Effects of calcium channel blockers on “dynamic” and “steady-state step” renal autoregulation

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Submitted 12 November 2003; accepted in final form 23 February 2004

Griffin, Karen A., Rifat Hacioglu, Isam Abu-Amarah, Rodger Loutzenhiser, Geoffrey A. Williamson, and Anil K. Bidani. Effects of calcium channel blockers on “dynamic” and “steady-state step” renal autoregulation. Am J Physiol Renal Physiol 286: F1136–F1143, 2004. First published March 2, 2004; 10.1152/ajprenal.00401.2003.—Renal autoregulation (AR) mechanisms provide the primary protection against transmission of systemic pressures and hypertensive renal damage. However, the relative merits of the “step” change vs. “dynamic” methods for the assessment of AR capacity remain controversial. The effects of 48–72 h of orally administered amlopidine (L-type) and mibebradil (T-type) calcium channel blockers (CCBs) on step and dynamic AR in Sprague-Dawley rats were compared. Both CCBs significantly impaired “steady-state step” AR (autoregulatory indexes = ~0.5 vs. ~0.1 in controls, P < 0.05; n = 9–10/group). By contrast, dynamic AR compensation in separate conscious rats (n = 12) was not significantly altered by either amlopidine (n = 10) or mibebradil (n = 6); fractional gain in admittance ~0.4–0.5 in all groups at frequencies in the range of 0.0025–0.025 Hz). However, both CCBs tended to attenuate the myogenic resonance peak along with shifting it to a significantly slower frequency (P < 0.001) during dynamic AR, but no consistent effects were observed on the tubuloglomerular feedback resonance peak. While the reasons for the insensitivity of dynamic vs. steady-state step AR capacity estimates to CCBs remain to be established, the present data indicate that dynamic AR methods may have a limited utility for assessing AR capacity but may provide potentially important insights into the operational characteristics of AR control mechanisms. A strong correlation was also observed between the average conductance and the admittance gain at the heart beat frequency (r = 0.77, P < 0.001), suggesting that such parameters may provide additional and possibly more meaningful indexes of BP transmission in conscious animals during dynamic AR.

renal hemodynamics; hypertension; myogenic response; tubuloglomerular feedback

RENA L AUTOREGULATION (AR) mechanisms, through proportionate increases in preglomerular resistance in response to episodic or sustained increases in blood pressure (BP), are believed to provide the primary protection against hypertensive glomerular injury (1, 2, 8, 23–25, 32, 36, 38). Support for this concept has been provided by the increased susceptibility to hypertensive renal damage observed in experimental and clinical states that are associated with impaired AR responses such as after renal mass reduction (RMR) and/or diabetes (2–6, 16–21, 24, 25, 37). However, despite extensive investigation, many aspects of the renal AR response remain controversial. These include the issue of the methodology most physiologically relevant for the assessment of AR capacity (efficiency), the precise nature of the BP trigger, as well as the contribution and operational characteristics of the individual control mechanisms that together are responsible for the real-time mediation of AR to BP changes (5, 26, 29, 32). Several different methodologies have been utilized to investigate these issues. Conventional “steady-state step” AR, which has been most frequently employed to investigate AR in both normal and disease states, has been questioned on the basis that “step” methods do not truly simulate the in vivo state. During conventional step AR, the steady-state responses of renal blood flow (RBF) and/or glomerular filtration rate (GFR) to sustained step changes in BP are analyzed, but BP in conscious animals does not change from one steady state to another but rather fluctuates over a wide range of time scales (frequencies) (5, 11, 26, 27, 30–32). Moreover, AR is not instantaneous (41), and conventional step AR methods typically examine the RBF response after the attainment of a steady state (the magnitude of the AR response) but not its kinetic aspects (11, 13, 26, 27, 30, 31). Therefore, “dynamic” methods, based on transfer function analysis of fluctuations in BP (input) and RBF (output), have been proposed as a possibly more physiological method of assessing AR efficiency in vivo (5, 11, 13, 26, 27, 30, 31, 38). Additionally, such dynamic AR methods may provide an assessment of the operational characteristics of the myogenic and tubuloglomerular feedback mechanisms through frequency domain analysis.

