

REDUCTION OF SYMPATHETIC HYPERACTIVITY BY ENALAPRIL IN PATIENTS WITH CHRONIC RENAL FAILURE

GERRY LIGTENBERG, M.D., PH.D., PETER J. BLANKESTIJN, M.D., PH.D., P. LIAM OEY, M.D., PH.D., INGE H.H. KLEIN, M.D., LIOE-TING DIJKHORST-OEI, M.D., FRANS BOOMSMA, PH.D., GEORGE H. WIENEKE, PH.D., ALEXANDER C. VAN HUFFELEN, M.D., PH.D., AND HEIN A. KOOMANS, M.D., PH.D.

ABSTRACT

Background Inhibition of angiotensin-converting enzyme (ACE) reduces the risk of cardiovascular problems in patients with chronic renal failure. This effect may be due in part to a decrease in sympathetic nervous activity, but no direct evidence of such an action is available.

Methods We studied muscle sympathetic-nerve activity in 14 patients with hypertension, chronic renal failure, and increased plasma renin activity before, during, and after administration of the ACE inhibitor enalapril. Ten other patients with similar clinical characteristics were studied before and during treatment with the calcium-channel blocker amlodipine. Normal subjects matched for age and weight were included in both studies.

Results At base line, mean (\pm SD) muscle sympathetic-nerve activity was higher in the group of patients who received enalapril than in the control subjects (35 ± 17 vs. 19 ± 9 bursts per minute, $P=0.004$). The baroreflex curve, which reflects changes in muscle sympathetic-nerve activity caused by manipulations of blood pressure with sodium nitroprusside and phenylephrine, was shifted to the right in the patients, but baroreflex sensitivity was similar to that in the control subjects (-2.1 ± 1.9 and -2.7 ± 1.3 bursts per minute per mm Hg, respectively; $P=0.36$). A single dose of the sympatholytic drug clonidine caused a greater fall in blood pressure in the patients than in the control subjects. Treatment with enalapril normalized blood pressure and muscle sympathetic-nerve activity (at 23 ± 10 bursts per minute) in the patients and shifted the baroreflex curve to the left, reflecting normal blood-pressure levels, without significantly changing sensitivity (-2.3 ± 1.8 bursts per minute per mm Hg, $P=0.96$). In the patients who received amlodipine, treatment also lowered blood pressure but increased muscle sympathetic-nerve activity, from 41 ± 19 to 56 ± 14 bursts per minute ($P=0.02$).

Conclusions Increased sympathetic activity contributes to hypertension in patients with chronic renal disease. ACE inhibition controls hypertension and decreases sympathetic hyperactivity. (N Engl J Med 1999;340:1321-8.)

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PATIENTS with essential hypertension,^{1,2} accelerated hypertension,³ or chronic renal failure⁴ have increased sympathetic activity, which contributes not only to their hypertension but also to atherogenesis and cardiac hypertrophy.^{5,6} In patients with congestive heart failure, sympathetic overactivity is associated with a poor prognosis and an increased risk of cardiac arrhythmias and sudden death.^{7,8} Angiotensin-converting-enzyme (ACE) inhibitors and calcium-channel blockers are widely used in all these conditions to lower blood pressure or improve cardiac function, but whether these two classes of drugs differ in their ability to control sympathetic overactivity is not known.

ACE inhibition is accompanied by a decrease in plasma catecholamine concentrations in patients with essential hypertension,⁹ suggesting that the drugs reduce sympathetic activity. However, in patients with congestive heart failure and chronic renal failure, renal clearance of catecholamines is reduced, which can make recognition of a decrease in sympathetic activity problematic.^{10,11} Muscle sympathetic-nerve activity can be measured directly and accurately by microneurography.^{12,13} The changes in muscle sympathetic-nerve activity during relaxation and contraction of various limbs and during hemodynamic-challenge studies are concordant,^{14,15} and the results are correlated with peripheral vascular resistance.¹⁵ In normal subjects, muscle sympathetic-nerve activity increases in response to single doses of nifedipine¹⁶ but does not change in response to captopril.¹⁷ In patients with accelerated hypertension, captopril decreased muscle sympathetic-nerve activity.³ In patients with congestive heart failure, short-term ACE inhibition with enalaprilat decreased muscle sympathetic-nerve activity slightly,¹⁸ whereas sustained ACE inhibition caused a marked decrease in such activity without affecting blood pressure.¹⁹ These results suggest that ACE inhibition can have delayed effects on sympathetic activity. The effect of long-

From the Departments of Nephrology and Hypertension (G.L., P.J.B., I.H.H.K., L.T.D.-O., H.A.K.) and Clinical Neurophysiology (P.L.O., G.H.W., A.C.H.), University Hospital Utrecht, Utrecht; and the Department of Internal Medicine, University Hospital Rotterdam, Rotterdam (F.B.) — both in the Netherlands. Address reprint requests to Dr. Ligtenberg at the Department of Nephrology and Hypertension, University Hospital Utrecht, Rm. F03.226, PO. Box 85.500, 3508 GA Utrecht, the Netherlands, or at gligtenb@digd.azu.nl.

term treatment with calcium-channel blockers is not known.

