Sympathetic modulation of renal blood flow by rilmenidine and captopril: central vs. peripheral effects

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1Department of Pharmacology and Toxicology, Cardiovascular Research Institute Maastricht, 6200 MD Maastricht, The Netherlands; 2Department of Circulation Control, National Cardiology Research Center, Moscow 121552, Russia; and 3Neuropharmacology, Baker Medical Research Institute, Prahran, Victoria 8008, Australia

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Janssen, Ben J. A., Elena V. Lukoshkova, and Geoffrey A. Head. Sympathetic modulation of renal blood flow by rilmenidine and captopril: central vs. peripheral effects. Am J Physiol Renal Physiol 282:F113–F123, 2002.—Renal blood flow (RBF) is modulated by renal sympathetic nerve activity (RSNA). However, agents that are supposed to reduce sympathetic tone, such as rilmenidine and captopril, influence RBF also by direct arteriolar effects. The present study was designed to test to what extent the renal nerves contribute to the renal hemodynamic response to rilmenidine and captopril. We used a technique that allows simultaneous recording of RBF and RSNA to the same kidney in conscious rabbits. We compared the dose-dependent effects of rilmenidine (0.01–1 mg/kg) and captopril (0.03–3 mg/kg) on RBF and RSNA in intact and renal denervated (RNX) rabbits. Because rilmenidine and captopril lower blood pressure, studies were also performed in sinoaortically denervated (SAD) rabbits to determine the role of the baroreflex in the renal hemodynamic response. Rilmenidine reduced arterial pressure, RBF, and RSNA dose dependently. In intact rabbits (n = 10), renal conductance (RC) remained unaltered (3 ± 5%), even after the 1-mg/kg dose, which completely abolished RSNA. In RNX rabbits (n = 6), RC fell by 18 ± 5%, whereas in SAD rabbits (n = 7) RC increased by 30 ± 20% after rilmenidine. In intact rabbits, captopril increased RSNA maximally by 64 ± 8%. RSNA did not rise in SAD rabbits. Despite the differential response or absence of RSNA, captopril increased RC to a comparable degree (maximally 40–50%) in all three groups. Using spectral analysis techniques, we found that in all groups, independently of ongoing RSNA, captopril, but not rilmenidine, attenuated both myogenic (0.07–0.25 Hz) and tubuloglomerular feedback (0.01–0.07 Hz) related fluctuations in RC. We conclude that, in conscious rabbits, the renal vasodilator effect of rilmenidine depends on the level of ongoing RSNA. Its sympatholytic effect is, however, blunted by a direct arteriolar vasocostrictor effect. In contrast, the renal vasodilator effect of captopril is not modulated by ongoing RSNA and is associated with impairment of autoregulation of RBF.

baroflex; renal sympathetic nerve activity; spectral analysis

THE KIDNEY PLAYS A KEY ROLE in the control of hemodynamics in essential hypertension and heart failure.

Drugs that increase renal blood flow (RBF) have beneficial effects in these patients. One of the pharmacological approaches to increase RBF is to inhibit the production of angiotensin II. Angiotensin-converting enzyme (ACE) inhibitors have well-known preferential renal vasodilator effects (31, 42). Besides humoral mechanisms, centrally mediated sympatholytic effects are thought to contribute to this effect of these drugs (27, 32). Because of the dense sympathetic innervation of the kidney, an alternative approach to induce renal vasodilation may be to lower ongoing renal sympathetic nerve activity (RSNA) (6). Reducing ongoing RSNA is thought to be beneficial, particularly in conditions with elevated sympathetic activity (8). RSNA may be reduced pharmacologically by centrally acting imidazoline- or α2-receptor agonists. Agents with affinity for imidazoline receptors, e.g., rilmenidine, decrease RSNA (5) and increase renal conductance in hypertensive rats (36) and humans (24). In addition, they have been reported to enhance natriuresis and diuresis (9, 17, 28). The renal effects of these drugs are probably not entirely mediated by their central sympatholytic action (37). Peripheral renal targets may mediate the renal response to these drugs, such as 1) a heterogeneous population of imidazoline receptors (10, 35), 2) renal α2-adrenoceptor mediated NO release (45), 3) atrial natriuretic peptide (28), and 4) vasopressin (38).

