogenic vasoconstriction, assessed at the level of the afferent arteriole, could account for the dynamic characteristics of this component and to examine how these kinetic attributes of the afferent arteriole might allow glomerular protection from BP power that is generated at frequencies above the myogenic operating range. To accomplish these goals, we developed a mathematical model based on the kinetic and steady-state attributes of the arteriolar response to pressure and used this model to construct transfer functions corresponding to the dynamic autoregulatory features. This model was then used to predict the impact of high-frequency pressure oscillations on afferent arteriolar tone and the predictions obtained were tested in the hydronephrotic kidney preparation. Our findings provide novel insights into the mechanisms protecting the glomerulus from BP transmission and challenge the existing concepts concerning the physiological role of the renal myogenic response.

Materials and Methods

An adaptation of the in vitro hydronephrotic rat kidney model was used to examine the kinetic attributes of the afferent arteriolar response to renal arterial pressure (RAP). Unilateral hydronephrosis was induced in male Sprague Dawley rats by ligating the left ureter under halothane anesthesia. Kidneys were harvested 6 to 8 weeks, when tubular atrophy had advanced to a stage allowing visualization of the microvasculature. The renal artery was cannulated and the kidney was excised with continuous perfusion. Kidneys were perfused with a modified Dulbecco’s Minimum Eagle’s Medium (GIBCO) at 37°C, equilibrated with 5% CO2 and containing (in mmol/L) 1.6 Ca2+, 30 bicarbonate, 5 glucose, 1 pyruvate, and 5 HEPES. Kidneys were allowed 1 hour to recover before initiation of experimental protocols.

The kidneys were perfused in a temperature-controlled chamber on an inverted microscope as described previously, but using a perfusion system that has two pressurized reservoirs (online Figure 1, which can be found in the online data supplement available at http://www.circresaha.org). The pressure within each reservoir was independently controlled by a back-pressure type regulator (described in Loutzenhiser). A solenoid valve was used to switch between perfusion reservoirs. Using this device a pressure change within each reservoir. Changes in diameter in response to changes in renal perfusion pressure (measured within the renal artery) were determined by online image processing at a sampling rate of 6 to 8 Hz.

The kinetic characteristics of the afferent arteriolar myogenic response and steady-state relationship between RAP and afferent diameters were used to construct a mathematical model of renal autoregulation. Results obtained with this model were then compared with the dynamic features of renal autoregulation observed in the intact kidney. To assess dynamic renal autoregulation in vivo, rats were anesthetized and a chronic blood flow probe (Transonic Systems) was placed on the left renal artery. An indwelling blood pressure sensor (model TA11PA-C40, Data Sciences) was implanted intraperitoneally and the sensor’s catheter was placed in lumen of the descending aorta below the level of the renal artery, as described previously. At least 1 week was allowed for recovery from surgery and establishment of the flow probe. Two simultaneous 1-hour recordings of BP and RBF were obtained on separate occasions (at least 24 hours apart) using a sampling rate of 200 Hz. These data were analyzed by fast Fourier transformation and frequency domain analysis as previously described.

Data are expressed as mean±SEM (standard error of the mean). The number of replicates (n) refers to the number of vessels. Differences between means were evaluated by ANOVA and Student’s t test. The Bonferroni correction was applied for multiple comparisons. A value of P<0.05 was considered significant. Use of animals complied with the regulations suggested by the National Institutes of Health and the Canadian Council on Animal Care.

Results

Figure 1 depicts photomicrographs of a hydronephrotic kidney perfused in vitro at an RAP of 80 (top) and 180 (bottom) mm Hg. Note the marked vasoconstrictor response of the afferent arteriole to elevated RAP. In contrast to the afferent arteriole, the efferent arteriole responds passively to elevated pressure. To construct a mathematical model of this myogenic response, we first determined the kinetics of the vasoconstriction by exposing kidneys to a rapid increase in RAP from 80 to 160 mm Hg. The kinetics of the vasoconstriction were then assessed when the RAP was returned to 80 mm Hg. The mean diameters were 15.0±1.1 μm at 80 mm Hg and 9.6±1.2 μm at 160 mm Hg (n=8). The time course for the responses, expressed as the percent of the maximal response, are presented in Figures 2A and 2B. The vasoconstrictor response exhibited an initial delay of ~0.3 seconds, approximated from the combined responses of the 8 vessels studied (Figure 2A). This delay was followed by a monotonic contractile response that had a time constant of 4 seconds. The vasodilator responses exhibited more variability and oscillations were frequently observed. However, in each case, the vasodilation exhibited an initial delay of approximately 1.0 second. The mean data representing the vasodilation (filled circles, Figure 2B) could be fit by a bi-exponential function with coefficients of 0.55 and 0.45 and time constants of 1 and 14 seconds, respectively.