We tested the hypotheses that sympathetic activity is increased in patients with hypertension who also have chronic renal failure and that it can be controlled by ACE inhibition but not by calcium-channel blockade. We therefore measured muscle sympathetic-nerve activity to determine whether these types of drugs would have differential effects on such activity over a range of blood-pressure levels and whether baroreflex function would be preserved in two groups of patients, one treated with the ACE inhibitor enalapril and the other treated with the calcium-channel blocker amlodipine.

METHODS

Study Participants and Study Design

Study 1

We studied 14 patients with chronic renal failure (creatinine clearance, 15 to 60 ml per minute). Six patients had polycystic kidney disease; two had obstructive uropathy; one each had chronic tubulointerstitial nephritis, IgA nephropathy, focal segmental glomerulosclerosis, and analgesic nephropathy; and two had chronic renal failure of unknown cause. In addition, we studied 14 normal subjects matched for age and weight. The mean (\pm SD) creatinine clearance of the patients was 31 ± 18 ml per minute. All had hypertension but were selected because they were normotensive without apparent volume overload while they were taking an ACE inhibitor. Patients who were taking other antihypertensive or vasodilator drugs and those with cardiac disease or diabetes mellitus were excluded.

The patients were asked to stop taking ACE inhibitors for at least three weeks, after which a 24-hour urine sample was collected for measurement of creatinine and norepinephrine. Blood pressure was measured weekly during this period, and no patient became severely hypertensive (diastolic blood pressure, >120 mm Hg). Microneurography and studies of baroreflex function were then conducted in a quiet room. Next, the effect of short-term ACE inhibition on muscle sympathetic-nerve activity was studied in nine of these patients. Five milligrams of enalaprilat was infused intravenously over a period of 5 minutes, and microneurography was conducted for 30 minutes. Two days later, the response to clonidine was determined as described below. Microneurography and baroreflex studies were repeated in 11 patients during treatment with 10 mg of enalapril daily for four to six weeks. In 9 of these 11 patients, the studies were again repeated four weeks after enalapril was discontinued; the other 2 patients declined to be reevaluated. The control subjects underwent microneurography and clonidine testing once.

Study 2

The effect of amlodipine was studied in 10 patients with hypertension and chronic renal failure. Three of these patients had polycystic kidney disease; two had obstructive uropathy; one each had IgA nephropathy, glomerulonephritis, and nephrosclerosis; and two had chronic renal failure of unknown cause. Ten normal subjects, matched for age and weight, were also studied. The mean creatinine clearance of the patients was 41 ± 22 ml per minute. These 10 patients were selected after discontinuation of therapy before the study. They underwent microneurography and baroreflex studies as described above, except that they were given 10 mg of amlodipine daily for four to six weeks instead of enalapril, and microneurography and baroreflex studies were not conducted after the drug was discontinued.

The studies were approved by the institutional committee for

studies in humans. All study participants gave written informed consent.

Measurements of Muscle Sympathetic-Nerve Activity and Baroreflex Function

All the participants were studied while supine in a room with a temperature of 23 to 25°C. A venous catheter was inserted into a vein in the forearm, and sodium bromide was administered to measure the extracellular-fluid volume. Systolic, diastolic, and mean arterial pressures and heart rate were obtained from continuous recordings of finger plethysmography (Finapres, Datex-Ohmeda, Louisville, Colo.). Cardiac output was measured by thoracic-impedance cardiography (model NCCOM 3, BoMed, Irvine, Calif.). For the recording of muscle sympathetic-nerve activity, a unipolar tungsten microelectrode was inserted into a fascicle of the peroneal nerve according to the technique of Vallbo et al.,¹³ as described previously.²⁰

The base-line measurements were completed in 1 to 2 hours, after which there was a 20-minute rest period. Blood samples were then obtained for measurements of plasma bromide, creatinine, norepinephrine, and renin activity. Muscle sympathetic-nerve activity, blood pressure, and heart rate were measured for three minutes. An intravenous infusion of sodium nitroprusside, 333 μ g per milliliter in 5 percent glucose, was then started at a rate of 33 μ g per minute and gradually increased to reduce mean arterial pressure in steps of 4 mm Hg (three minutes per step) until a reduction of at least 12 mm Hg was obtained. The nitroprusside infusion was then discontinued, after which blood pressure and sympathetic-nerve activity returned to base-line levels within a few minutes. Twenty minutes later, an intravenous infusion of phenylephrine, 333 μ g per milliliter in 0.9 percent saline, was started at a rate of 33 μ g per minute and gradually increased to increase mean arterial pressure in steps of 4 mm Hg until an increase of at least 12 mm Hg was obtained. The phenylephrine infusion was then discontinued, after which blood pressure and sympathetic-nerve activity returned to base line within a few minutes.