This study was designed to examine to what extent the central nervous system contributes to the renal vascular effects of rilmenidine and captopril, an ACE inhibitor. We used a recently developed technique that allows simultaneous recording of RBF and RSNA to the same kidney in conscious rabbits (15). We studied the dose-dependent effects of rilmenidine and captopril on RBF and RSNA in intact as well as bilaterally renal denervated rabbits. Because both drugs lower blood pressure, the sympathetic control of RBF may be altered by a baroreflex-mediated increase in RSNA. To exclude this possibility, effects of rilmenidine and captopril on RBF and RSNA were also studied after sino-
aortic denervation (SAD). Furthermore, the SAD rabbits may serve as a model with elevated ongoing RSNA (19, 33). Rilmenidine and captopril were chosen because these agents have been studied extensively before. Furthermore, the hemodynamic effects of these agents occur relatively quickly and allow the construction of a dose-response curve within a few hours. In addition to the steady-state effects, we evaluated the rilmenidine- and captopril-induced dynamic changes in RBF with spectral analysis techniques. These methods give insight into the different mechanisms controlling RBF, such as sympathetic nerves, myogenic tone, and tubuloglomerular feedback (TGF), all of which occur at quite different frequency domains (13, 14, 16).

MATERIALS AND METHODS

Animal Preparations

The experiments were performed in male and female rabbits (2.4–3.1 kg) bred at the Baker Medical Research Institute. The rabbit colony is derived from an original multicolored English strain with “Dutch Belted” introduced in 1994. All procedures were performed in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (1990) and were approved by the Animal Experimentation Committee of the Alfred Hospital/Baker Medical Research Institute. Rabbits were housed individually under controlled temperature, humidity, and dark-light cycle and fed a controlled diet of pellets (0.5% sodium chloride) and vegetables but with water ad libitum.

The present pharmacological studies were conducted in the same animal preparations that were described in a previous paper describing the effects of a short hypoxic stimulus (15). At the end of the study, the animals were anesthetized with pentobarbitone sodium (60 mg/kg) and euthanized by an overdose of this agent.

Implantation of the device to simultaneously record RBF and RSNA. The device was constructed and implanted as described in detail previously (15). In short, a Doppler crystal housed in a silicone cuff (1.4 mm) with two coiled wires was sutured on the left renal artery. The renal nerves were gently slipped into the two spirals, and the entire preparation was embedded in silicone gel. The connectors of the electrode were placed under the skin at the back of the animal and retrieved while the animal was under local anesthesia (procaine 1%, Citanest, Astra Pharmaceuticals). The implantation of the device did not result in denervation of the kidney or increase of plasma renin levels (15). Experiments were performed in these rabbits between days 4 and 11 after surgery.

Renal denervation and renal Doppler flow probe implantation. In a second group of rabbits, bilateral renal denervation (RNX) was performed at least 7 days before the first experiment. With the use of fine forceps, the nerves were stripped from the renal arteries, and the vessels were painted with ethanol. After this procedure, a Doppler flow probe was placed on the left renal artery and embedded in silicone gel. As described before (15), RNX decreased renal norepinephrine content by 98%.

SAD. The deafferentation of aortic and carotid sinus barosensors was performed according to the procedure described by Korner et al. (18). The carotid sinus was bilaterally exposed, and all nerves were carefully stripped from the bulbus using fine forceps. In addition, the aortic depressor nerve was cut using iris scissors, avoiding any damage to the laryngeal nerve. Seven to ten days after SAD, the renal Doppler/electrode device was implanted as described in Implantation of the device to simultaneously record RBF and RSNA.

Implantation of catheters. On the day of the experiment, minor operative procedures were performed while the rabbits were under local prilocaine anesthesia. A transcutaneous 22-gauge, 25-mm Teflon catheter (Jelco, Critikon) was placed in the central ear artery. The catheter was then connected to a Statham P23Dc pressure transducer (Gould, Bernie, MD) for continuous measurements of arterial pressure and heart rate (HR). For intravenous injections, an ear vein was cannulated.

