Chapter 5

Sympathetic hyperactivity in hypertensive chronic kidney disease patients is reduced during standard treatment.

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Abstract

Standard treatment in chronic kidney disease (CKD) patients includes an angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB). CKD is often characterized by sympathetic hyperactivity. This study investigates the prevalence of sympathetic hyperactivity (quantified by assessment of muscle sympathetic nerve activity, MSNA) in a sizable group of patients with CKD and assessed whether chronic ACEi or ARB normalizes increased MSNA.

In 74 CKD patients (creatinine clearance 54 ± 31 ml/min) MSNA, blood pressure and plasma renin activity (PRA) were measured in absence of antihypertensive drugs except of diuretics. In a subgroup of 31 patients another set of measurements were obtained after at least 6 weeks enalapril (10mg orally), losartan (100mg orally) or eprosartan (600mg orally).

Patients as compared with controls (n=82) had higher mean arterial pressure (MAP, 113 ± 13 and 89 ± 7 mmHg), age-adjusted MSNA (31 ± 9 and 19 ± 7 bursts/min) and log plasma renin activity (log PRA) logPRA (2.67± 036 and 2.40± 0.32 fmol/L/sec) (all $p<0.001$). In 82% of the patients age-adjusted MSNA was higher than the mean of controls. During ACEi or ARB therapy (n=31) MAP (115 ± 11 to100 ± 9 mmHg) and age-adjusted MSNA (31 ± 8 to 23 ± 7 bursts/min) decreased (both $p<0.01$), but were still higher than in controls (both $p< 0.01$). Multiple regression analysis identified age and PRA as predictive for MSNA.

In conclusion, sympathetic hyperactivity occurs in a substantial proportion of hypertensive CKD patients. Angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor (ARB) treatment reduce, but not normalize MSNA.

Introduction

Angiotensin-converting enzyme inhibition (ACEi) and AngII receptor blockade (ARB) are well accepted as the cornerstones of the treatment of CKD patients, because they may help to prevent the progression of kidney failure. Chronic kidney disease (CKD) is often characterized by the presence of sympathetic hyperactivity. This may be important because of its effect on cardiovascular function and structure [1-4]. Previously we have shown that these agents reduce sympathetic outflow hyperactivity [5-7]. Because sympathetic hyperactivity might affect clinical outcome, it seems important to know its prevalence and to what extent it is normalized by ACEi and ARB. Therefore the aims of the present study were, firstly: to assess the prevalence of sympathetic hyperactivity by quantifying MSNA in a sizable group of hypertensive CKD patients in comparison with controls and to establish factors that predict sympathetic activity, and secondly: to assess the efficacy of ACEi and ARB to fully normalise sympathetic activity.

Methods

Subjects

Consecutive patients with hypertension (i.e. using antihypertensive drugs and/or blood pressure >145/90 mmHg when off medication) with stable chronic kidney disease (CKD) could enter the study. CKD was defined as a condition with persistent proteinuria and/or decreased glomerular filtration rate and/or anatomical abnormalities (in the case of polycystic kidney disease). Patients with clinically manifest heart failure, diabetics and patients on drugs influencing

sympathetic activity, such as betablockers and immunosuppressive agents were excluded.

In 74 patients with various renal diagnoses (polycystic kidney disease (41), IgA nephropathy (7), focal segmental glomerulosclerosis (2), nephrosclerosis (3) chronic glomerulonephritis (2), Alport disease (1), chronic tubulointerstial nephritis (2), analgesic nephropathy (2), obstructive uropathy (2), reflux nephropathy (3), chronic pyelonephritis (1) and chronic kidney disease of unknown cause (8)) we obtained a MSNA measurement when they were off antihypertensive medication. Renal diagnosis was made on clinical criteria and confirmed by ultrasound, other radiological procedures and/or kidney biopsy when appropriate.

Control subjects (n=82) had normal kidney function, normal blood pressure and were not on any medication.

Protocol

All of the subjects gave informed consent to participate in the study, which was approved by the institutional committee for studies on humans.

All patients were on chronic antihypertensive treatment before the study, which in all cases included an ACEi or an ARB. Patients were studied at baseline when taken off antihypertensive medication for more than two weeks. None of the patients were on other medication known to affect sympathetic activity, such as centrally acting agents. Diuretics were continued to maintain normovolemia, which was quantified by assessment of extracellular fluid volume (ECV).