Clonidine Test

The participants were studied while supine in a quiet room. Blood pressure and heart rate were recorded with an automatic oscillometer (model 1400, Omega, Broken Arrow, Okla.) at five-minute intervals. After base-line values were measured for one hour, the participants were given clonidine, a central sympatholytic agent, in a dose of 300 μ g orally, and recordings were continued for three hours.

Laboratory Analysis

The bromide-distribution volume was measured as described previously²¹ and normalized for lean body mass.²² Plasma norepinephrine concentrations were measured by high-performance liquid chromatography with fluorescence detection,²³ and plasma renin activity was measured by radioimmunoassay.²⁴ Urinary norepinephrine concentrations were measured by high-performance liquid chromatography with fluorescence detection after pre-column derivatization.²⁵

Analysis of Muscle Sympathetic-Nerve Activity

Muscle sympathetic-nerve activity was expressed as the number of bursts per minute or as the number of bursts per 100 heartbeats, to correct for differences in heart rate. The continuous measurements of mean arterial pressure and heart rate per minute obtained by finger plethysmography were averaged. Baroreflex curves were constructed by plotting changes in mean arterial pressure against changes in muscle sympathetic-nerve activity or heart rate. The sensitivity of the baroreflex to changes in blood pressure, expressed as changes in muscle sympathetic-nerve activity and heart rate, was calculated for each participant by least-squares analysis of the linear part of the baroreflex curves that included the value obtained while the participant was resting and

was expressed as the number of bursts per minute per millimeter of mercury and the number of beats per minute per millimeter of mercury, respectively. For the clonidine test, mean arterial pressure was calculated as the diastolic pressure plus one third of the pulse pressure. These results were averaged for the period from 90 to 150 minutes after the ingestion of clonidine, the period in which the nadir in the blood pressure occurs.

Statistical Analysis

Differences between the patients and control subjects were evaluated with the Mann-Whitney U test. Some patients did not participate in all phases of the first study. This was corrected for by evaluating the results of each phase with the corresponding base-line results of the same patient in paired tests. The resulting differences were evaluated with the Wilcoxon signed-rank test, one-way analysis of variance for repeated measures, and Student-Newman-Keuls tests for post hoc analysis. Values are given as means ±SD. All statistical tests were two-sided.

RESULTS

Study 1

Comparison of Base-Line Results in Patients with Chronic Renal Failure and Control Subjects

After the discontinuation of therapy with ACE inhibitors, the patients became hypertensive. Eleven needed diuretics to control extracellular-fluid volume. The cardiac output of these patients was normal, and the extracellular-fluid volume was similar to that of the control subjects (Table 1). Plasma renin activity and plasma norepinephrine concentrations were high, but urinary norepinephrine excretion was low. The base-line sympathetic-nerve activity was higher in the patients than in the control subjects, and the base-line baroreflex curves for muscle sympathetic-nerve activity and heart rate of the patients were shifted to the right of those of the control subjects (Fig. 1A and 1B). Baroreflex sensitivity was normal. Clonidine decreased blood pressure more in the patients than in the normal subjects (by 27±7 mm Hg vs. 19±6 mm Hg, P=0.04); heart rate also decreased more in the patients than in the control subjects (by 16±5 beats per minute vs. 12±4 beats per minute, P=0.04).

Effects of Short-Term ACE Inhibition in Patients with Chronic Renal Failure

In the nine patients with chronic renal failure who were given a single intravenous dose of enalaprilat, the mean arterial pressure decreased from 119±15 mm Hg to 112±19 mm Hg (P=0.01). This decrease was associated with a slight increase in muscle sympathetic-nerve activity (from 29±15 bursts per minute to 34±16 bursts per minute, P=0.005). Heart rate did not change significantly. An infusion of sodium nitroprusside in these patients produced an identical decrease in blood pressure but increased muscle sympathetic-nerve activity from 32±13 bursts per minute to 45±15 bursts per minute (P=0.002) and heart rate from 66±7 beats per minute to 76±10 beats per minute (P<0.001). These effects on muscle

