

Moxonidine Normalizes Sympathetic Hyperactivity in Patients with Eprosartan-Treated Chronic Renal Failure

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Abstract. Enalapril and losartan reduce but not normalize sympathetic hyperactivity in patients with hypertensive chronic renal failure (CRF). This study assessed the effect of chronic eprosartan on BP and sympathetic activity, and assessed the effect of moxonidine during chronic eprosartan treatment. In 11 stable patients with CRF (creatinine clearance 47 ± 10 ml/min), muscle sympathetic nerve activity (MSNA; peroneal nerve), BP, and baroreceptor sensitivity were measured in the absence of antihypertensive drugs (except diuretics) during chronic eprosartan therapy (600 mg for 6 wk) and in 9 patients after moxonidine (0.2 mg for 6 wk) was added. Normovolemia was controlled by diuretics and confirmed by extracellular fluid volume measurements. BP, heart rate, and MSNA were higher in patients than in 22 controls.

During eprosartan therapy, mean arterial pressure (111 ± 9 to 98 ± 7 mmHg, $P < 0.001$), heart rate (71 ± 10 to 65 ± 8 bpm, $P < 0.001$), and MSNA (35 ± 10 to 27 ± 8 bursts/min, $P < 0.001$) decreased. After the addition of moxonidine ($n = 9$), a further reduction of mean arterial pressure to 89 ± 7 mmHg ($P < 0.05$) and of MSNA to 20 ± 10 bursts/min ($P < 0.05$) occurred. Sympathetic activity in patients with CRF can be normalized, and angiotensin II–independent sympathetic hyperactivity contributes to the pathogenesis of renal hypertension. Sympathetic hyperactivity is associated with poor cardiovascular outcomes, implying that reduction might be beneficial to the patients. The addition of moxonidine to angiotensin II antagonist treatment might be appropriate.

Chronic renal failure (CRF) is often characterized by the presence of sympathetic hyperactivity (1–3). This contributes to the pathogenesis of renal hypertension. It is also associated with cardiovascular morbidity and mortality independently of its effect on BP (4). These data suggest that reducing sympathetic hyperactivity might be beneficial. Previously we have shown that both the angiotensin-converting enzyme (ACE) inhibitor enalapril and the angiotensin II (AngII) antagonist losartan reduce but not normalize sympathetic hyperactivity, when quantified by measuring muscle sympathetic nerve activity (MSNA) (5,6). These studies indicate that AngII mediated mechanisms are important in the pathogenesis of renal hypertension. The data also suggest that an additional intervention is needed to normalize sympathetic activity.

Eprosartan is an AngII antagonist with a chemical structure distinct from losartan and most other AngII antagonists. Some but not all experimental evidence suggests that eprosartan has a higher affinity to presynaptic Ang receptors than other AngII antagonists, thereby more effectively reducing sympathetic activity (7,8). In the study presented here, we evaluated in

patients with CRF the effects of eprosartan on BP and MSNA. Second, we hypothesized that if sympathetic activity is not normalized during chronic eprosartan, addition of a centrally acting sympatholytic agent with a mode of action different from AngII antagonists would further decrease sympathetic activity.

Materials and Methods

Subjects

Eleven (two women) hypertensive stable patients with CRF participated (Table 1). Their renal diagnoses were as follows: polycystic kidney disease ($n = 4$), urological disorders ($n = 3$), IgA nephropathy ($n = 1$), Alport disease ($n = 1$), and unknown ($n = 2$). Patients with clinically manifest heart disease (congestive heart failure, coronary heart disease, or atrial fibrillation) or diabetes mellitus, as well as patients known to have had adverse reactions to ACE inhibitors or AngII antagonists or who were receiving drugs known to influence sympathetic activity, were excluded. The patients were selected because they had a stable creatinine clearance between 30 and 70 ml/min and were hypertensive (sitting office BP $> 145/90$ mmHg) after stopping all antihypertensive medications, in the presence of normovolemia judged clinically from the absence of edema and confirmed with volume measurements. To control this normovolemic state, six patients were maintained on therapy with diuretics throughout the study. The data of the patients were compared with data obtained in a historical group of matched healthy subjects (Table 1).

In 11 patients, we obtained adequate MSNA measurements twice (baseline and during chronic eprosartan therapy) and in nine patients three times (baseline, during chronic eprosartan therapy, and during chronic therapy with eprosartan combined with moxonidine). The two cases of failure were caused by an inability to find an adequate MSNA signal and by refusal of the patient to undergo the third study.