To further develop the model, we examined the relationship between steady-state diameter and RAP over perfusion pressures ranging from 60 to 180 mm Hg. In these studies, pressures were held for at least 1 minute at each step. As illustrated in Figure 3A, the afferent arteriole did not constrict until RAP was elevated above 80 mm Hg. At pressures above this threshold, vessels responded with graded pressure-dependent decreases in diameter. The changes in diameter at RAPs between 80 and 180 mm Hg could be fit to by simple quadratic equation (%
change_{max} = 68 - (1.05 \times \text{RAP}) + (0.002 \times \text{RAP}^2)

The myogenic response of the afferent arteriole did not exhibit rate dependence. This is illustrated by the original tracing in Figure 3B and mean data in Figure 3C (n=9). As depicted, the change in afferent arteriolar diameter that was observed when RAP was increased from 80 to 160 mm Hg over a 3-minute interval was identical to that observed when the same RAP change was presented as a step (P=0.94). If a rate-dependent component of the myogenic response were present one would anticipate a biphasic response to the pressure step, characterized by an initial peak (P) of the pressure-induced vasoconstriction to levels exceeding that elicited by the slow-pressure ramp.

Using the above equation and the parameters derived from our kinetic studies (Figure 2), we developed a simple mathematical model. When pressure was increased (at t=0), an initial delay of 0.3 seconds was imposed. Thereafter, the diameter at any given time (D_t) was calculated as the diameter at t=0 (D_0) plus the incremental change in diameter (eg, D_t = D_0 + dD). For pressure increases dD = (D_0 - D_0) (1 - e^{-(t-0.3)/4}), where D_0 is the steady-state diameter. When RAP was decreased at t=0, an initial delay of 1.0 second was imposed. Thereafter, the D_t was calculated as above where dD = (D_0 - D_0) (1 - 0.55(1 - e^{-0.15t}) - 0.45(1 - e^{-0.15t})). Ongoing processes were allowed to continue during the delays. For example, during the 1-second delay for vasodilation the previously initiated vasoconstrictor response was allowed to proceed. A schematic diagram of the program is presented in online Figure 4. To relate the calculated pressure-induced change in diameter to changes in RBF, we assumed that the pressure-dependent resistance (R_{myogenic}) represented 60% of the total renal vascular resistance (R_{total} = 0.6 R_{myogenic} + 0.4 R_{constant}) and calculated the change in this component of resistance from the 4th power of the change in afferent arteriolar radius (R_{myogenic}/R_{myogenic} = r/r^4). As depicted in Figure 4A, this simple model exhibited steady-state autoregulation to a step increase in RAP.

A goal of our study was to relate the kinetic features of the arteriolar myogenic response to the dynamic characteristics of renal autoregulation observed in vivo using frequency domain analysis. This required a calculation of fractional gain and phase as a function of frequency. To accomplish this end, sinusoidal pressure waves of differing frequencies were passed through the mathematical model. Figure 4B illustrates responses to RAP waves presented at 1.0 and 0.05 Hz. At a frequency of 1.0 Hz, the change in pressure occurs too rapidly to evoke compensatory adjustments in diameter within each cycle. Thus, changes in RBF occur in phase with the changes in RAP (phase=0) and the change in RBF is proportional to the change in RAP (fractional gain=1). At a frequency of 0.05 Hz, the arteriole adjusts tone within each cycle and compensates for the change in RAP. In this example, a 60% change in RAP (input) elicited only a 16% change in RBF.
The modest changes in RBF observed during the cycle reflect the limitations imposed by the kinetics of the myogenic response. Within each cycle, the change in RBF precedes the change in RAP resulting in a positive phase angle of 1.7 radians. Using this approach, gain and phase angle were calculated at frequencies ranging from 0.001 to 1.0 Hz.