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS WITH CHRONIC RENAL FAILURE AND THE CONTROL SUBJECTS IN STUDY 1.*

CHARACTERISTIC	PATIENTS (N=14)	CONTROL SUBJECTS (N=14)	P VALUE
Sex (M/F)	9/5	7/7	0.70
Age (yr)	48±6	47±7	0.68
Creatinine clearance (ml/min)	31±18	98±16	<0.001
Serum creatinine (mg/dl)†	3.9±1.9	1.0±0.1	<0.001
Extracellular-fluid volume (ml/kg of lean body mass)‡	305±23	296±27	0.35
Weight (kg)	77±7	76±9	0.74
Systolic blood pressure (mm Hg)	165±20	133±9	<0.001
Diastolic blood pressure (mm Hg)	93±12	72±6	<0.001
Mean arterial pressure (mm Hg)	118±15	92±6	<0.001
Heart rate (beats/min)	68±10	60±9	0.02
Cardiac output (liters/min)	7.5±2.0	8.6±1.8	0.14
Plasma renin activity (ng/ml/hr)§	3.8±2.3	0.7±0.2	<0.001
Plasma norepinephrine (pg/ml)¶	252±111	108±61	0.003
Urinary norepinephrine (µg/24 hr)	14±8	41±21	0.006
Muscle sympathetic-nerve activity			
Bursts/min	35±17	19±9	0.004
Bursts/100 heartbeats	53±26	33±17	0.01
Baroreflex sensitivity			
For heart rate (beats/min/mm Hg)	-1.1±1.2	-1.4±1.8	0.54
For muscle sympathetic-nerve activity (bursts/min/mm Hg)	-2.1±1.9	-2.7±1.3	0.36

*Plus-minus values are means ±SD.

†To convert values for serum creatinine to micromoles per liter, multiply by 88.4.

‡The normal range in our laboratory is 273 to 334 ml per kilogram of lean body mass.

§To convert values for plasma renin activity to nanograms per liter per second, multiply by 0.28.

¶To convert values for plasma norepinephrine to nanomoles per liter, multiply by 0.0059.

||To convert values for urinary norepinephrine to nanomoles per day, multiply by 5.9.

sympathetic-nerve activity and heart rate were significantly greater than those produced by treatment with enalaprilat (P=0.01 and P=0.03, respectively).

Effects of Long-Term ACE Inhibition in Patients with Chronic Renal Failure

Eleven patients were studied after treatment with enalapril for four to six weeks (Table 2). Nine patients took diuretics before and during enalapril treatment. Serum creatinine concentrations did not change significantly, and extracellular-fluid volume remained normal in all 11 patients. During treatment with enalapril, blood pressure and heart rate decreased to normal levels (values in the control subjects were as follows: systolic pressure, 134±9 mm Hg; diastolic pressure, 73±6 mm Hg; mean arterial pressure, 93±6 mm Hg; and heart rate, 60±10 beats per minute); urinary norepinephrine excretion also decreased. Mus-