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Table 1. Effects of eprosartan in hypertensive patients with chronic renal failure

| Characteristic | Patients | | Controls |
|--|--------------------------|----------------------------|-------------|
| | Baseline | Eprosartan | |
| No. (male) | 11 (9) | | 22 (18) |
| Age (yr) | 45 ± 14 | | 45 ± 14 |
| BMI (kg/m ²) | 26.2 ± 2.4 | 26.3 ± 2.2 | 25.2 ± 2.3 |
| Plasma creatinine (μmol/L) | 217 ± 40 ^a | 219 ± 47 ^a | 92 ± 15 |
| Creatinine clearance (ml/min) | 47 ± 10 ^a | 48 ± 13 ^a | 105 ± 18 |
| Systolic arterial pressure (mmHg) | 147 ± 12 ^a | 130 ± 10 ^b | 126 ± 15 |
| Diastolic arterial pressure (mmHg) | 94 ± 8 ^a | 82 ± 6 ^b | 70 ± 8 |
| Mean arterial pressure (mmHg) | 111 ± 9 ^a | 98 ± 7 ^b | 88 ± 9 |
| Heart rate (beats/min) | 71 ± 10 ^a | 65 ± 8 ^c | 62 ± 10 |
| log Plasma renin activity (fmol/L/sec) | 2.64 ± 0.17 ^a | 3.11 ± 0.38 ^{a,b} | 2.34 ± 0.18 |
| MSNA (burst/min) | 35 ± 10 ^a | 27 ± 8 ^b | 20 ± 11 |
| MSNA (burst/100 bpm) | 46 ± 13 ^a | 41 ± 9 ^d | 31 ± 16 |
| Baroreceptor sensitivity for: | | | |
| MSNA (bursts/min per mmHg) | 1.55 ± 0.95 | 1.71 ± 0.8 | |
| Heart rate (beats/min per mmHg) | 0.71 ± 0.43 | 0.92 ± 0.53 | |

Values are mean ± SD. Arterial blood pressures represent values obtained in supine position. BMI, body mass index; MSNA, muscle sympathetic nerve activity.

^a $P < 0.001$ compared with controls.

^b $P < 0.001$ compared with baseline.

^c $P = 0.02$ compared with baseline.

^d $P = 0.05$ compared with baseline.

Protocol

All patients provided informed consent to participate in the study, which was approved by the institutional committee for studies on humans. They were all receiving chronic antihypertensive treatment, which included an ACE inhibitor or an AngII antagonist. Patients were studied on three occasions: when taken off antihypertensive medication for more than 2 wk, during chronic (6 wk) eprosartan therapy (600 mg, once daily) or during chronic (6 wk) therapy with eprosartan combined with 0.2 mg of moxonidine (600 mg, both once daily). Vitamin D supplements, phosphate binders, and/or hydroxymethylglutaryl (HMG)–coenzyme A reductase inhibitors were continued.

The subjects underwent an identical set of measurements while they were in the supine position in a quiet room with an ambient temperature of 22 to 24°C. All study sessions were done in the morning between 2 and 5 h after drug intake. These measurements included supine BP, heart rate, MSNA, baroreflex sensitivity, extracellular fluid volume (ECFV), and plasma renin activity (PRA). BP was measured in a recumbent position by an automatic oscillometric device (Accutorr Plus; Datascope Corp, Paramus, NJ). Means of three measurements are presented. During the baroreflex sensitivity assessments, BP was recorded continuously by finger plethysmography (Finapres; Datex-Ohmeda, Louisville, CO). The Finapres device is especially suitable for analysis of changes in BP during short-term interventions (5,6). MSNA was recorded with a unipolar tungsten microelectrode placed in a muscle nerve fascicle of the peroneal nerve by means of the technique of Vallbo *et al.* (9), and described by us previously (5,6,10,11). The correct position of the electrode is evaluated by means of a Valsalva maneuver: the patient is asked to blow into a mouthpiece of an aeroid manometer to 40 mmHg for 15 s while BP, heart rate, and MSNA are continuously recorded. The BP overshoot after the restart of breathing is associated with a short pause in neural activity. The neural signal during the BP overshoot is consid-

ered to be the background noise. This procedure is done at the beginning and at the end of the study session. Success rate of obtaining an adequate neural signal is approximately 85%. The heartbeat intervals were measured from the electrocardiogram. The sample frequency is 200 Hz. An intravenous cannula for infusion and blood sample collection was inserted into an antecubital vein.