To relate these findings to the observed myogenic kinetics in the intact kidney, dynamic renal autoregulation was studied in chronically instrumented rats (n=12). Arterial pressure and RBF data records of 30 minutes in length were collected at a sampling rate of 200 Hz. After low-pass filtering and resampling to a 20-Hz rate, the records were broken into segments of 8192 samples (approximately 7 minutes), with successive segments overlapping by 50%. Using fast Fourier transforms applied to each data segment, transfer functions for fractional gain and phase angle were calculated for the data record using spectral analysis as described in the literature.8–10 Figure 5B depicts the transfer functions obtained in the conscious rat preparation and the results obtained from the mathematical model. The normalized gain (fraction of the gain at 1 Hz) is used to facilitate comparisons. The myogenic operating frequency obtained with the model was 0.3 Hz. This value is reasonably close to the operating frequency of ~0.25 Hz seen in the intact kidney. However, a number of differences are apparent. The model did not incorporate TGF. Thus, the signal seen at ~0.06 Hz in the intact kidney was not predicted by the model. Further, the model did not incorporate resonance interactions with vasomotion or passive distention, which may contribute to the resonance peak near 0.3 Hz and the gains in excess of 1.0 at higher frequencies (eg, reference 10).

It is suggested that alterations in pressure occurring faster than the operating frequency are handled passively by the renal vasculature and transmitted downstream without attenuation. This interpretation is based on the observed fractional gains above 1.0 at frequencies greater than 0.3 Hz. Indeed, our mathematical model demonstrates that the kinetics of the myogenic response do not allow compensation during each cycle at high frequencies (Figure 4B). However, in spite of the gain of 1.0, our model indicates that high-frequency pressure oscillations elicit a sustained afferent arteriolar vasoconstriction, rather than evoking a passive response. This is illustrated by Figures 6A and 6B. Figure 6A depicts the response of the model to pressure pulses of 1-second duration. The contraction occurs because the response to the pressure stimulus continues during the 1-second delay in vasodilation. When presented with a train of such pulses, the
contractile responses summate. Thus, the model predicts that pressure oscillations presented at rates above the operating frequency will elicit a sustained vasoconstriction. This behavior is also apparent in Figure 4B. Note that although diameter does not change during each cycle when a pressure wave is presented at 1.0 Hz, the afferent arteriole was not dilated, but rather exhibited a constriction to ~50% of basal diameter. This behavior is further illustrated in Figure 6B, in

Figure 3. Steady-state diameters at RAPs of 60 to 180 mm Hg (A). Note graded vasoconstriction was elicited at RAPs above 80 mm Hg. Percent change from basal (60 mm Hg) diameter were fit a simple quadratic equation. Tracing (B) and mean data (C, n=9) illustrate that the myogenic response of the afferent arteriole did not exhibit rate-dependence. P indicates peak response over the initial 30 seconds at maximal RAP; S, sustained response seen after the first minute.

Figure 4. Steady-state (A) and dynamic (B) autoregulatory responses of mathematical model (see text for details). B, Responses to oscillating pressure signals presented at 1.0 and 0.05 Hz and calculation of fractional gain and phase angle at each frequency.
which a pressure increase presented at 2 Hz is shown to result in a vasoconstriction. The magnitude of this response was similar to that elicited by a sustained pressure step, suggesting that it is the peak pressure that determines the magnitude of the vasoconstriction. This latter prediction is further illustrated by Figures 6C and 6D, in which diameter responses are evoked by changes in systolic pressure but not by changes in mean or diastolic pressure. Note that in Figure 6D, an
increase in systolic pressure elicited afferent arteriolar vasoconstriction even when mean pressure was maintained constant by decreasing diastolic pressure. If correct, these predictions of the model would explain how the afferent arteriolar myogenic response might be able to protect the glomerulus from pressure oscillations occurring faster than its operating frequency. As discussed earlier, the pulse rate of the rat is 4 to 6 Hz and represents a major peak in the BP power spectrum.

These predictions were tested using the hydronephrotic kidney preparation. The tracing presented in Figure 7A illustrates an afferent arteriolar response to a single pressure pulse of 1-second duration. Figure 7B illustrates the sustained vasoconstriction elicited by a 2-Hz oscillating pressure signal. Moreover, as shown by this tracing, the vasoconstrictor response to a static pressure step from 80 to 140 mm Hg was similar in magnitude to that elicited by an oscillating signal of 140/80 mm Hg (2 Hz, measured within the renal artery), as predicted by the model (Figure 6B). Figure 7C illustrates that the afferent arteriole is able to respond to pressure oscillations presented at the heart rate frequency (6 Hz). In this experiment, the static pressure in the 2 reservoirs was first set to 70 and 140 mm Hg. The solenoid was then activated to elicit an oscillating pressure signal at the cannula tip (eg, online Figure 2B).