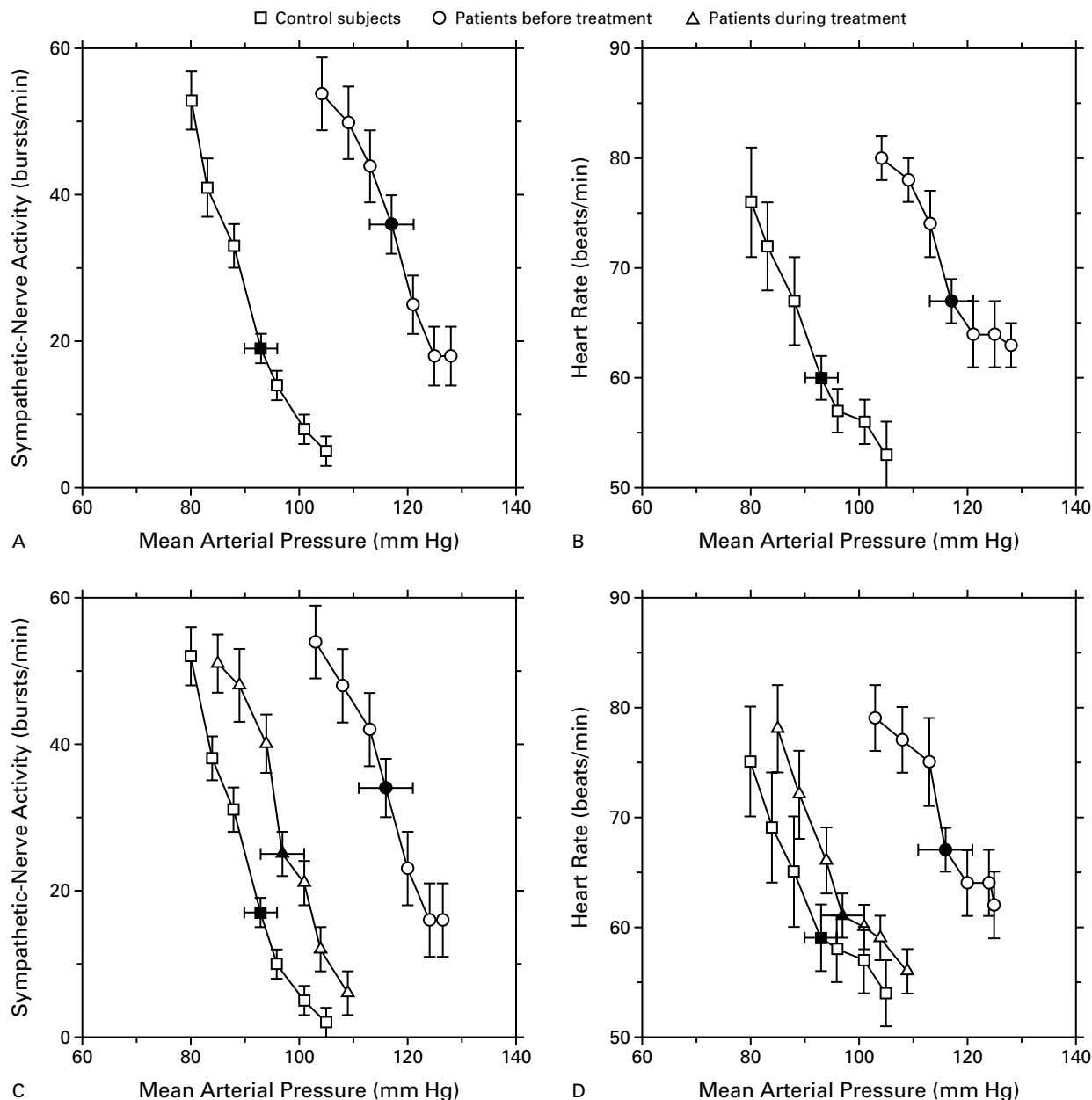


Figure 1. Baroreflex Response to Changes in Mean Arterial Pressure in Patients with Chronic Renal Failure before and during Long-Term Treatment with Enalapril and in Control Subjects.

Muscle sympathetic-nerve activity and heart rate were plotted against mean arterial pressures that were approximately 4, 8, and 12 mm Hg below and 4, 8, and 12 mm Hg above the resting levels (solid symbols). Tests were conducted at base line in 14 patients with chronic renal failure and 14 control subjects (Panels A and B) and before and during treatment with enalapril in 11 patients and 11 control subjects (Panels C and D). Values are means \pm SE.

cle sympathetic-nerve activity decreased to values that were not significantly different from those in the control subjects (23 ± 10 vs. 17 ± 7 bursts per minute). Treatment with enalapril shifted the baroreflex curves for muscle sympathetic-nerve activity and heart rate to the left, but did not change the sensitivities

(slopes) (Fig. 1C and 1D). In fact, these curves were indistinguishable from those of the control subjects by statistical analysis.

Nine of these 11 patients were studied four weeks after enalapril was discontinued. During this period hypertension again developed (systolic blood pres-

TABLE 2. EFFECTS OF THE ADMINISTRATION OF ENALAPRIL FOR FOUR TO SIX WEEKS IN 11 PATIENTS WITH HYPERTENSION AND CHRONIC RENAL FAILURE.*

VARIABLE	BEFORE ENALAPRIL	DURING ENALAPRIL	P VALUE
Weight (kg)	76±11	77±12	0.84
Extracellular-fluid volume (ml/kg of lean body mass)†	302±30	294±25	0.50
Systolic blood pressure (mm Hg)	163±21	136±18	<0.001
Diastolic blood pressure (mm Hg)	92±14	77±12	<0.001
Mean arterial pressure (mm Hg)	116±16	98±13	<0.001
Heart rate (beats/min)	66±9	61±8	0.009
Serum creatinine (mg/dl)‡	3.9±1.9	4.0±2.1	0.77
Plasma renin activity (ng/ml/hr)§	3.3±0.5	7.7±1.2	<0.001
Urinary norepinephrine (µg/24 hr)¶	15.4±9.3	10.5±5.7	0.02
Muscle sympathetic-nerve activity			
Bursts/min	31±13	23±10	<0.001
Bursts/100 heartbeats	49±24	40±20	<0.001
Baroreflex sensitivity			
For heart rate (beats/min/mm Hg)	-1.5±1.7	-0.9±0.9	0.27
For muscle sympathetic-nerve activity (bursts/min/mm Hg)	-2.3±2.4	-2.3±1.8	0.96

*Plus-minus values are means ±SD.

†The normal range in our laboratory is 273 to 334 ml per kilogram of lean body mass.

‡To convert values for serum creatinine to micromoles per liter, multiply by 88.4.

§To convert values for plasma renin activity to nanograms per liter per second, multiply by 0.28.