After instrumentation, the subjects rested for 20 min. Baseline measurements for BP, heart rate, and MSNA were obtained, blood was sampled for measurement of PRA and bromide, and bromide was injected intravenously for measurement of the ECFV. Next, baroreflex sensitivity was assessed as the response of MSNA and of heart rate to changes in BP induced by subsequent continuous infusion of sodium nitroprusside and phenylephrine. Sodium nitroprusside (333 μg/ml in glucose 5%) was infused starting at a rate of 33 μg/min and individually increased (in 3-min steps) to obtain a reduction of mean arterial pressure of at least 12 mmHg. After a second 20-min rest period, a continuous infusion of phenylephrine (333 μg/ml in saline 0.9%) was started at a rate of 33 μg/min and individually increased (in 3-min steps), to increase mean arterial pressure by at least 12 mmHg. The nerve activity was monitored online (Poly 5; Inspectors Research Systems, Amsterdam, The Netherlands) and stored on disk for offline analysis.

Laboratory Analyses

Bromide distribution volume, as an index of extracellular fluid volume, was calculated from plasma bromide concentration in blood samples obtained at 90, 120, and 150 min after injection of 4 g of sodium bromide. Plasma bromide was measured colorimetrically at 440 nm by the gold bromide technique and corrected for plasma bromide before injection. The distribution volume was corrected for bromide penetration into erythrocytes for plasma water content and

for the Donnan equilibrium effect and expressed as ml/kg lean body mass (12). Plasma bromide levels range between 1 and 3 mmol/L, which is well below the therapeutic and toxic level (12). Lean body mass, estimated from weight and height, is the most suitable index for normalization of body fluid volumes in humans and allows comparison between men and women (13). The normal range in our laboratory is 273 to 334 ml/kg of lean body weight. PRA was measured by RIA (14).

Data Analyses

Data are given as mean \pm SD, unless indicated otherwise. MSNA was expressed as the number of bursts of sympathetic activity per minute or as the number of bursts per 100 heart beats to correct for differences in heart rate. Intraobserver and interobserver reproducibility are, respectively, $4.5\% \pm 0.5\%$ and $6.2\% \pm 0.7\%$ (6). During the sodium nitroprusside and phenylephrine infusion, MSNA was counted for 1 min during each infusion step. The results of the continuous registration of BP and heart rate were averaged per minute. Baroreflex sensitivity was expressed as changes in MSNA and heart rate versus BP. It was calculated for each subject by least-squares analysis of the linear part of the baroreflex curves that included the baseline value and expressed as the number of bursts per minute per millimeter of mercury and the number of beats per minute per millimeter of mercury, respectively.

Statistical Analyses

PRA was analyzed after logarithmic transformation. Baseline characteristics of patients and controls were compared by unpaired *t* test. Differences between different occasions of patients were examined by repeated-measure ANOVAs. If variance reached statistical significance, the means were analyzed by Student-Newman-Keuls test in parametric variables and Kruskal-Wallis ANOVA on ranks in non-parametric variables. A *P* value of 0.05 was considered to be statistically significant.

Results

When untreated, BP, heart rate, PRA, and MSNA in the patients were clearly higher than in controls (Table 1). The ECFV was within normal limits (patients 313 ± 22 , controls 303 ± 28 ml/kg lean body mass [LBM]). Six weeks of treatment with eprosartan reduced mean arterial pressure by $12\% \pm 6\%$ ($P < 0.001$) and MSNA by $23\% \pm 11\%$ ($P < 0.001$) (Table 1). Heart rate decreased, and, as expected, PRA increased. Six weeks after the addition of moxonidine ($n = 9$) to the eprosartan treatment, BP and MSNA were further decreased; mean arterial pressure decreased from 98 ± 7 to 89 ± 7 mmHg ($P < 0.05$) and MSNA from 26 ± 9 to 20 ± 8 ($P < 0.001$). Mean arterial pressure and MSNA became identical to controls (88 ± 10 mmHg and 20 ± 10 bursts/min, respectively) (Figure 1). Heart rate (from 65 ± 9 to 66 ± 8 bpm) and PRA remained unchanged after the addition of moxonidine. Baroreceptor sensitivity did not change (baseline, during eprosartan therapy, and during the combination eprosartan and moxonidine therapy: MSNA, 1.55 ± 0.95 , 1.71 ± 0.80 , and 1.71 ± 0.85 bursts/min mmHg; heart rate, 0.71 ± 0.43 , 0.92 ± 0.53 , and 0.71 ± 0.43 beats/min mmHg; Figure 2). Throughout the study period, ECFV and plasma creatinine levels did not change.