Experimental Protocol

During the experiments, rabbits were kept in a standard single-rabbit holding box (15 cm high and wide and 35 cm long) with a wire top and raised wire grid floor. The arterial line and the wires from the Doppler probe and renal nerve electrode were connected to the data-acquisition equipment, and hemodynamics were allowed to stabilize for at least 45–60 min. Experiments were performed on 3 separate days at 48-h intervals in random order. In one of the experiments, rilmenidine (dissolved in saline) was injected intravenously using a cumulative dosing schedule (0.01, 0.03, 0.1, 0.3, 0.6, and 1 mg/kg) at 15-min intervals. Because part of the drug is eliminated over the course of the experiment, the indicated dose is slightly overestimated. On the other 2 days, either captopril (0.003, 0.01, 0.03, 0.1, 0.3, 1, and 3 mg/kg) or saline (0.5 ml) was injected every 15 min (time control). Experiments were conducted in 10 intact, 6 RNX, and 9 SAD rabbits. Because in some rabbits (2 intact, 1 RNX, and 2 SAD) either the Doppler flow probe signal or RSNA signal was lost over time, the number of observations for renal conductance (RC) and RSNA varies between 8 and 10 for the intact, 5–6 for the RNX, and 7 and 9 for the SAD group.

Data Acquisition and Data Processing

Arterial pressure, RSNA, and RBF were recorded at 1 kHz (15). In each experiment, a short 15- to 30-s segment of original signals was stored on disk. These data were used to evaluate the efficacy of SAD as explained in Verification of SAD. During the pharmacological experiments, beat-to-beat values of mean arterial pressure (MAP), pulse interval (PI), RBF, and integrated RSNA were calculated on-line and stored on computer disk for later analysis.

Steady-state hemodynamic effects were defined as the average values taken between 10 and 15 min after each intravenous injection of rilmenidine, captopril, or saline. To facilitate a comparison among rabbits, average RBF and renal conductance were normalized to 100 units in the control period before a drug or saline was added. Similarly, we normalized integrated RSNA to 100 units after subtraction of the baseline noise, which was set as the value of RSNA during periods in which no obvious bursts occurred (15). HR was calculated as 60,000/PI.

Spectral Analysis

The dynamic fluctuations of MAP, HR, RC, RBF, and RSNA were investigated in the frequency domain using fast Fourier transform algorithms (15). Relative stable 10-min segments were selected from the tracings obtained during the 0.3-mg/kg dose of rilmenidine and the 3-mg/kg dose of captopril because at these doses the drugs had equipotent
blood pressure-lowering efficacy. A 10-min segment selected from the control period before the drug was given served as the appropriate control. Because equidistantly sampled data are required for a fast Fourier transform, the beat-to-beat values of each parameter in such segments were interpolated (cubic spline) and resampled at 20.48 Hz. The resulting time series were divided into half-overlapping sequential sets of 200 s. Before calculation of spectral power, each segment was subjected to linear trend removal and cosine tapering. For each parameter, spectral power was calculated as the average over the sequential data sets.

To determine the extent to which fluctuations of MAP cause those of RBF, the admittance gain, phase, and coherence between MAP and RBF were calculated (15). When the admittance gain equals one, it indicates that the output (RBF) fluctuates with the same relative amplitude as the input (MAP). An admittance gain of one does not necessarily mean that RBF oscillations passively follow the MAP oscillations. Only when the phase is close to zero do the MAP and RBF changes occur simultaneously. An admittance gain of less than one would mean that the imposed fluctuations by MAP are buffered. A gain close to zero would indicate perfect autoregulation of RBF. Gains of more than one suggest that fluctuations in MAP are either amplified in the renal vascular bed or that the oscillations in RBF are generated within the vascular bed itself. This does not exclude autoregulatory mechanisms. For instance, when the myogenic response is amplified by sympathetic nerves and the resulting change in flow is greater than the original change in pressure, the admittance gain will be greater than one at a specific frequency.

The power spectra were divided into four different domains: 1) a high-frequency domain containing oscillations that are linked to the breathing cycle (HF: 0.6–2 Hz); 2) a midfrequency domain (MF: 0.25–0.6 Hz) containing oscillations associated with sympathetic nerve firing; 3) a low-frequency range (LF: 0.07–0.25 Hz), which comprises oscillations related to myogenic control; and 4) a very-low-frequency band (VLF: 0.01–0.07 Hz), including fluctuations related to TGF as well as other undefined low-frequency fluctuations (13, 15). In each frequency band, the sum of powers and the average of the gain, phase, and coherence were determined. These values were used for statistical purposes.