¶To convert values for urinary norepinephrine to nanomoles per day, multiply by 5.9.

sure, 160±18 mm Hg; diastolic blood pressure, 89±12 mm Hg), and muscle sympathetic-nerve activity increased to 31±10 bursts per minute. The baroreflex curves shifted back to the right to reflect high blood-pressure levels (data not shown), similar to those before treatment with enalapril. These results rule out the possibility that time or habituation had a role in the normalization of sympathetic activity during enalapril treatment.

We compared the effects of short-term and long-term ACE inhibition in nine patients (Fig. 2). Long-term inhibition caused a larger decrease in blood pressure than short-term inhibition, in association with a fall in muscle sympathetic-nerve activity that did not occur during short-term inhibition.

Study 2

Comparison of Base-Line Results in Patients with Chronic Renal Failure and Control Subjects

All 10 patients in the second study initially had hypertension, including 6 who were taking diuretics. The estimated extracellular-fluid volume was normal, and muscle sympathetic-nerve activity and plasma renin activity were high (Table 3). The baroreflex

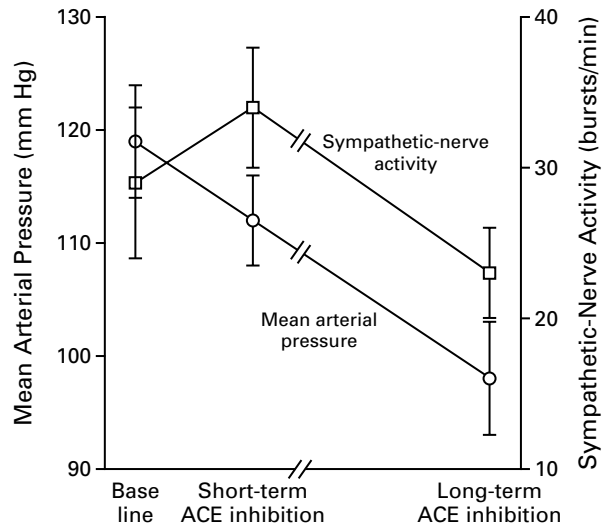


Figure 2. Changes in Mean Arterial Pressure and Muscle Sympathetic-Nerve Activity during an Intravenous Infusion of Enalaprilat and during Long-Term Treatment with Enalapril in Nine Patients with Chronic Renal Failure.

The mean arterial pressure was decreased by both long-term treatment with enalapril (P<0.001) and a short-term infusion of enalaprilat (P=0.007). Muscle sympathetic-nerve activity was decreased by long-term treatment with enalapril (P<0.001) and increased by a short-term infusion of enalaprilat (P=0.005). Values are means ±SE. ACE denotes angiotensin-converting enzyme.

curves for muscle sympathetic-nerve activity and heart rate of the patients were shifted to the right of those of the control subjects, but the sensitivities (slopes) were normal (Fig. 3).

Effects of Long-Term Calcium-Channel Blockade in Patients with Chronic Renal Failure

During the four to six weeks of treatment with amlodipine, the dose of diuretic was increased in four patients and diuretic therapy was started in two others to reduce extracellular-fluid volume and edema, but volume depletion did not develop in any patient (Table 3). The serum creatinine concentrations of the patients did not change. The decline in blood pressure was similar to that among the patients treated with enalapril, but muscle sympathetic-nerve activity and heart rate increased rather than decreased (Table 3). Treatment with amlodipine shifted the baroreflex curves of the patients to the left (Fig. 3). These curves were parallel during amlodipine treatment, as they were during enalapril treatment, with no apparent change in baroreflex sensitivity, except that the elevation in blood pressure did not decrease the heart rate. However, because amlodipine increased resting muscle sympathetic-nerve activity and heart rate, the curves were also shifted upward, implying that sympathetic activity

TABLE 3. CHARACTERISTICS OF THE CONTROL SUBJECTS AND THE PATIENTS WITH CHRONIC RENAL FAILURE IN STUDY 2.*

CHARACTERISTIC	CONTROL SUBJECTS (N=10)	PATIENTS (N=10)		P VALUE†	P VALUE‡
		BEFORE	DURING		
		AMLODIPINE	AMLODIPINE		
Sex (M/F)	6/4	7/3		1.00	
Age (yr)	46±9	47±12		0.80	
Serum creatinine (mg/dl)§	0.9±0.2	3.3±1.6	3.6±1.8	<0.001	0.25
Creatinine clearance (ml/min)	92±13	41±22	39±19	<0.001	0.40
Extracellular-fluid volume (ml/kg of lean body mass)¶	288±24	296±26	306±27	0.40	0.33
Body weight (kg)	75±11	74±11	74±11	0.81	0.33
Systolic blood pressure (mm Hg)	133±7	165±10	143±14	<0.001	<0.001
Diastolic blood pressure (mm Hg)	72±7	94±6	83±8	<0.001	0.003
Mean arterial pressure (mm Hg)	91±6	118±7	103±8	<0.001	<0.001
Heart rate (beats/min)	58±9	65±9	69±9	0.10	0.03
Plasma renin activity (ng/ml/hr)	0.7±0.2	5.1±4.6	9.2±7.8	<0.001	0.04
Muscle sympathetic-nerve activity					
Bursts/min	21±9	41±19	56±14	0.01	0.02
Bursts/100 heartbeats	37±18	62±26	81±16	0.02	0.03
Baroreflex sensitivity					
For heart rate (beats/min/mm Hg)	-1.1±0.8	-1.3±0.6	-0.8±0.8	0.61	0.21
For muscle sympathetic-nerve activity (bursts/min/mm Hg)	-2.4±1.6	-2.3±1.3	-2.2±2.0	0.93	0.82