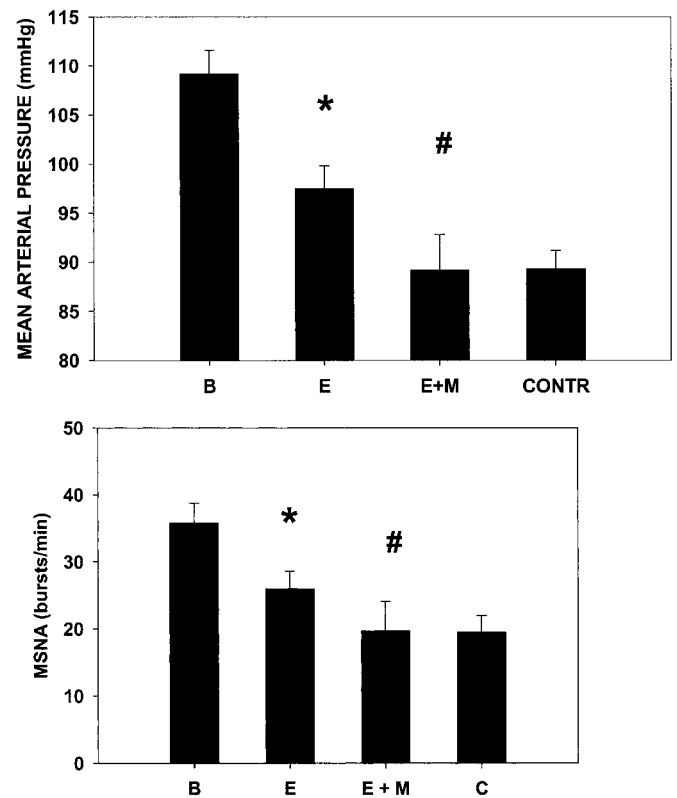


Figure 1. (a) Mean arterial pressure (mmHg) in patients with chronic renal failure ($n = 9$) when untreated (B = baseline), during chronic eprosartan (E) and chronic E combined with moxonidine (E + M) treatment. Controls (CONTR) are healthy age-matched persons ($n = 22$). Data are means \pm SD. * $P < 0.05$ baseline versus E. # $P < 0.05$ E versus E + M. (b) Muscle sympathetic nerve activity (MSNA, burst/min) in patients with chronic renal failure ($n = 9$) when untreated (B = baseline) during chronic E and chronic E + M treatment. Controls (CONTR) are healthy age-matched persons ($n = 22$). Data are means \pm SD. * $P < 0.05$ baseline versus E. # $P < 0.05$ E versus E + M.

Discussion

To our knowledge, this is the first study to indicate that sympathetic hyperactivity in patients with CRF chronically treated with an AngII antagonist is further reduced and normalized after the addition of moxonidine. This study adds new information to the knowledge of the pathogenesis of the sympathetic hyperactivity in renal hypertension. It confirms earlier data that AngII-mediated mechanisms are important, but the study suggests that AngII-independent mechanisms are also involved.

AngII can stimulate sympathetic activity on various levels. It increases central sympathetic outflow, and facilitates ganglionic transmission and synaptic noradrenaline release by stimulation of presynaptic receptors. Previously, we have demonstrated in hypertensive patients with CRF that both enalapril and losartan therapy reduce but do not normalize MSNA (5,6). These results underscore the relevance of AngII in the pathogenesis of renal hypertension, and they indicate that both agents pass the blood-brain barrier. The study presented here