**Verification of SAD**

The effectiveness of SAD was verified in two ways. First, traditional sigmoidal blood pressure-HR curves were constructed using intravenous injections of phenylephrine hydrochloride (0.5 mg/ml, Sigma, St. Louis, MO) and sodium nitroprusside (1 mg/ml, Fluka, Fig. 1A). Second, spectral analysis techniques were employed. For this purpose, the amplitude and time relations of the frequencies inherent in the original blood pressure and RSNA signal were compared. As indicated in Fig. 1B, under resting control conditions, the dominant rhythm in RSNA was at the cardiac rate of 4 Hz. As described by Barman et al. (2), this can be largely explained by baroreceptor afferents entraining sympathetic outflow. The peak at lower frequencies is due to respiratory modulation of RSNA. In contrast, in SAD rabbits, bursts of RSNA were no longer synchronized to the cardiac cycle, and there was no dominant cardiac-related peak in the power spectrum of RSNA (Fig. 1C). The strength of the coupling between the pressure and RSNA oscillations was quantified by the calculation of the cross-correlation function. As shown in Fig. 1D, under resting conditions, the cross-correlation between blood pressure and RSNA was significantly blunted after SAD. Due to baroreceptor unloading induced by the 3-mg/kg dose of captopril, RSNA power increased at the cardiac rate in intact (Fig. 1B), but not in SAD, rabbits (Fig. 1C). Functional baroreceptor deafferentation was indicated by 1) the depressed gain of the sigmoidal pressure HR curve, 2) the lack of coherence between MAP and RSNA, and 3) the lack of spectral changes in response to reductions in pressure induced by baroreceptor unloading.

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Statistical Analysis

Data are means ± SE, unless otherwise indicated. To compare the steady-state hemodynamic changes in the control, RNX, and SAD animals, a split plot or “nested” repeated analysis of variance was performed with group differences as the between factor and the repeated doses of saline (time control study) and captopril or rilmenidine as the within factor. From the latter, dose-response relationships were determined by linear and nonlinear polynomial orthogonal contrasts (39). Differences among groups were identified with the between groups term and the group × dose interaction. A Bonferroni adjustment of the t-statistic was made, with the number of hypotheses tested and the number of variables examined taken into consideration. Furthermore, the Greenhouse-Geisser coefficient was used to redress the “relatedness” of the repeated measurements. Statistical significance was accepted at $P < 0.05$.

RESULTS

Steady-State Effects of Rilmenidine

The time control data obtained with saline injections in the three different groups of animals are presented in Fig. 2, which shows that, in each group, hemodynamic variables were stable during the recording period. Baseline MAP and HR were significantly higher in the SAD than in the intact or RNX rabbits. Figure 3 summarizes the effects of rilmenidine in the three preparations. Rilmenidine dose dependently reduced MAP, HR, and RBF in all rabbits. The reductions of MAP were greater in SAD than in intact and RNX rabbits. The decline of RSNA was not different in intact and SAD rabbits. RC was not altered in intact rabbits; however, in RNX rabbits, RC fell when high doses of the agent were applied. In contrast, in SAD rabbits, RC rose by 30% at the 0.3- and 0.6-mg/kg doses. This vasodilator effect was diminished after the 1-mg/kg dose.

Steady-State Effects of Captopril

The dose-dependent, steady-state effects of captopril are compared in Fig. 4. In all groups MAP fell significantly ($P < 0.001$) in a dose-dependent manner, whereas HR remained unaltered. In the intact rabbits, average RSNA increased by 64 ± 8% after the highest dose. This was not observed in the SAD group, showing that the increase in RSNA after captopril is derived from baroreceptor unloading. In all rabbits, captopril dose dependently increased RBF and RC. The magnitude of the increase in RBF and RC was comparable in all three groups, despite the different effects on RSNA.