*Plus-minus values are means ±SD.

†Comparisons are between normal subjects and patients.

‡Comparisons are between the patients before and during treatment with amlodipine.

§To convert values for serum creatinine to micromoles per liter, multiply by 88.4.

¶The normal range in our laboratory is 273 to 334 ml per kilogram of lean body mass.

||To convert values for plasma renin activity to nanograms per liter per second, multiply by 0.28.

and heart rate remained elevated over a range of blood-pressure levels. Enalapril, which lowered resting sympathetic-nerve activity and heart rate, shifted these curves downward and nearly normalized sympathetic-nerve activity and heart rate over the same range of blood-pressure levels.

DISCUSSION

Hypertension usually develops in patients with chronic renal failure. It is caused at least in part by both retention of extracellular fluid and inappropriate stimulation of the renin-angiotensin system.²⁶ The results in the patients we studied confirmed these mechanisms. When the extracellular-fluid volume was controlled, often with diuretics, plasma renin activity and blood pressure were still high, and treatment with an ACE inhibitor normalized blood pressure. However, this explanation seems incomplete, because the patients also had high levels of muscle sympathetic-nerve activity. The increased hypotensive response to clonidine suggests the presence of sympathetic overactivity as a component of the hypertension.

Short-term ACE inhibition with enalaprilat low-

ered blood pressure and increased muscle sympathetic-nerve activity slightly. However, as reported by others,¹⁷ an infusion of nitroprusside that brought about a similar decrease in blood pressure caused a larger increase in muscle sympathetic-nerve activity, indicating a relative suppression of this activity by enalaprilat. Similar differential effects were found with respect to heart rate. We think that the inhibition of sympathetic tone by enalaprilat was probably masked by a baroreflex-mediated increase in that tone. Muscle sympathetic-nerve activity normalized during long-term treatment with enalapril and returned to pretreatment values after it was discontinued, justifying the conclusion that ACE inhibition controls sympathetic overactivity in patients with chronic renal failure.

Baroreflex sensitivity was preserved. Clinically, this is important, because sympathetic inhibition may lead to orthostatic symptoms. The leftward shift of the baroreflex curve during enalapril treatment coincided with a fall in resting sympathetic-nerve activity and heart rate, suggesting that the shift is important in the expression of the modulatory action of enalapril on

