Sympathetic Hyperactivity in Hypertensive Chronic Kidney Disease Patients Is Reduced During Standard Treatment

Jutta Neumann, Gerry Ligtenberg, Inge H.T. Klein, Peter Boer, P. Liam Oey, Hein A. Koomans, Peter J. Blankestijn

Abstract—Standard treatment in chronic kidney disease (CKD) patients includes an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. 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 angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker normalizes increased MSNA. In 74 CKD patients (creatinine clearance 54±31 mL/min), MSNA, blood pressure, and plasma renin activity were measured in the absence of antihypertensive drugs except for diuretics. In a subgroup of 31 patients, another set of measurements was obtained after ≥6 weeks of enalapril (10 mg PO), losartan (100 mg PO), or eprosartan (600 mg PO). Patients as compared with control subjects (n=82) had higher mean arterial pressure (113±13 versus 89±7 mm Hg), MSNA (31±13 versus 19±7 bursts per minute), and log plasma renin activity (2.67±0.36 versus 2.40±0.32 fmol/L per second; all P<0.001). During angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker therapy (n=31), mean arterial pressure (115±11 to 100±9 mm Hg) and MSNA (33±11 to 25±9 bursts per minute) decreased (both P<0.01) but were still higher than in control subjects (both P<0.01). Multiple regression analysis identified age and plasma renin activity as predictive for MSNA. In conclusion, sympathetic hyperactivity occurs in a substantial proportion of hypertensive CKD patients. Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker treatment reduces but does not normalize MSNA. (Hypertension. 2007;49:506-510.)

Key Words: sympathetic hyperactivity • muscle sympathetic nerve activity • renal hypertension • chronic kidney disease • ACE inhibition • angiotensin II receptor blocker

Angiotensin-converting enzyme inhibition (ACEi) and angiotensin II (Ang II) receptor blockade (ARB) are well accepted as the cornerstones of the treatment of chronic kidney disease (CKD) patients, because they may help to prevent kidney failure progression. 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 We have shown previously that these agents reduce sympathetic 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, first, to assess the prevalence of sympathetic hyperactivity by quantifying muscle sympathetic nerve activity (MSNA) in a sizable group of hypertensive CKD patients in comparison with control subjects and to establish factors that predict sympathetic activity and, second, to assess the efficacy of ACEi and ARB to normalize sympathetic activity.

Methods

Subjects
Consecutive patients with hypertension (ie, using antihypertensive drugs and/or blood pressure ≥145/90 mm Hg when off medication) with stable CKD could enter the study. CKD was defined as a condition with persistent proteinuria and/or decreased glomerular filtration rate and/or anatomic abnormalities (in the case of polycystic kidney disease). Patients with clinically manifest heart failure, diabetics, and patients on drugs influencing sympathetic activity, such as β-blockers and immunosuppressive agents, were excluded.

In 74 patients with various renal diagnoses, including polycystic kidney disease (41), IgA nephropathy (7), focal segmental glomerulosclerosis (2), nephrosclerosis (3), chronic glomerulonephritis (2), Alport disease (1), chronic tubulointerstitial nephritis (2), analgesic nephropathy (2), obstructive uropathy (2), reflux nephropathy (3), chronic pyelonephritis (1), and CKD of unknown cause (8), we obtained an 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 and normal blood pressure and were not on any medication.

Received November 12, 2006; first decision November 18, 2006; revision accepted December 18, 2006.
From the Departments of Nephrology (J.N., G.L., I.H.T.K., P.B., H.A.K., P.J.B.) and Clinical Neurophysiology (P.L.O.), University Medical Center, Utrecht, The Netherlands.
Correspondence to Peter J. Blankestijn, Department of Nephrology and Hypertension, Room F03.226, University Medical Center, PO Box 85500, 3508 GA Utrecht, The Netherlands, E-mail p.j.blankestijn@umcutrecht.nl
© 2007 American Heart Association, Inc.

Hypertension is available at http://www.hypertensionaha.org

DOI: 10.1161/01.HYP.0000256530.39695.a3

506
**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 of the 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 ≥2 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, that is, in untreated condition and during chronic treatment (≥6 weeks) with ACEi or ARB. Ten patients were studied on chronic enalapril (10 mg once daily), 10 patients on losartan (100 mg once daily), and 11 patients on eprosartan (600 mg once daily). 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, reintroduced on medication, and studied for the second time. Control subjects were studied once.

The subjects underwent an identical set of measurements in the supine position in a quiet room with an ambient temperature of 22°C to 24°C. All of the study sessions were done in the morning between 2 and 5 hours after drug intake. These measurements included supine blood pressure, heart rate, MSNA, and plasma renin activity (PRA). Blood pressure was measured in a recumbent position by an automatic oscillometric device (Accutorr Plus, Datascope Corp). The means of 3 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 Vallbo et al and described by us previously. The correct position of the electrode is important. The nerve activity was monitored online (Poly 5 software, Inspectors Research Systems) and stored on disk for offline analysis. ECV was quantified by the bromide distribution volume during treatment with an ACEi or an Ang II receptor blocker. Patients were studied while on chronic medication and then taken off medication and studied again, and 16 patients were first taken off medication and then studied, reintroduced on medication, and studied for the second time. Control subjects were studied once.

The mean arterial pressure represents values obtained in supine position. The restart of breathing is associated with a short pause in neural activity. This background noise, that is, signal without neural activity. This signal during the blood pressure overshoot is considered to be the number of bursts of sympathetic activity per minute or bursts per 100 heartbeats to correct for differences in heart rate. The best description of the relationship between age and MSNA is predictive for MSNA (MSNA = −21.1 + 0.71 × age + 7.74 × log PRA; \( r^2 = 0.45; P < 0.001 \)). In control subjects, only age was predictive for MSNA (MSNA = 3.94 + 0.33 × age; \( r^2 = 0.301; P = 0.002 \)). Figure 1 shows the relation between age and MSNA in control subjects and patients. PRA was higher in patients than in control subjects. ECV in patients was 321 ± 33 mL/kg of lean body mass.