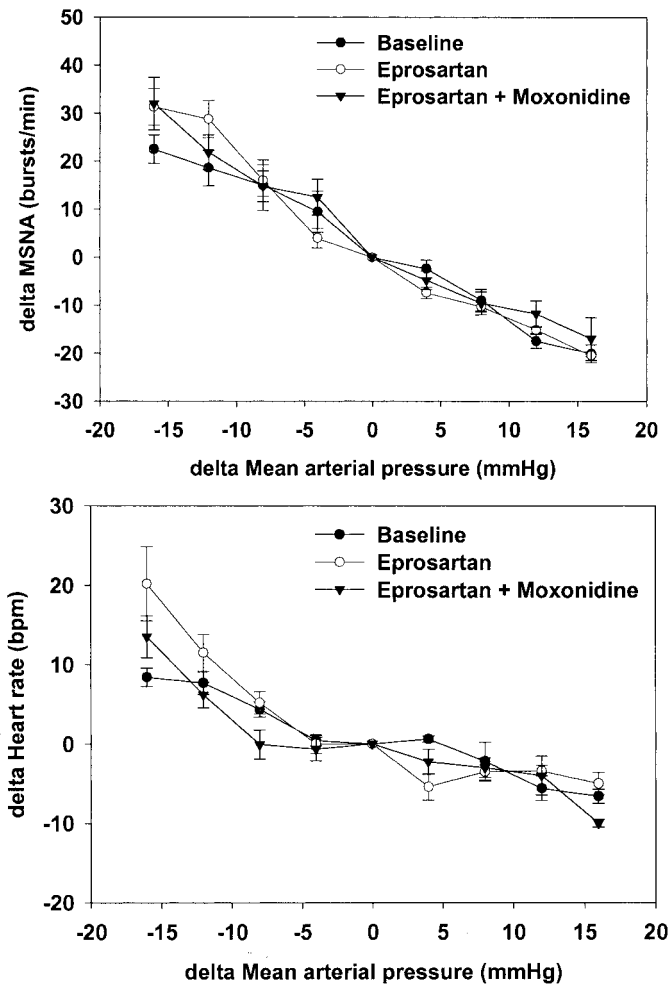


Figure 2. Baroreflex response to changes in mean arterial pressure (MAP, mmHg) in patients with chronic renal failure without antihypertensive treatment, during chronic eprosartan and chronic eprosartan combined with moxonidine treatment. Changes in MAP are plotted against changes in muscle sympathetic nerve activity (MSNA) and heart rate. Differences in slopes were NS.

confirms that hypertensive patients with CRF exhibit sympathetic hyperactivity. Heart rate is also increased, suggesting that not only MSNA, which is the centrally originated sympathetic activity to the resistance vasculature, but also the sympathetic activity affecting heart rate is increased.

The chemical structure of eprosartan is distinct from that of most other AngII antagonists (15). It passes the blood-brain barrier in experimental models (16). Studies comparing AngII antagonists in this respect are not available. Some experimental studies suggest that eprosartan has a higher sympatho-inhibiting potential than other AngII antagonists (7,8). The study presented here shows a $23\% \pm 11\%$ reduction in MSNA by eprosartan, which is comparable to the MSNA reduction of approximately 20% during losartan or enalapril (6). Also, heart rate decreased significantly, giving support to the notion that cardiac sympathetic activity is decreased as well. This study indicates that in humans, eprosartan passes the blood-brain barrier. It suggests that its capacity to reduce MSNA is com-

parable to that of losartan and enalapril. The dose-response curve of eprosartan in essential hypertension with respect to the effect on BP is flat above 600 mg, suggesting that the present dosage is optimal. We cannot exclude the possibility that a higher dosage would have a more pronounced sympatho-inhibiting effect.

Moxonidine is a high affinity agonist of imidazoline I_1 receptors, which are located in the rostral ventrolateral medulla (RVLM) of the brainstem. Stimulation of these receptors reduces central sympathetic outflow, and subsequently BP, by a decrease in peripheral vascular resistance (17,18). After oral ingestion, peak concentration are achieved within 1 h. The plasma half-life is 2 h, and this is extended in kidney failure (19). The duration of the antihypertensive effect is much longer than the plasma half-life suggests, which implies retention in the central nervous system. The sympatho-inhibitory effect of moxonidine seems to be mediated almost entirely by its effect on these brainstem receptors. It has low affinity to central nervous system α_2 adrenoceptors, explaining why it is associated with fewer side effects than the centrally acting compound clonidine (17,18). Its antihypertensive efficacy is well established in essential hypertension; it is comparable to most other antihypertensive agents (17). In the study presented here, addition of moxonidine to chronic treatment with an AngII antagonist resulted in a 9 ± 3 mmHg reduction of mean arterial pressure. This effect is comparable to the approximately 10 mmHg reduction with this dose during chronic treatment in patients with essential hypertension (20). This study was not specifically designed to monitor side effects, but it confirms an earlier study in patients with CRF in which addition of moxonidine to treatment with an ACE inhibitor or an AngII antagonist was well tolerated and resulted in a decrease in BP and a slower decline in GFR than calcium antagonist treated patients (21). We found a $24\% \pm 11\%$ further reduction of MSNA. In patients with essential hypertension, a 19% reduction was seen when patients received monotherapy with an identical dose (20). In that study, doubling the dose provided no additional effect on MSNA. The addition of moxonidine had no influence on baroreceptor sensitivity—that is, the capacity to increase or decrease MSNA or heart rate to buffer short-term BP fluctuations. In that respect, moxonidine does not differ from clonidine, which also does not affect baroreceptor sensitivity, when assessed by identical methodology (22,23).