The postulate that myogenic tone is determined exclusively by systolic pressure was further examined by the experiments summarized in Figure 8. In these studies, the effects of independently altering systolic versus diastolic or mean pressure on afferent arteriolar tone was examined. Pressure oscillations were presented at 1.5 Hz and perfusion pressures were measured within the renal artery (eg, online Figure 3). In Figure 8A, systolic pressure was increased and diastolic pressure was decreased to maintain a constant mean perfusion pressure (99.2±0.2, 99.4±0.4, and 100.2±0.4 mm Hg; P=0.11, n=10). Despite the fact that mean pressure did not change, the afferent arteriole constricted in a graded manner from 14.2±0.4 to 11.6±0.8 and 8.3±0.8 μm (P<0.0001) as systolic pressure was increased from 100.0±0.4 to 120.1±0.3 and 140.8±0.3, confirming the predictions of the model (Figure 6D). As further illustrated in Figure 8A, when perfusion pressure was switched from an oscillating signal of 140/59 mm Hg to a sustained signal of 140 mm Hg, diameters did not change (8.3±0.8 versus 8.6±0.8 μm; P=0.37), although in this case, mean pressure was increased.

Figure 8B further illustrates the lack of effect of changes in mean pressure on the level of myogenic tone. To establish a submaximal myogenic vasoconstriction, systolic pressure was increased to 140 mm Hg, a pressure in dynamic range of the myogenic response (Figure 3A). In the arterioles studied in the experiments depicted in Figure 8B, static elevations in pressure from 80 to 140 mm Hg decreased diameters from 15.4±0.9 to 9.7±1.1 μm. Increasing pressure to 160 mm Hg caused significant further vasoconstriction to 7.7±0.9 μm (not shown; P=0.004, n=7). These kidneys were then exposed to oscillating pressures, maintaining systolic pressure near 140 mm Hg (eg, 139.7±0.6, 138.3±0.9, and 135.2±2.6 mm Hg; P=0.16 between groups, n=7). Mean pressure was then reduced by decreasing diastolic pressure. Despite a reduction in mean pressure from 130.7±0.3 to 119.5±0.5 and 107.8±1.3 mm Hg (P<0.0001) and diastolic pressure from 122.9±0.8 to 103.9±1.4 and 84.8±3.4 mm Hg (P<0.0001), afferent tone was maintained constant (10.6±1.2, 10.7±1.1, and 10.6±1.0 μm; P>0.80), suggest-
ing that it is the systolic pressure alone that determines the level of myogenic tone.

This point is further illustrated by the tracing presented in Figure 8C. In this case, systolic pressure was elevated modestly and diastolic pressure was reduced markedly, resulting in a decrease in mean perfusion pressure (Figure 8C, open circles). Despite the drop in mean perfusion pressure, the afferent arteriole constricted in response to the elevated systolic pressure. These observations support the predictions of the mathematical model and suggest that the function of the myogenic response of the afferent arteriole is not to maintain mean glomerular pressure constant, but rather to protect the glomerulus from elevations in systolic pressure.

Discussion

The present study demonstrates that the kinetic attributes of the afferent arteriolar myogenic response are sufficient to account for the fast component of renal autoregulation revealed by frequency domain analysis in the intact kidney in vivo. However, our findings challenge a number of existing concepts. It is generally assumed that the afferent arteriole responds passively to high-frequency pressure oscillations. Both the in vitro model and the mathematical construct derived from its kinetic features exhibited a sustained vasoconstriction when presented with high-frequency (>1 Hz) pressure signals. Of primary importance, we found that the magnitude of the resulting vasoconstriction was not affected by changes in mean perfusion pressure, but rather was determined exclusively by peak or systolic pressure. Thus, increases in systolic pressure elicited afferent arteriolar vasoconstriction even if mean perfusion pressure was reduced. These findings are inconsistent with the current view that the myogenic mechanism exists to maintain RBF and PGC constant, and suggest a primary role in protecting the glomerulus from the systolic pressure excursions presented at the pulse rate.