Dynamic Effects of Rilmenidine

In Fig. 5, the effect of rilmenidine (0.3 mg/kg) on spectral power of MAP, RC, and RSNA is presented. Associated with the average reduction of RSNA, the spectral power of RSNA was reduced over all frequency bands. Associated with the fall in blood pressure, the spectral power of MAP was significantly reduced over the VLF, LF, and MF ranges. In SAD rabbits, the same

![Fig. 2. Steady-state changes in hemodynamics during repeated saline injections in intact, RNX, and SAD rabbits. Average control (CON) values of RSNA (C), renal blood flow (RBF; D), and renal conductance (RC; E) were normalized to a value of 100. A and B: MAP and HR, respectively. * $P < 0.05$, difference (whole curve) between SAD and intact or RNX.](http://ajprenal.physiology.org/DownloadedFrom/10.220.33.4.onOctober20,2017)
Fig. 3. Steady-state changes in hemodynamics during cumulative intravenous rilmenidine injections in intact, RNX, and SAD rabbits. *$P < 0.05$, difference (whole curve) between SAD and intact or RNX rabbits. **$P < 0.05$ different (whole curve) between SAD and RNX rabbits only.

Fig. 4. Steady-state changes in hemodynamics during cumulative intravenous captopril injections in intact, RNX and SAD rabbits. *$P < 0.05$, difference (whole curve) between SAD and intact or RNX rabbits.
pattern was observed (data not shown). In intact rabbits, rilmenidine-induced changes in the spectral power of RC occurred in the same frequency bands as for blood pressure. As expected, when renal nerves were absent, rilmenidine did not change the spectral power of RC in the MF band of RNX rabbits. Interestingly, MF spectral power of MAP was also not altered. In the RNX animals, changes in spectral power were limited to the VLF range. The effects of rilmenidine on the admittance gain between MAP and RBF are presented in Fig. 6. In all of the preparations, rilmenidine did not alter the admittance gain between MAP and RBF at any frequency. The average admittance value in the VLF band (pooled over all 3 preparations) was 0.93 ± 0.13. After rilmenidine, this value was not significantly altered (1.17 ± 0.16, P > 0.2). The average phase delay in the VLF range also remained unaltered with pressure fluctuations leading the flow fluctuations with ≈3 s. These data indicate that there was a comparable decline in the amplitude of MAP and RBF oscillations.

**Dynamic Effects of Captopril**

The effect of captopril on spectral power of MAP, RC, and RSNA is presented in Fig. 7. Associated with the average fall in blood pressure, in intact rabbits the spectral power of MAP was slightly but significantly (P = 0.04) reduced in the LF band. Furthermore, in these animals, captopril significantly reduced RC power in the LF and MF bands, suggesting a reduction of myogenic and sympathetic influences, respectively. In contrast, the amplitude of MF (P = 0.02) and HF (P = 0.03) fluctuations of RSNA was enhanced after the 3-mg/kg dose of captopril. In RNX animals, comparable changes in LF power of MAP and RC were observed as was found in intact rabbits.

Captopril, unlike rilmenidine, significantly changed the dynamic characteristics of renal autoregulatory behavior (Fig. 8). In the three groups of rabbits, in control conditions, admittance gain values lower than one were found in the VLF band, whereas the gains greater than one were found at higher frequencies. Captopril markedly altered this pattern. However, the alterations were very similar in all groups, indicating that these dynamic effects were not influenced by the renal nerves or by baroreceptor afferents. In the VLF band, the admittance gain increased from 0.59 ± 0.08 to 0.92 ± 0.06 (data are averages over all rabbits, P < 0.01). This was associated with an increase in coherence in the VLF range from 0.38 ± 0.04 to 0.64 ± 0.05 (P < 0.05), whereas the phase relationship became close to zero (from 2.0 ± 0.8 to 0.2 ± 0.4 s, P < 0.01). In the LF band, captopril reduced the admittance gain from 1.44 ± 0.09 to values close to one (0.97 ± 0.05, P < 0.01). The average coherence between MAP and RBF increased from 0.57 ± 0.03 to 0.69 ± 0.05. In control conditions, LF pressure oscillations preceded the LF flow oscillations by 1.0 ± 0.1 s. After captopril the
average phase delay was significantly shortened to 0.3 ± 0.1 s, P < 0.02. These dynamic changes indicate that, in the presence of captopril, the relationship of MAP and RBF oscillations has been altered as such that they occur now more synchronized and with the same relative amplitude.