A subgroup of 31 patients was studied twice, i.e. in untreated condition and during chronic treatment (at least six weeks) with ACEi or ARB. Ten patients were studied on chronic enalapril 10 mg o.d., 10 patients on losartan 100 mg o.d. and 11 patients were on eprosartan 600 mg o.d.. Controls were studied once. The order of studies was randomized, that is 15 patients were firstly studied while on chronic medication and then taken off medication and studied again, and 16 patients were first taken off medication and then studied, re-instituted on medication and studied for the second time.

The subjects underwent an identical set of measurements, in supine position in a quiet room with an ambient temperature of 22-24°C. All study sessions were done in the morning between 2 and 5 hours after drug intake. These measurements included supine blood pressure, heart rate, muscle sympathetic nerve activity (MSNA) and plasma renin activity (PRA). Blood pressure was measured in a recumbent position by an automatic oscillometric device (Accurtorr Plus, Datascope Corp, Paramus, NJ, USA). Means of three measurements are presented. MSNA was recorded with a unipolar tungsten microelectrode placed in a muscle nerve fascicle of the peroneal nerve using the technique of Wallin et al. [8] and described by us previously [6]. 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 15s, while blood pressure (Finapress, Ohmeda, Engelwood, CO, USA), heart rate (ECG) and MSNA are continuously recorded. The sample frequency of all signals is 200 Hz. The blood pressure overshoot after the restart of breathing is associated with a short pause in neural activity. The neural signal during the blood pressure overshoot is considered to be the background noise, that is signal without electrical activity. 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 heart beat intervals were measured from the ECG. After instrumentation the subjects rested for 20 minutes. Baseline measurements for blood pressure, heart rate and MSNA were obtained during approximately 15 minutes; blood was sampled for measurement of PRA.

The nerve activity was monitored on-line (software: Poly 5, Inspectors Research Systems, Amsterdam, The Netherlands) and stored on disk for off-line analysis. ECV was quantified by the bromide distribution volume as described previously and normalized for lean body mass [9,10]. The normal range in our laboratory is 273 to 334 ml/kg lean body mass (mean ±SD are 305±28 ml/kg). PRA was measured by radioimmunoassay (RIA) [11].

Data analysis

Data are mean ± SD, unless indicated otherwise. MSNA was expressed as the number of bursts of sympathetic activity per min or as the number of bursts per 100 heartbeats to correct for differences in heart rate. The best description of the relationship between age and MSNA was obtained with a quadratic regression.

Statistical methods

PRA was analyzed after logarithmic transformation. Baseline parameters analysis was performed with **S**tudent's unpaired t test between patients and healthy controls. Pearson correlations coefficients were calculated followed by stepwise linear regression when significant correlations were found. Only independent variables were included in regression analyses. The Z test was used to compare the adjusted MSNA above the mean between groups.

Statistical significance was defined as $P < 0.05$. All the analyses were performed with the statistical package SigmaStat 3.1 (Systat Software Inc).

Results

The patient characteristics are summarized in the Table. Patients were older than controls. As expected, creatinine clearance (Cockcroft-Gault method) was lower, whereas blood pressure, MSNA and PRA were higher in patients than in healthy controls. Also, MSNA expressed per 100 heart beats was higher, 47±19 versus 28±15 bursts/100 heart beats.

Multiple regression analysis in patients revealed age and PRA as predictive for MSNA (MSNA = -21.1 + 0.71 *x* age + 7.74 *x* log PRA; r^2=0.45, p<0.001). In controls only age was predictive for MSNA (MSNA = 3.94 + 0.33 *x* age; r^2 = 0.30, p=0.002). Figure 1 shows the relation between age and MSNA in control subjects and patients.

Age adjusted MSNA was in 82% of patients higher than the mean in controls, 31±9 versus 19±7 bursts/min (figure 1). PRA was higher in patients than in controls. ECV in patients was 321±33 ml/kg lean body mass.