Studies employing transfer function and frequency domain analysis of RBF and BP measurements have extensively characterized the dynamic features of renal autoregulation (eg, references 6 through 10). Two systems are consistently demonstrated. The predominant system operates at 0.1 to 0.2 Hz in the anesthetized rat and slightly faster (0.25 to 0.3 Hz) in conscious animals. The slower component operating at 0.03 to 0.05 Hz is dependent on an intact TGF.7,9 Cupples and Loutzenhiser8 demonstrated that the in vitro perfused hydro nephrotic kidney preparation lacks this TGF-dependent component but exhibits the same fast component as that seen in the conscious rat. Moreover, when perfusion pressure was reduced below the myogenic threshold, this signature was abolished, supporting the premise that the myogenic response is the underlying mechanism. The modeling approach used in the present study demonstrates that the kinetic features of the myogenic response, assessed at the level of the individual arteriole, are sufficient to account for the dynamic signature.
of this component, further linking it to the myogenic mechanism. Holstein-Rathlou and Marsh \(^7\) derived a mathematical model incorporating both TGF and myogenic vasoconstriction to specifically predict the transfer functions generated by each component. Because information on the kinetic characteristics of the myogenic response were not available at that time, they estimated these parameters. To mimic a fast component operating at 0.1 to 0.2 Hz, a rate-independent myogenic response with a time constant of 4 to 12 seconds was required. The kinetic parameters reported in the present study are consistent with these required properties.

A major finding of the present study is that the afferent arteriole is capable of modulating tone in response to pressure oscillations that are presented at rates that are well above the myogenic operating frequency. Dynamic autoregulatory studies consistently demonstrate fractional gains of 1 or higher at BP frequencies above 0.3 Hz. These observations have been interpreted as indicating that the renal vasculature responds passively to high-frequency BP signals. Our modeling study confirms that the kinetic attributes of the myogenic response result in fractional gains of 1 at frequencies above 0.3 Hz, but clearly demonstrates that this does not reflect a passive behavior to high-frequency signals. Rather, when exposed to BP signals oscillating faster than the myogenic operating frequency, the afferent arteriole responds with a sustained vasoconstriction. Although this type of response would not prevent the transmission of a pulsatile pressure, it would attenuate the magnitude of the peak downstream pressure. This ability of the afferent arteriole to respond to pulsating pressure signals might have been anticipated. Although myogenic responses are assessed using static pressure signals experimentally, in vivo BP is presented exclusively as complex, high-frequency signals. We further found that, at the high frequencies predominating in vivo, afferent tone is adjusted to appropriately respond to the peak pressure excursion, or systolic BP. We propose that this mechanism allows the afferent arteriole to protect the glomerulus from BP power that is normally present at the pulse rate. Because this attribute was observed both in the intact arteriole and in the mathematical model, it is a direct consequence of the kinetic characteristics of myogenic response of the afferent arteriole. The short activation delay and the relatively long delay in relaxation are the major kinetic features contributing to this behavior.

When presented with an oscillating pressure signal, myogenic tone was sensitive exclusively to changes in systolic pressure and did not respond to changes in mean perfusion pressure. This observation has significant physiological implications. It is generally assumed that the myogenic response subserves renal autoregulation and functions to maintain RBF and GFR constant as BP is altered. Under most conditions, mean BP and systolic BP would be anticipated to change in concert and a response based exclusively on systolic BP would concomitantly regulate RBF and GFR. Similarly, when autoregulation is assessed experimentally, similar changes in mean and systolic BP are generally used. Thus, one would normally see an association of autoregulation with the myogenic response. Indeed, experimental models demonstrating impaired myogenic vasoconstriction exhibit impaired autoregulation (eg, references 20 and 21). However, the primary determinant of GFR and RBF is mean perfusion pressure not peak pressure, and mean pressure did not influence myogenic tone. In fact, elevating systolic pressure activated myogenic vasoconstriction even if mean perfusion pressure was concomitantly reduced. Clearly this response is counter-regulatory in regard to maintaining GFR. The implications of these observations are self-evident. We suggest that the primary role of the myogenic response is not necessarily to maintain a constant PGC and GFR, but rather to protect the glomerulus from the excursions in systolic BP that are present at the pulse rate.