DISCUSSION

By using simultaneous recordings of RBF and RSNA to the same kidney in preparations from conscious rabbits, this study provides evidence that the renal hemodynamic effects of the imidazoline receptor agonist rilmenidine were dependent on the level of ongoing RSNA. In conditions where there was elevated RSNA, a sympathetically mediated vasodilation occurred, whereas in the absence of RSNA a direct vasoconstrictor effect was observed. In contrast, the renal hemodynamic effect of captopril was not dependent on ongoing RSNA. The captopril-induced renal vasodilatation was similar regardless of whether RSNA was enhanced or even present. The renal vasodilator effects of captopril, unlike those of rilmenidine, were associated with impaired autoregulation of blood flow.

Steady-State Effects of Rilmenidine and Captopril

To evaluate whether renal nerves modulate the renal hemodynamic effects of rilmenidine and captopril, we compared the renal hemodynamic effects of increasing doses in intact, RNX, and SAD rabbits. The latter preparation was chosen as a model of presumed sympathetic hyperactivity (19) and to evaluate the potential role of the baroreflex in the effects of these blood pressure-lowering agents. Baseline blood pressure and hyperactivity values were indeed higher in the SAD group, which suggests that the normalization of blood pressure, which is known to return gradually to predenervation levels between 5–36 days after deafferentation (33), has not been completed. In SAD rabbits, the hypotensive response to rilmenidine was enhanced. Therefore, it is reasonable to assume that these rabbits had some form of neurogenic hypertension. It was not possible to judge from our multifiber nerve preparations whether sympathetic activity was truly higher in the SAD group than in the intact rabbits, as only relative changes in RSNA could be compared between groups.

In conscious rabbits, the rilmenidine-induced renal hemodynamic effects were dependent on ongoing RSNA as well as a direct vascular effect. Vasodilation occurred in the SAD rabbits, whereas in RNX rabbits a vasoconstrictor response was found. The present study was not designed to evaluate the pharmacology of the receptors involved in this latter response, but presumably the vasoconstriction was due to \(a_2\)-receptor stimulation because rilmenidine has an affinity for such receptors (9, 10, 37). In intact animals, rilmenidine did not alter renal conductance. This suggests that in this resting preparation the vasodilator and vasoconstrictor effects were equally strong. The present observation is in accordance with previous studies that evaluated the role of renal nerves in the control of RBF with electrical stimulation techniques (7). At low levels of stimulation, renal nerves did not control renal conductance. Only when high levels of electrical activity were imposed did tonic renal vascular changes occur. Elevated RSNA can be observed in hypertensive conditions (8), which may explain why rilmenidine increases renal conductance in hypertensive rats (36) and hypertensive patients (24). In resting conditions in rabbits, baseline RSNA is relatively low because sympathetic bursts do not occur with every heartbeat and do not show a profound 0.3-Hz modulation, which is only present during stressful conditions such as hypoxia (15) or hemorrhage (25).

Captopril reduced blood pressure to a comparable degree in all three preparations. In intact, but not SAD, rabbits, the fall in blood pressure was accompanied by a 64 ± 8% increase in postganglionic RSNA. This indicates that the increase in sympathetic activity is due to baroreceptor unloading. Furthermore, it excludes the possibility that captopril has a central sympatholytic effect. In contrast, captopril may have enhanced the baroreflex-mediated RSNA response by a central effect on AT1 receptors (4, 20). This is supported by the observation that in renal hypertensive rabbits captopril increased RSNA more than when the calcium antagonist nicardipine...
Dynamic Effects of Rilmenidine and Captopril

Renal nerves modulate RBF variability in several physiological conditions (3, 15, 26, 45). As recently demonstrated by Nafz et al. (29), oscillations of RBF exert an antihypertensive effect when renal perfusion pressure is reduced. Associated with the steady-state reduction of RSNA, rilmenidine decreased the amplitude of the RSNA oscillations over a wide frequency range. Conversely, after captopril both RSNA and the amplitude of the RSNA oscillations in the MF band were increased. Because the response time of the renal vasculature is fast enough to follow RSNA oscillations, 0.5 Hz, RSNA fluctuations in the MF band are usually transmitted into comparable oscillations of MAP, RBF, and RC, especially when RSNA is increased during hypoxia or hemorrhage (15, 25). Here we show that the inverse is also true. When rilmenidine reduced RSNA variability, this resulted in a comparable decrease in MAP and RC variability. The dynamic coupling between RSNA and RC in the MF band was different for captopril. During ACE inhibition, MF power of RC declined despite the increase in RSNA power in the MF band. In other words, captopril inhibited the renal vascular response to the 3-s rhythm in sympathetic nerve firing, which may point to a prejunctional inhibitory effect of the drug. The MF fluctuations in RC contribute only to a small degree (5–10%) to total RC variation. Hence, the physiological significance of...
this potential sympatholytic effect can be considered to be small.