Table. Baseline characteristics of chronic kidney disease patients and healthy controls

	Patients (n=74)	**Controls (n=82)**
Age (yr)	44 ± 12	34 ± 14*
Gender (M/F)	54 / 20	59 / 23
Body mass index (kg/m^2)	25.5 ± 3.3	24.0 ± 2.8
Creatinine clearance (ml/min per 1.73m^2)	54 ± 31	96 ± 13
Muscle sympathetic nerve activity (bursts/min)	31 ± 11	17 ± 9*
Systolic arterial pressure (mmHg)	155 ± 19	125 ± 15*
Diastolic arterial pressure (mmHg)	92 ± 11	71 ± 9*
Mean arterial pressure (mmHg)	113 ± 13	89 ± 10*
Heart rate (bpm)	65 ± 10	63 ± 9
Plasma renin activity (fmol/L/sec)	430 (20-3480)	280 (40-980)*
log Plasma renin activity (fmol/L/sec)	2.67 ± 0.36	2.40 ± 0.32*

Values are mean ± SD, except plasma renin activity [median(range)].
Arterial blood pressure represents values obtained in supine position.
* $p < 0.001$ controls versus patients.

In 31 patients a second set of measurements was done during treatment with an ACEi or an AngII receptor blocker. The reductions in blood pressure (enalapril 15±9%, losartan 15±6% and eprosartan 12±6%) and in MSNA (enalapril 20±8%, losartan 22±8% and eprosartan 23±11%) during the three treatments did not differ. Therefore in further analysis the data were taken as one group. Blood pressure (MAP 115±11 mmHg) and age adjusted MSNA (31±8 bursts/min), gender distribution (22 males) and renal diagnosis ((polycystic kidney disease (13), IgA nephropathy (4), focal segmental glomerulosclerosis (1), Alport disease (1), chronic tubulointerstial nephritis (2), obstructive uropathy (2), reflux nephropathy (3) and chronic kidney disease of unknown cause (5)) were identical to the whole group indicating that this was a representative subgroup. In this group age-adjusted MSNA was in 90% of

untreated patients higher than the mean in controls (figure 2).

Age-adjusted MSNA and MAP were reduced during treatment from 31±8 to 23±7 bursts/min and from 115±11 to 100±9 mmHg (both p< 0.01). Age adjusted MSNA was still higher in 71% of patients than the mean of controls (p<0.01) (figure 2). Heart rate was reduced during eprosartan (from 71±10 to 65±8 beats/min, p<0.05), but remained unchanged during enalapril and losartan.

The change in MSNA correlated with the MSNA in untreated condition (r=0.48, r=0.0063), but showed no relation with change in blood pressure or baseline PRA. MSNA did not correlate with ECV.

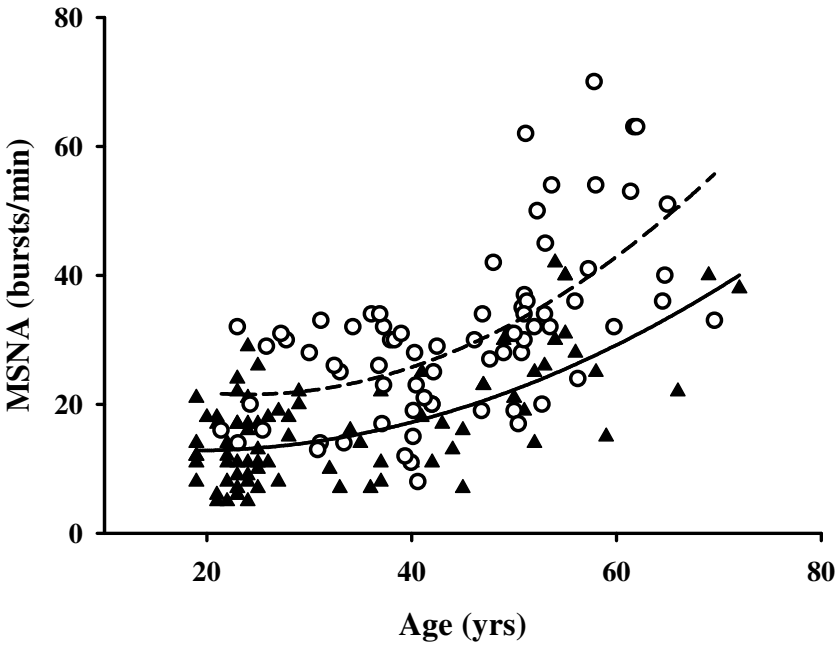

Figure 1

Relation between age and muscle sympathetic nerve activity (MSNA) for patients (when taken off antihypertensive medication) (○, dashed line; r=0.61, p<0.01) and controls (▲, continuous line; r=0.67, p<0.01)