We have recently reported a comparison of step vs. dynamic AR methods after graded renal mass reduction (RMR) (6). For reasons that remain to be clearly defined, substantially less AR capacity is seen by dynamic compared with the steady-state step methodology in control rats. Moreover, significant impairment of AR capacity compared with control rats was observed after severe (3/4) RMR by step but not dynamic methods. However, a significant attenuation of the characteristic resonance peak at the myogenic frequency (~0.3 Hz) was observed after RMR. The precise genesis of this resonance peak and its relationship to AR capacity remain uncertain (11, 26, 27, 30–32, 38). Given that calcium channel blockers (CCBs) are known to impair renal AR (18–21, 30, 33–36), it was reasoned that an examination of the effects of CCBs on dynamic and step AR may yield useful insights regarding these issues as well as provide a more critical assessment of the

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relative merits of the two methodologies in the assessment of renal AR.

METHODS

Male Sprague-Dawley rats (body wt 250–350 g) were used for these studies. All rats were fed a standard diet (Purina, Richmond, IN) and synchronized to a 12:12-h light (600–1800)-dark (1800–600) cycle. All rats received food and water ad libitum throughout the study. All animals were cared for in accordance with the Guide for the Care and Use of Laboratory Animals (National Academy Press, 1986).

Dynamic AR studies. The week before the scheduled studies, radiotransmitters (Data Sciences, St. Paul, MN) and chronic RBF probes (Transonic System, Ithaca, NY) were installed under pentobarbital sodium anesthesia (50 mg/kg ip). Each rat had a BP sensor (model TA11PA-C40) inserted into the aorta via a femoral artery below the level of the renal arteries, and the radio-frequency transmitter was fixed to the peritoneum as previously described (2, 18–21).

An ultrasonic transit-time (1RB) flow probe was placed around the renal artery and packed in Dacron mesh to ensure proper alignment of the probe and vessel (5). The probe cable was secured to back muscles, routed subcutaneously, and exteriorized at the back of the neck. Flow probes were validated as previously described (5, 17). After the rats were allowed to recover for 1 wk, the flow probes were connected to a transonic flowmeter (T106, Transonic Systems), and ~60-min simultaneous recordings of BP and RBF were obtained at a sampling rate of 200 Hz in conscious unrestrained rats. One to two recordings were obtained in each rat (n = 12) at intervals of 24–48 h, and the results were averaged for each rat after processing (see below). After these recordings in the basal state, the rats (n = 10) received amlodipine (100 mg/l of drinking water). After 48–72 h of receipt of the drug, repeat one to two recordings of BP and RBF were obtained at intervals of 24–48 h as was done for the basal recordings. In four rats, amlodipine was then discontinued and, after a washout period of 3–5 days, the rats received the same standard rodent chow, but one formulated to contain mibefradil (0.06%). After 48–78 h of the initiation of the mibefradil diet, BP and RBF recordings were repeated. Two of the rats were placed directly on mibefradil after the basal recordings without first receiving amlodipine.

Subsegments of 30 min in duration from each recording that were free of noise or other artifacts were then selected from each data record. The resulting 30-min signals were resampled to a sampling rate of 20 Hz using a low-pass anti-aliasing filter to remove variations in the signals at >10-Hz rate. Each time sequence of 36,000 data points was then subjected to linear trend removal (5, 39). The transfer functions of the dynamic relationship between BP (input) and RBF (output) were analyzed using standard methods. The BP and RBF power spectra were determined using fast Fourier transforms based on Welch’s averaged periodogram method (50% overlap of 7 segments of 8,192 samples and a Hanning window applied) (5, 39). Power and output auto power spectra and cross power spectra were then calculated for each segment and averaged. The admittance function was computed as the ratio of cross spectrum to BP power spectrum (5, 27, 30, 31). The coherence function was also computed from the cross and auto power spectra. Fractional gain in admittance (FGA) was obtained by normalizing admittance gain by the conductance computed over the entire 30-min record. The natural frequencies of the myogenic and tubuloglomerular feedback (TGF) mechanisms were determined from their characteristic signature resonance peaks in fractional gains between 0.1 and 0.3 Hz and between 0.025 and 0.1 Hz, respectively, by inspection of individual records, and then averaged across each record (5). The peak phase angle in the phase responses between 0.08 and 0.2 Hz was similarly determined and averaged across each record.