In intact RNX and SAD rabbits, rilmenidine reduced the amplitude of the LF and VLF fluctuations of both MAP and RBF. However, as indicated by the unchanged admittance gain, the decline in the amplitude of these MAP and RBF fluctuations was of the same magnitude. This indicates that after rilmenidine, RBF dynamics in response to pressure fluctuations are not altered. In contrast to these findings with rilmenidine, captopril had marked effects on the dynamic control of RBF. After the highest dose of captopril, LF myogenic oscillations in RC were completely abolished. LF myogenic oscillations probably originate from spontaneous intracellular Ca²⁺ oscillations in the arteriolar smooth muscle cells (1, 43). In the renal vascular bed, these oscillations are found at ≈0.15 Hz. They may arise in the afferent arterioles (30) and can be entrained by certain stimuli, here being pressure-induced arteriolar stretch or RSNA (26). Recently, it has been shown that the dynamic Ca²⁺ signaling in arterial smooth muscles is under the control of the local renin-angiotensin system and can be blunted by captopril as well as losartan (1). This may be the reason that the effect of captopril on the LF fluctuations was similar in all three preparations and that inhibition of the RAS system dominated the sympatholytic effect.

Similarly, as found by He and Marsh (12) in rats, captopril increased the admittance gain at frequencies <0.1 Hz. In the VLF band, the admittance gain rose significantly from 0.6 to 0.9, meaning that the magnitude of the flow oscillations was now similar to those of pressure. In addition, the phase relationship between MAP and RBF became close to zero. These findings are compatible with an attenuation of TGF during ACE inhibition (40). Recent studies showed that TGF responses were also absent in ACE-deficient (41) as well as in AT₁A receptor-deficient (34) mice and could be restored to near-normal levels with angiotensin II (41). From simulation studies Feldberg et al. (11), concluded that the myogenic response is a prerequisite to obtaining any degree of autoregulation of RBF by the TGF mechanism. Conversely, myogenic oscillations can be present when TGF is absent (30). These aforementioned studies were all done in isolated preparations from or those from anesthetized animals. The new aspect of the present study is therefore that the dynamic effects of ACE inhibition are now shown to be true in a preparation from an intact conscious animal and, second, that they are not influenced by sympathetic nerves. This is also supported by the lack of change in admittance gain by rilmenidine.

A potential point of concern in the interpretation of the present results may have been that the renal hemodynamic changes related to rilmenidine and captopril are due to the fact that blood pressure may have dropped below the autoregulatory range. Hence, it would be no surprise that renal autoregulation was impaired by captopril. However, several arguments speak against this. First, in rabbits, autoregulation is preserved down to 70 mmHg (44) and in our dynamic analysis pressures varied between 60 and 80 mmHg. Second, as reported by Sorenson et al. (40), resetting of renal autoregulation is a relatively fast process and occurs within 10 min. Only in the SAD group, which received rilmenidine, was blood pressure below 60 mmHg. However, changes in dynamic control were never different between groups but only between agents. Renal autoregulatory efforts were attenuated with captopril but not with rilmenidine. Therefore, these data suggest that the present dynamic changes in renal vascular control are drug specific and not entirely related to the pressure fall.

In conclusion, renal hemodynamic effects of rilmenidine are mediated by a central sympatholytic as well as direct vascular effect. However, the renal vasodilator effect is dependent on the level of ongoing sympathetic activity. In contrast, the renal vasodilatation induced by captopril was not influenced by the central nervous system but was predominantly due to a peripheral inhibition of renal myogenic and TGF oscillations. This implies that, despite the captopril-induced reduction of systemic arterial pressure, pressure oscillations are further transmitted into the renal vascular bed and probably prevent a further fall in glomerular pressure, which may contribute to the diuretic effect of the drug.

Fig. 8. Comparison of renal vascular admittance gains in intact (A), RNX (B), and SAD (C) rabbits in control conditions before (thin lines) and after the 3-mg/kg dose of captopril (thick lines). *P < 0.05 different from control in the indicated frequency bands.
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