These findings pose an intriguing question of teleologic relevance. Is the phenomenon of renal autoregulation simply an ancillary manifestation of a renal-protective mechanism that functions predominantly to prevent pressure-dependent glomerular injury? It has been argued that the precise regulation of GFR serves to provide a stable setting for normal renal excretory function. However, a deranged excretory function does not seem to be the primary manifestation of impaired autoregulation. Rather, diminished renal autoregulatory capacity is associated with an increased susceptibility of the kidney to hypertension-induced glomerular injury. For example, experimental models of diabetes exhibit impaired autoregulation and increased glomerular injury.\(^4,20\) The Fawn-Hooded rat and the Brown Norway rat exhibit a genetic susceptibility for glomerular injury, especially in the setting of hypertension and this is associated with impaired myogenic vasoconstriction.\(^21–24\) Glomerular injury in the remnant kidney model of chronic renal disease has been strongly linked to deranged autoregulation.\(^2,3\) Moreover, in this model, the degree of hypertension-dependent glomerular injury correlates remarkably with systolic blood pressure.\(^17,18\) Impaired autoregulation clearly reflects a deranged myogenic response. However, the primary consequence appears to be an increased susceptibility to the damaging effects of systolic pressure.

In summary, we have shown that the kinetic attributes of the afferent arteriolar response to pressure, assessed in the in vitro perfused hydronephrotic rat kidney model, account for the dynamic features of autoregulation attributed to the myogenic mechanism in vivo. Moreover, we observed that the afferent arteriole is capable of sensing and responding to changes in the systolic pressure presented at frequencies approximating the heart rate and that, in this setting, myogenic tone is adjusted to the systolic pressure. We suggest that these properties of the renal myogenic response represent the primary mechanism protecting the kidney from the damaging effects of the BP power that is normally present at the pulse frequency.

**Acknowledgments**

This study was supported by grants from the Medical Research Council of Canada (R.L.) and the NIH (A.B.). RL is an AHFMR Senior Medical Scholar. The authors thank Dr William A. Cupples, Dr Karen Griffin, and Dr Geoffrey Williamson for their helpful comments and suggestions. The authors also wish to thank Dr Martina Reslerova for the photomicrographs presented in Figure 1 and Dr Xuemei Wang for her assistance with the revisions.
References
Renal Myogenic Response. Kinetic Attributes and Physiological Role
Rodger Loutzenhiser, Anil Bidani and Lisa Chilton

Circ Res. published online May 30, 2002;
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/early/2002/05/30/01.RES.0000024262.11534.18.citation

Data Supplement (unedited) at:
http://circres.ahajournals.org/content/suppl/2002/06/17/90.12.1316.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the
Editorial Office. Once the online version of the published article for which permission is being requested is
located, click Request Permissions in the middle column of the Web page under Services. Further information
about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/
Figure 1 ONLINE. Schematic diagram of the dual-reservoir perfusion system used in the present study. Renal arterial pressure was measured with the lumen of the renal artery, as described in the Methods. Rapid changes in renal arterial pressure (see Figure 2 online) were imposed by the solenoid valve. By driving this valve at 1-2 Hz, the effects of oscillating pressure signals could be assessed. In such experiments, systolic (peak) and diastolic (nadir) pressures could be set independently, by adjusting the head-pressure of each reservoir.
Figure 2 ONLINE. A. Temporal profile of pressure step elicited by dual reservoir perfusion system. Pressure changes were attained within ~50 msec (49±1 and 50±1 msec for upstroke and downstroke, respectively). B. Pressure pulses delivered at rate of 6 Hz.
Figure 3 ONLINE. Simultaneous measurements of the pressure transients recorded directly at cannula tip (black line) and via intra-cannula catheter (red line, used for sampling renal arterial pressure). In practice, the accuracy of pressure measurements were verified by comparing peak and nadir measurements obtained at low frequency (0.1 Hz) to those obtained at high frequency (>1 Hz), for each preparation. In general, accurate sampling could be obtained at frequencies up to 2 Hz. Errors were encountered at higher frequencies, due to the time constant for pressure measurements obtained through the intra-cannula catheter (above).
Figure 4 ONLINE. Schematic diagram of model used to calculate diameter changes in response to pressure signals. Change in pressure at time $t_0$ initiated response (constriction or dilation) only after delay (0.3 for contraction, 1 second for dilation). The responses evoked by the previous event were allowed to continue during the delay. Following the delay, diameters approached steady-state values (time $t_\omega$) at a rate determined by the kinetic parameters for constriction and dilation, accordingly.