AR efficacy (compensation) was assessed by the FGA at frequencies <0.025 Hz, as previous studies have shown that the maximum attenuation of RBF fluctuations only occurs at these low frequencies and is believed to result from the combined contribution of myogenic and TGF mechanisms (11, 26, 27, 29–32). Additionally, the impact of CCBs was examined on admittance gains at higher frequencies (0.5–8 Hz), a frequency range that is usually not included in the analysis of transfer functions during dynamic AR studies.

Conventional steady-state step AR. These studies were performed in a separate set of three groups of rats, i.e., control and those having received amlodipine (100 mg/l of drinking water) or mibefradil in rat chow (0.06%) for 48–96 h before the step AR studies. The rats were anesthetized with inactin (100 mg/kg ip) and surgically prepared as described previously (16, 17). In brief, a tracheostomy was performed using polyethylene (PE-200) tubing, and a carotid and a femoral artery were cannulated with PE-50 tubing and connected to a Windograf recorder (model 40–8474, Gould, Glen Burnie, MD) for continuous recording of renal perfusion pressure. A femoral vein was cannulated with PE-50 tubing, and a 150 mM NaCl bolus equal to 1% of the body weight was administered, followed by a continuous maintenance infusion of 150 mM NaCl at 0.055 ml/min for replacement of surgical and ongoing fluid losses. An ultrasonic transit time (1RB) flow probe was placed around the left renal artery for measurement of RBF by a flowmeter, and AR studies were performed using aortic micromanipulators positioned above and below the left renal artery to raise or lower renal perfusion pressure (RPP) measured via the femoral or the carotid artery catheter, as previously described (4–6, 16, 17). The RBF was allowed to stabilize for 1–2 min at each pressure before RBF measurements were made. Flow probes were validated as previously described (5, 17). The AR index (AI) was calculated by the method of Semple and de Wardener (41) as follows: AI = [(RBF2 – RBF1)/ RBF1]/[(RPP2 – RPP1)/RPP1]. An AI of zero indicates perfect AR, whereas an AI of one indicates that the vessels act as passive conduits for blood flow.

Statistical analysis. All results are expressed as means ± SE. Statistical analysis was performed using analysis of variance, followed by a Student-Newman-Keuls test or by Kruskall-Wallis non-parametric analysis of variance, followed by Dunn’s multiple comparison test, as appropriate. A P of >0.05 was considered nonsignificant (15).

RESULTS

Dynamic AR studies. The average BP during the conscious recordings was not significantly altered from the control state by either amlodipine or mibefradil (control, 97.8 ± 3.1; amlodipine, 96.4 ± 2.3; mibefradil 98.0 ± 2.7 mmHg). Similarly, the average RBF during the conscious recordings was not significantly altered from the control state (7.7 ± 1.0 ml/min) by either amlodipine (8.0 ± 0.6 ml/min) or mibefradil (9.3 ± 1.8 ml/min).

Figure 1, A–E, presents the transfer function analysis for the dynamic AR studies with the mean results for each individual parameter assessed for the three sets of recordings (basal, amlodipine, and mibefradil). As can be noted from the overview (the quantitative comparisons are presented separately), the BP and RBF power spectra were not different between the three sets of recordings (Fig. 1, A and B). Similarly, there were no significant differences in the mean coherence between BP and RBF (Fig. 1C). Coherence was >0.6 at frequencies >0.05 Hz in all groups but declined to 0.4–0.5 at frequencies <0.05 Hz. Pretreatment with either CCB did cause significant alterations in both the phase angle of the myogenic response (Fig. 1D) and the fractional gain at the myogenic “resonance” peak (Fig. 1E) compared with that during the control recordings (see below). Thus both the magnitude and frequencies of the myogenic resonance peaks in phase and fractional gain were reduced by CCB treatment. However, CCB treatment had no
significant effects on the fractional gains in admittance at frequencies >0.5 Hz including the heartbeat frequency (~6 Hz), although there was a trend toward a decreased FGA at 0.5–1 Hz after amlodipine and mibefradil treatment compared with the basal state.