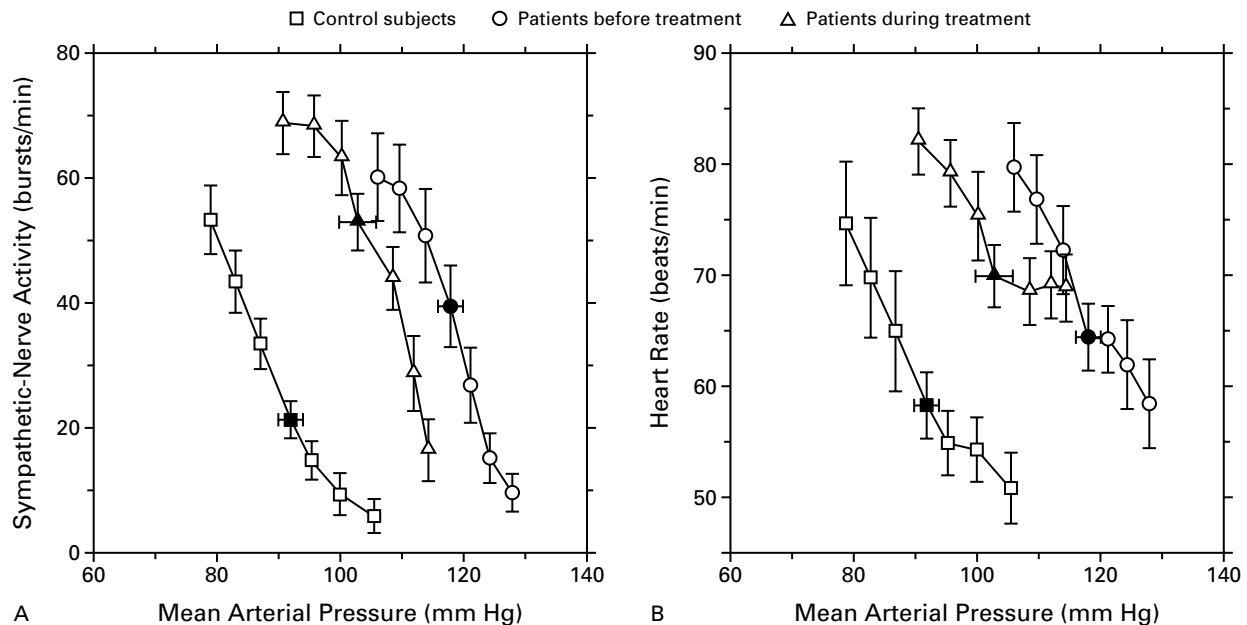


Figure 3. Baroreflex Response to Changes in Mean Arterial Pressure in 10 Patients with Chronic Renal Failure before and during Long-Term Treatment with Amlodipine and in 10 Control Subjects.

Muscle sympathetic-nerve activity (Panel A) and heart rate (Panel B) were plotted against mean arterial pressures that were approximately 4, 8, and 12 mm Hg below and 4, 8, and 12 mm Hg above the resting levels (solid symbols). Values are means \pm SE.

the sympathetic system. This action probably contributed to the delayed fall in blood pressure, with which it was associated.

The reason amlodipine increased sympathetic-nerve activity and heart rate in the patients is unclear. We used diuretics to control extracellular-fluid volume, but not to the point of depletion. In normal subjects, a single dose of nifedipine increased heart rate, muscle sympathetic-nerve activity, and cardiopulmonary baroreflex sensitivity.¹⁶ Long-term treatment with amlodipine did not change the baroreflex sensitivity in the patients in our study, nor did other calcium-channel blockers do so in patients with essential hypertension.²⁷ The shift upward and to the left in the baroreflex curves is compatible with resetting of the baroreflex to a lower blood-pressure level, suggesting that the increased resting sympathetic activity and heart rate are baroreflex-driven. In any case and in clear contrast to the effects of enalapril, amlodipine caused a reduction in blood pressure that was associated with an increase in sympathetic activity.

To understand why ACE inhibition controls sympathetic overactivity in patients with chronic renal failure we have to consider the pathogenesis of this condition. Muscle sympathetic-nerve activity is increased in patients undergoing hemodialysis, but not in those who have undergone bilateral nephrectomy,⁴ indicating that the kidney itself is the source of the sympathetic overactivity. In rats, stenosis of the

renal artery,²⁸ partial renal ablation by arterial ligation,²⁹ or intrarenal injection of phenol³⁰ causes excitation of renal afferent nerves. The resultant increase in brain sympathetic output can be prevented by selective denervation of these nerves.^{29,30} In these models of renal dysfunction, however, plasma renin activity is also increased. Because angiotensin II stimulates sympathetic activity by a direct action on the brain,^{31,32} sympathetic overactivity in patients with renal disease could also be due to activation of the renin-angiotensin system.

Our finding of an association between high plasma renin activity and muscle sympathetic-nerve activity fits both mechanisms. ACE inhibition may decrease sympathetic activity, either by decreasing the effects of angiotensin II on the brain or by reducing renal afferent nervous activity through improving renal perfusion. The latter seems less likely, considering that amlodipine can also increase renal perfusion.

We studied patients who had hypertension but who did not have extracellular-fluid overload, although some required diuretic therapy. We do not know whether sympathetic activity is also increased in hypertensive patients who have volume overload, as is the case for plasma renin activity.²⁶ We also do not know whether the inhibition of sympathetic activity caused by ACE inhibition occurs only when sympathetic tone is increased. Short-term treatment with captopril decreased elevated muscle sympathetic-nerve

activity in patients with accelerated hypertension, but it did not alter normal activity in patients with essential hypertension.³ If ACE inhibitors block the actions of angiotensin II on the central nervous system, their efficacy depends on their ability to penetrate the blood-brain barrier.

Because sympathetic overactivity may have a role in the development of cardiac hypertrophy,^{5,6} the ability of ACE inhibitors, unlike calcium-channel blockers, to decrease sympathetic activity may reduce the risk of cardiovascular problems in patients with renal failure. Indeed, ACE inhibition may be more effective than calcium-channel blockade in reducing left ventricular hypertrophy in patients with chronic renal failure.³³

In conclusion, we found that sympathetic activity is increased in patients with chronic renal failure and renin-dependent hypertension. In these patients, ACE inhibition controls hypertension and decreases sympathetic hyperactivity, whereas calcium-channel blockade increases such hyperactivity further.

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