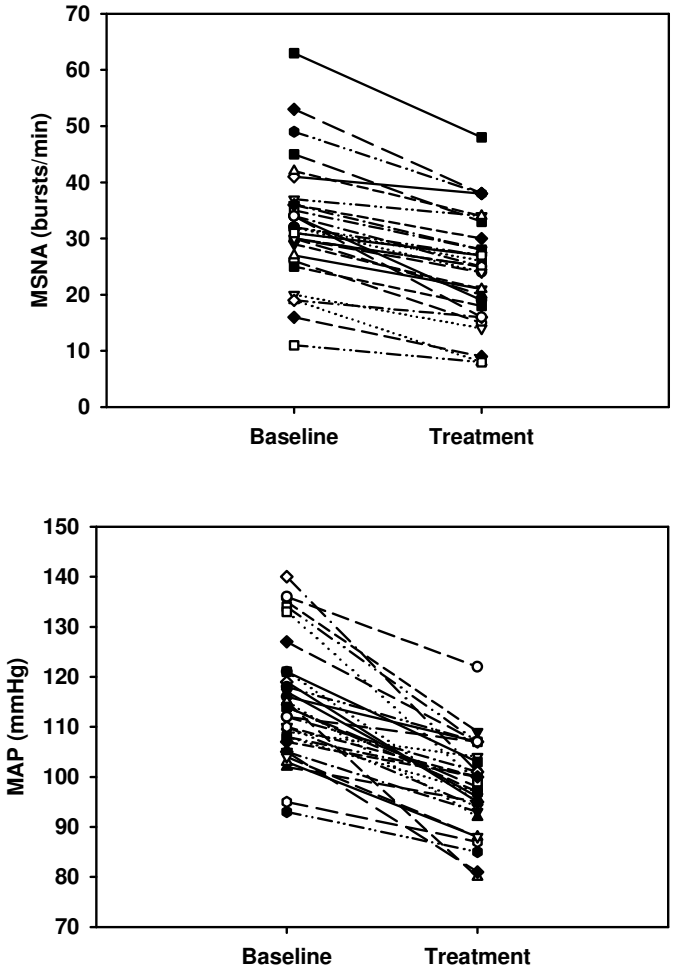

Figure 2

Individual results of muscle sympathetic nerve activity (MSNA) and mean arterial pressure (MAP) in chronic kidney disease patients (n=31) when taken off antihypertensive medication (Baseline) and during chronic treatment with an ACE inhibitor or and angiotensin II receptor blocker (Treatment).

Discussion

To the best of our knowledge, our database represents the largest available set of data on MSNA assessments in CKD patients. All measurements in patients as well as in healthy controls were done using an identical protocol. This

present study shows that sympathetic activity quantified by assessment of MSNA is increased in a substantial proportion of hypertensive CKD patients. In patients, MSNA correlates with PRA and is reduced by ACEi and ARB, suggesting that in CKD patients the activated renin-angiotensin system contributes to the pathogenesis of sympathetic hyperactivity or that the hyperactivities of the two systems share a common origin. The data indicate that chronic treatment with an ACEi or ARB does not normalize MSNA, suggesting that also other mechanisms are involved. However, we can not exclude that higher dosages of ACEi or ARB or the combination of these agents would have resulted in more profound suppression.

Three decades ago it was already shown that in CKD patients the sympathetic nervous system is activated[12-14]. Converse et al. were the first to show that MSNA, which is the centrally originated sympathetic activity directed towards the resistance vasculature is increased in hemodialysis patients[15]. The present study indicates that in a substantial proportion of hypertensive CKD patients SNA is increased. In fact, in more than 80% of patients MSNA is higher than the mean of healthy controls.