Figure 2, A and B, illustrates the effects of the two CCBs on the operational characteristics of TGF and myogenic mechanisms. CCBs had no significant or consistent effect on the natural frequency of the TGF system, but the apparent natural frequency of the myogenic mechanism was shifted to a slower frequency by both amlodipine and mibefradil (Fig. 2A). Figure 2B shows the resonance peak effects of the two CCBs on the TGF and myogenic resonance peaks. While the two CCBs had directionally opposite effects on the TGF resonance peak, both
tended to attenuate the myogenic resonance peak, with the attenuation being significant for mibefradil \((P < 0.01)\). These effects on the operational characteristics of the myogenic mechanism are also reflected in the changes in the peak phase angle between 0.08 and 0.2 Hz (control 79.5 ± 5.3 vs. 54.0 ± 4.7 and 50.4 ± 3.4° for amlodipine and mibefradil groups, \(P < 0.01\)) and the frequency at which it is observed (0.17 ± 0.006, 0.14 ± 0.004, and 0.11 ± 0.01 Hz, respectively, \(P < 0.05\) maximum for all comparisons).

Figure 3 shows the results of conventional step AR studies in control and CCB-treated rats. As can be noted, step changes in RPP between 140 and 100 mmHg resulted in significant changes in RBF in both the amlodipine- and mibefradil-treated rats \((P < 0.01\) maximum) but not in the control rats.

Figure 4 compares the AR efficiency assessed (as the AI) using the step protocol against that assessed (as the FGA) by the dynamic AR protocol. For the latter, the mean FGA attained at frequencies ranging from 0.0025 to 0.01 Hz and from 0.01 to 0.025 Hz are presented separately. Significantly better AR capacity is seen in control rats with the step AR protocol (AI of <0.1) than with the dynamic protocol (FGA of 0.5 at frequencies <0.025 Hz). Moreover, in contrast to the significant AR impairment demonstrated after CCBs by the step AR protocol, no significant impact of CCBs is observed on dynamic AR capacity.

Figure 5 depicts the relationship between the average renal conductance obtained during the dynamic AR studies and the admissibility gain at the heartbeat frequency in individual ani-
mals during the control (basal) state and after 48 h of amlo-
dipine or mibefradil administration. Note that while there was
no discernable impact of CCB treatment on this relationship,
an evaluation of the entire population revealed a strong corre-
lation between these two parameters (r = 0.77, P < 0.001).
Thus increased levels of mean renal vascular resistance (lower
conductance) were associated with reduced admittance gain at
the heartbeat frequency, consistent with the concept that the
basal renal vascular tone is an important determinant of the
transmission of the pulse pressure transient (as reflected by
alterations in the pulsatile character of RBF).

DISCUSSION

The renal AR response to changes in RPP is mediated by at
least two separate control mechanisms, the pregglomerular vas-
cular myogenic response and the TGF system (8, 11, 13,
26–32, 36, 38, 44). It is generally acknowledged that Ca entry
through voltage-gated Ca channels in response to pressure-
duced depolarization is an early and critical event in the
myogenic response (12, 14, 33, 35, 36). Predictably, CCBs
have been demonstrated to impair the myogenic response in
several model systems (7, 12, 33–36, 43). Although the signal
transduction pathways responsible for the TGF response re-
main controversial (26, 27, 36, 43), CCBs also impair TGF,
possibly by blocking afferent arteriolar vasoconstriction (34,
36, 43). Consistent with these effects, administration of L-type,
and more recently T-type, CCBs impairs whole kidney and
single-nephron AR responses (7, 19, 22, 33, 36, 43). Also
consistent with these findings, in the present study we observed
that the steady-state renal AR capacity to step changes in RPP
in rats who had received either amlo dipine or mibefradil for
48–72 h was reduced by ~50% compared with control rats. By
contrast, AR compensation in response to BP fluctuations
during dynamic AR studies did not show significant differ-
ces between control and CCB-treated rats. These results are
very similar to our previous observations in rats with 3/4 RMR,
which also failed to show differences from control rats in AR
compensation during dynamic AR studies, despite a significant
impairment in steady-state step AR responses (5).