The RVLM of the brainstem contains both imidazoline I_1 and AngII receptors. Microinjection of AngII into the RVLM increases BP and peripheral sympathetic activity, and these effects are blocked by AngII antagonists (24,25). Microinjection of moxonidine into the RVLM also reduces BP by a reduction of sympathetic activity. Ligands for AngII receptors and imidazoline receptors have structural similarities. However, experimentally, moxonidine has no cross-reactivity with AngII receptors (26), making it unlikely that effects of moxonidine in this study are merely explained by a more complete blockade of the AngII receptors. We cannot exclude the possibility that the effect of moxonidine is a nonspecific effect of

BP reduction. We have not studied the effect of the addition of other antihypertensive agents to AngII antagonist treatment.

The study presented here and our previous studies indicate that in renal hypertension, blocking AngII-mediated mechanisms only partially reduces BP and sympathetic hyperactivity. The study shows that after eliminating the effects of the enhanced renin-angiotensin system, central mechanisms sensible to imidazoline I₁ receptor agonism are still involved in maintaining increased BP. Whether these central mechanisms are identical to those in essential hypertension or whether they are specific to the uremic environment is unknown. We have recently shown that increasing the frequency of hemodialysis from three to six times weekly results in a decrease in MSNA, without effect on PRA (27). The MSNA returned to its initial level after the patients returned after 6 mo to the three-times-a-week regimen. This finding points to mechanism(s) independent of the renin-angiotensin system in the pathogenesis of sympathetic hyperactivity. Also, in patients with heart failure who receive chronic treatment with an ACE inhibitor or AngII antagonist, MSNA was normalized only after the addition of clonidine (22).

The present data may have important implications for the treatment of patients with CRF. There is substantial evidence that sympathetic hyperactivity should be considered as a cardiovascular risk factor (1–3). Sympathetic activity is associated with all-cause mortality and poor cardiovascular outcomes in patients with CRF, suggesting that treatment of sympathetic hyperactivity could be beneficial. ACE inhibitors appear to be particularly effective in reducing left ventricular hypertrophy in patients with CRF (28–30). A retrospective analysis in hemodialysis patients receiving ACE inhibitors, independent of its effect on BP, found that it seems to be associated with a dramatic reduction in mortality (31). In patients with CRF not on dialysis, ACE inhibitor therapy also improved survival rates independent of its effect on BP (32). A recent study shows that in dialysis patients with dilated cardiomyopathy, addition of carvedilol, which has been shown to reduce cardiac sympathetic activity, possibly by its effect on prejunctional beta₂-adrenergic receptors (33), to the standard therapy regimen including ACE inhibitors, cardiovascular morbidity and mortality are reduced as compared with placebo (34). These latter data suggest that in selected patients, addition of an additional sympatholytic agent may improve prognosis. Indeed, ACE inhibitors and AngII antagonists have now been accepted both in Europe and the United States as first-choice treatment in patients with CRF, combined with diuretics or ultrafiltration to obtain normovolemia (35,36). Both Guidelines Committees recognized that in patients with CRF, a third agent is often necessary to obtain normotension. A sympatholytic agent such as moxonidine might be an appropriate choice. Whether this addition indeed improves clinical outcomes in patients with CRF remains to be established.

In conclusion, this study shows that the combination of an AngII antagonist with the centrally acting sympatholytic agent moxonidine normalizes both BP and MSNA in hypertensive normovolemic patients with CRF. The data indicate that apart from the enhanced activity of the renin-angiotensin system,

AngII-independent mechanisms are also involved in the pathogenesis of renal hypertension.

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