Our hypothesis is that renal ischemia is critical in the pathogenesis. The presence of sympathetic hyperactivity is not related to kidney function. Experimental studies have indicated that only minimal kidney damage without affecting function, results in hypertension of central origin[16]. The idea that kidney damage and not function is critical is strengthened by our previous findings that patients with hypertensive polycystic kidney disease with normal kidney function have increased MSNA[17] and that MSNA does not change after unilateral nephrectomy for transplantation purpose [5].

Both ACEi and ARB treatment reduced MSNA by 20-25%. In the dosage used in the present study, the effects of the various treatments did not differ. This could indicate two pathophysiologic mechanisms. Firstly, the findings may be interpreted as a support for the well established facts that AngII stimulates sympathetic activity on various levels. It increases central sympathetic outflow (which can be detected by MSNA), facilitates ganglionic transmission and

synaptic noradrenaline release by stimulation of presynaptic receptors. Secondly, the relation of the hyperactivities of the renin and sympathetic system could point at a common origin, i.e. kidney ischemia. The fact that MSNA is not normalized suggests that other mechanisms are involved as well. In this study it is not investigated whether these agents also block sympathetic activity on a peripheral level (which is not detected by MSNA measurements) and might show differences in this respect. Finally, the absence of a relation between the decrease in MSNA and blood pressure shows that part of the action of the renin system on sympathetic activity does not result in an effect on blood pressure.
An important feature of the present study is that subjects were studied when clinically normovolemic, which was evidenced by assessment of ECV. Most patients had an ECV within the normal range or only slightly increased. Previously, we have shown that hypervolemia suppresses sympathetic activity**,** parallel to PRA [5]. This indicates that normal sympathetic activity in the presence of hypervolemia should be considered abnormal.

In the population of hypertensive CKD patients of this study more than 80% had a MSNA above the mean of controls. There is substantial evidence that sympathetic hyperactivity is detrimental to the patients. The consequences of the sympathetic hyperactivity are multiple and include the pathogenesis of functional and structural cardiovascular abnormalities. It contributes to the hypertension. The finding that heart rate did not increase despite the substantial blood pressure reduction, indicates that baroreceptor set point was set on a lower level [5-7]. In fact, heart rate slightly decreased during eprosartan, whereas it remained unchanged during enalapril and losartan, which might indicate that, despite identical effects on MSNA, agents differently affect inotropic sympathetic activity.
Furthermore, there is substantial evidence that sympathetic activity also affects cardiovascular prognosis without its effect on blood pressure [1-4]. ACE inhibition or AngII receptor blocker treatment are the cornerstones of treatment of CKD patients. A recent study shows that in dialysis patients with dilated cardiomyopathy addition of carvedilol to the standard therapy regimen, which included an ACE inhibitor or AngII receptor blocker, reduces cardiovascular

morbidity and mortality as compared with placebo [18]. Another study in CKD patients, who were almost all on an ACE inhibitor or an AngII receptor blocker, suggests that the addition of moxonidine may help to slow down kidney failure progression [19]. Also in heart failure, a condition characterized by high activity of the renin and sympathetic system, the addition of a beta-blocker to standard therapy improves prognosis. It remains to be established, but it seems worth studying, whether adding a sympatholytic agent, such as moxonidine or a beta blocker, to standard treatment reduces cardiovascular risk in CKD patients. Recently, we have shown that such combination results in normalization of sympathetic hyperactivity in chronic kidney disease patients [7].

This study is limited in the sense that we have not tested higher dosages of ACEi or ARB treatment or the combination of these two types of treatment. The fact that the three treatments result in identical reductions in both blood pressure and MSNA is compatible with the idea that the maximum effect is obtained. The study indicates that a sympatholytic agent, with a mechanism other than ACEi or ARB, is needed to fully normalize blood pressure and MSNA. Also in heart failure patients, who have activated renin and sympathetic systems, MSNA was only normalized after adding clonidine to chronic treatment with an ACEi or ARB [20].

In conclusion, sympathetic hyperactivity occurs in a substantial proportion of CKD patients, which in dialysis patients, is associated with increased cardiovascular risk [21,22]. Decreasing the activity of the renin-angiotensin system by ACE inhibition or ARB treatment reduces sympathetic activity, suggesting a cause-effect relationship between these 2 effects or a common origin**,** possibly kidney ischemia.

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