As in the previous study (5), significantly less AR compen-
sation was seen during dynamic compared with the step AR
protocols in control rats. Analysis of the RBF response to step
changes shows that after an initial change, the RBF reaches a
steady-state value after several seconds (9, 29, 30, 41). AR
capacity is assessed by the degree to which the steady-state
RBF has been restored to the control level, and this is reflected
in the calculated AI (42). Theoretically, the FGA at frequencies
<0.025 Hz should be similar to the calculated AI during
steady-state step AR. Nevertheless, the actual values attained
in untreated rats are about fourfold higher, even at frequencies
<0.01 Hz. The reasons for the differing estimates of AR capa-
city using these two approaches remain to be established.
Although the dynamic AR studies were performed in conscious
rats and the step AR studies in anesthetized rats, anesthesia per
se does not account for these discrepancies as similar results
have been obtained for both step and dynamic protocols in
conscious as well as anesthetized rats (1, 5, 9, 11, 13, 26, 31, 38).
However, it is possible that these two methodologies
assess differing aspects of the vascular responses to changes in
BP. As discussed previously, one possible contributing factor
may be the difference in BP inputs during step and dynamic
AR protocols (5). Although during the present step AR studies,
the steady-state RBF response to relatively large and sustained
changes in average (mean) BP [direct current (DC) BP power]
was analyzed, essentially similar steady-state AR capacity
estimates have been obtained with smaller BP steps (9, 13, 28).
By contrast, during dynamic AR the RBF buffering is assessed in
response to BP inputs, which are not only relatively small
but are also intrinsically transient [alternating current (AC) BP
power at frequencies <0.025 Hz] (26), and in the setting of rats
who already have achieved a basal renal vascular resistance in
proportion to their ambient average BP and AR capacity.
Transfer function analysis during dynamic AR studies may
also be compromised by concurrent changes in RBF in re-
sponse to BP-independent events, such as neurohormonal and
metabolic renal vascular inputs (5, 38). Such superimposed
RBF variability, combined with the small and transient BP
inputs and the nonlinear nature of the AR control mechanisms,
likely accounts for the low coherence that is generally observed
at frequencies <0.05 Hz, although the low coherence per se is
also not expected to alter the low-frequency FGA. Neverthe-
less, it is of interest that with significantly larger BP inputs as
in sinoaortic-denervated rats, both the coherence and the low-
frequency FGA are improved compared with that observed
in control rats with similarly denervated kidneys, although the
AR compensation is still less than that observed during step
protocols (38).

In any event, the present results additionally demonstrate
that the estimates of dynamic AR compensation are largely
insensitive to even interventions such as the CCBs, which
would be clearly expected to alter AR capacity and in fact do
impair step AR. It needs to be acknowledged, however, that in
contrast to the present results, an impairment of dynamic AR
compensation has been observed by Just et al. (30) with the
dihydropyridine CCB nifedipine in the dog. A possible expla-
nation for the differences in the results may be that in the dog
study nifedipine was infused into the renal artery at a concen-
tration that essentially completely abolished step AR re-
sponses, whereas in the present study only a ~50% impairment
in steady-state step AR capacity was seen. It is possible that a
significant impairment in dynamic AR is only demonstrable with extreme impairment of AR capacity (30, 31). Thus the present data challenge the validity of current interpretations of FGA at frequencies <0.01 as providing consistent and physiologically relevant estimates of AR compensation capacity, at least in the absence of severe impairments. Such concerns are further reinforced when the data are considered from the perspective of glomerular pressure transmission. The FGA estimated from dynamic AR studies (~0.5 at 0.025 Hz) suggests that ~50% of the fluctuations in BP would be transmitted downstream to the glomerular capillaries. Similar values are reported for the spontaneously hypertensive rat (SHR) (13, 26, 27), findings which are clearly inconsistent with the protective function ascribed to renal AR in preventing hypertensive glomerular injury. By contrast, steady-state step AR capacity estimates correlate more closely with the underlying susceptibility to hypertensive renal damage in experimental animal models, particularly those characterized by predominantly glomerular injury. For instance, the SHR strain exhibits strong AR responses during step AR (1, 4, 13) and is quite resistant to hypertensive glomerular injury despite fairly severe hypertension. Of interest, the glomerulosclerosis (GS) that does develop later in life in these SHR is seen initially in the juxtamedullary nephrons, which also show less AR capacity, particularly with aging (28, 40). Conversely, the fawn-hooded hypertensive rat exhibits impaired step renal AR and a greatly enhanced propensity to develop proteinuria and GS even at a relatively young age (44). Similarly, severe RMR (~3/4) is associated with an impairment of steady-state step AR and a greatly increased vulnerability to hypertensive glomerular injury (2–6). Moreover, 5/6 renal ablation in the SHR strain, as in other strains, impairs steady-state step AR and is associated with the acute development of malignant nephrosclerosis (4). Of particular interest to the present studies is the observation that administration of CCBs to rats with remnant kidneys and preexistent AR impairment essentially abolishes the residual steady-state step AR capacity and greatly enhances the development of GS despite the concurrent reductions in average systemic BP (18–21).

As currently applied, dynamic assessment of AR only assesses the response to that fraction of AC BP power that resides at frequencies <1 Hz but not at the heartbeat frequency, which constitutes the largest component of AC BP power (5, 32). In the present study, we evaluated the admittance gain at the heartbeat frequency as an index of the transmission of this BP signal. In this context, it is of interest that no significant effects of CCBs were observed on this parameter. This is not entirely unexpected, as the transmission of all components of BP power (including DC BP power and the AC BP power at the heartbeat frequency) is expected to be a function of the achieved average ambient resistance (conductance) (5), and differences in conductance were not present between the control (basal) state and after amlodipine or mibefradil treatment. The lack of an effect of CCBs on conductances likely represents the combined effects of a lack of a significant AR myogenic tone at the relatively low ambient pressures present in these normotensive rats in the basal state as well as the potential effects of counterregulatory mechanisms that may have been triggered in response to an initial decrease in BP after the CCBs were initiated. Nevertheless, the importance of the average ambient resistance (conductance) as a determinant of the transmission of BP power at the heartbeat frequency is suggested by the strong correlation between conductance and the absolute admittance gains at the heartbeat frequency in individual animals, even within the relatively narrow normal range of ambient BP and conductances.

These data suggest that, at least from the perspective of BP transmission and susceptibility to hypertensive injury, an analysis of admittance gains at the heartbeat frequency during dynamic AR studies may provide important information, particularly in hypertensive animals. Such analysis is usually not performed, as there is the general assumption that the relatively slow time constants of the renal AR mechanisms (<0.3 Hz) would not allow the vasculature to respond to BP oscillations at this frequency (10, 11, 13, 26, 27, 30–32). However, the assumption that the vasculature responds passively to such signals and that high-frequency (>0.3 Hz) BP oscillations are freely transmitted to the glomerular capillaries has been challenged by recent observations in the in vitro perfused hydro-nephrotic kidney model (32). These studies have demonstrated that, contrary to previous concepts, the afferent arteriole can respond to high-frequency BP oscillations and adjusts tone (conductance) in response to the magnitude of the peak or systolic BP. Thus proportionate vasoconstriction elicited in response to increases in systolic pressures would protect against the glomerular transmission of both the DC BP power and the AC BP power at the heartbeat frequency. It is possible that steady-state step AR methods, although performed using essentially static BP signals, nevertheless provide an indirect estimate of the capability of the afferent arteriole to set vascular resistance in response to changes in BP signals in vivo at the heartbeat frequency (5, 32).

Despite the failure of current dynamic methods to provide valid AR compensation estimates, such methods may nevertheless provide potentially important insights into the operational characteristics of the AR control mechanisms and their modification by CCBs. Although its precise genesis remains uncertain, the resonance peak seen at frequencies between 0.2 and 0.3 Hz has been attributed to the myogenic mechanism (10, 11, 13, 26, 27, 30–32, 38). The observed effects of CCBs on this resonance peak strongly support such interpretations. It is of note that the significant blunting of this resonance peak after CCBs is similar to that observed previously after 3/4 RMR and, in both instances, is associated with an impairment of step AR (5). These data suggest that such alterations in the “myogenic” resonance peaks (seen in both FGA and phase; Fig. 1) may provide a qualitative index of the strength of the myogenic AR response. However, the precise relationship between alterations in the myogenic resonance peak during dynamic AR studies and AR impairment during step AR protocols remains to be defined. Such uncertainty is also suggested by the fact that both CCBs and RMR impair steady-state step AR, but only CCBs cause a shift in the apparent natural frequency of the myogenic mechanism to slower frequencies. The precise cellular and/or biomechanical basis for these shifts in the operating frequency of the myogenic mechanism also remains to be elucidated but may reflect the impact of submaximal Ca channel blockade on the kinetics of myogenic vasoconstriction.

It is of interest that no significant effects of CCBs were noted on either the amplitude or frequency of the resonance peak believed to be generated by the TGF system. Nevertheless, CCBs have been shown to inhibit TGF responses in other
model systems (34, 36). In any event, the present data show that impairment of steady-state step AR capacity is not necessarily associated with alterations in the TGF signature assessed by dynamic AR protocols. The reasons remain unclear. However, it is possible that such alterations in TGF resonance peak or frequency are only observed with interventions that directly alter the signal transduction pathways of the TGF system. Nevertheless, such dissociation between impairment in steady-state step AR without an apparent alteration in the operational characteristics of the TGF system during dynamic AR suggests that these two control mechanisms may subserve different aspects of the renal hemodynamic responses to BP changes (5). Such a possibility is also suggested by the fact that impairment of steady-state step AR is associated with an enhanced susceptibility to hypertensive injury without any evidence of a significant impairment of fluid volume homeostasis (4–6, 32, 44, 45). Based on the observations in the in vitro perfused hydrophobic nephrotic kidney model which have indicated that the magnitude of the myogenic response is determined by the peak (systolic) rather than average pressure, we have previously suggested that the primary function of the myogenic component of renal AR may be to protect glomerular capillaries from systolic pressures rather than to regulate RBF and GFR per se, which are a function of the average rather than systolic pressures (32). The additional regulation of RBF and GFR that may be needed to serve the metabolic and/or volume needs of the animal may be achieved through additional adjustments of basal ambient preglomerular resistance at any given BP through TGF and possibly other mechanisms and/or inputs (5, 36).

In conclusion, the present study supports our previous interpretations that dynamic AR studies may be of limited utility for obtaining a valid assessment of the true AR capacity (5). Thus the impairment in AR capacity in response to CCB treatment was revealed by steady-state step but not dynamic AR protocols. Nevertheless, the effects of CCBs on the natural frequency and resonance peak of the myogenic mechanism suggest that such transfer function analysis provides a potentially important tool to examine the dynamic operational characteristics of the renal vascular myogenic response to BP fluctuations in conscious animals. Moreover, the close relationship that was observed between average conductance and the admittance gain at the heartbeat frequency suggests that analysis of the transfer functions at these frequencies may provide additional parameters to assess BP transmission in conscious rats during investigations of hypertensive renal damage.

ACKNOWLEDGMENTS
The authors thank Angela Powell, Theresa Herbst, and Rizalita Redovan for technical assistance and Martha Prado for secretarial assistance.

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GRANTS
This work was supported by National Institutes of Diabetes and Digestive and Kidney Diseases Grants DK-40426 and DK-671653 and the Office of Research and Development of the Department of Veterans Affairs.

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