In 31 patients, a second set of measurements was done during treatment with an ACEi or an Ang II receptor blocker.

**Baseline Characteristics of CKD Patients and Healthy Control Subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n=74)</th>
<th>Controls (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44±12</td>
<td>34±14*</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>54/20</td>
<td>59/23</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.5±3.3</td>
<td>24.0±2.8</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min 1.73 m²</td>
<td>54±31</td>
<td>96±13*</td>
</tr>
<tr>
<td>MSNA, bursts per minute</td>
<td>31±13</td>
<td>17±9*</td>
</tr>
<tr>
<td>Systolic arterial pressure, mm Hg</td>
<td>155±19</td>
<td>125±15*</td>
</tr>
<tr>
<td>Diastolic arterial pressure, mm Hg</td>
<td>92±11</td>
<td>71±9*</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>113±13</td>
<td>89±10*</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>65±10</td>
<td>63±9</td>
</tr>
<tr>
<td>PRA, fmo/L per s</td>
<td>430 (20 to 3480)</td>
<td>280 (40 to 980)*</td>
</tr>
<tr>
<td>Log PRA, fmo/L per s</td>
<td>2.67±0.36</td>
<td>2.40±0.32*</td>
</tr>
</tbody>
</table>

*Values are mean±SD, except PRA, which is median (range). Arterial blood pressure represents values obtained in supine position.

**Results**

The patient characteristics are summarized in the Table. Patients were older than control subjects. As expected, creatinine clearance (Cockcroft-Gault method) was lower, whereas blood pressure, MSNA, and PRA were higher in patients than in healthy control subjects. Also, MSNA expressed per 100 heartbeats was higher (47±19 versus 28±15 bursts per 100 heartbeats; \( P < 0.01 \)).

Multiple regression analysis in patients revealed age and PRA as predictive for MSNA (MSNA = −21.1 + 0.71 × age + 7.74 × log PRA; \( r^2 = 0.45; P < 0.001 \)). In control subjects, only age was predictive for MSNA (MSNA = 3.94 + 0.33 × age; \( r^2 = 0.301; P = 0.002 \)). Figure 1 shows the relation between age and MSNA in control subjects and patients. PRA was higher in patients than in control subjects. ECV in patients was 321±33 mL/kg of lean body mass.

In 31 patients, a second set of measurements was done during treatment with an ACEi or an Ang II receptor blocker.

**Data Analysis**

Data are mean±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 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 parameter analysis was performed with Student's unpaired t test between patients and healthy control subjects. Pearson correlations coefficients were calculated followed by stepwise linear regression when significant correlations were found. Only independent variables were included in regression analyses. Statistical significance was defined as \( P < 0.05 \). All of the analyses were performed with the statistical package SigmaStat 3.1 (Systat Software Inc).
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 3 treatments did not differ; therefore, in further analysis, the data were taken as 1 group. Blood pressure (mean arterial pressure: 115±11 mm Hg) and MSNA (33±11 bursts per minute) during treatment from 33±11 to 25±9 bursts per minute and from 115±11 to 100±9 mm Hg (both P<0.01; Figure 2). MSNA was still higher in patients than in control subjects (P<0.01). Heart rate was reduced during enalapril (from 71±10 to 65±8 bpm; P<0.05) but remained unchanged during enalapril and losartan. The change in MSNA correlated with the PRA. MSNA did not correlate with ECV.

**Discussion**

To the best of our knowledge, our database represents the largest available set of data on MSNA assessments in CKD patients. All of the measurements in patients, as well as in healthy control subjects, were done using an identical protocol. This 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 2 systems share a common origin. The data indicate that chronic treatment with an ACEi or ARB does not normalize MSNA, suggesting that other mechanisms are involved. However, we cannot exclude that higher dosages of ACEi or ARB or the combination of these agents would have resulted in more profound suppression.

That the sympathetic nervous system is activated in CKD patients was already shown some 3 decades ago. Converse et al were the first to show that MSNA, which is the centrally originated sympathetic activity directed toward the resistance vasculature, is increased in hemodialysis patients. The present study indicates that in a substantial proportion of hypertensive CKD patients MSNA is increased. In fact, in >80% of patients, MSNA is higher than the mean of healthy control subjects.

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 already minimal kidney damage not affecting function results in centrally originated hypertension. Also, our previous findings that hypertensive polycystic kidney disease patients with normal kidney function have increased MSNA and that MSNA does not change after unilateral nephrectomy for transplantation purposes strengthen the idea that kidney damage and not function is critical.

Both ACEi and ARB treatment reduced MSNA by 20% to 25%. In the dosage used in the present study, the effects of the various treatments did not differ. This might indicate 2 pathophysiological mechanisms. First, the findings may be taken as support for the well-established fact that Ang II stimulates sympathetic activity on various levels. It increases central sympathetic outflow (which can be detected by MSNA) and facilitates ganglionic transmission and synaptic noradrenaline release by stimulation of presynaptic receptors. Second, the relation between the hyperactivities of the renin and sympathetic system may indicate a common origin, that is, kidney ischemia. The fact that MSNA is not normalized suggests that other mechanisms are involved as well. 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 is not investigated in this study. Finally, the absence of a relation between the decrease in MSNA and in 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 reference range or only slightly increased. Previously, we have shown that hypervolemia suppresses sympathetic activity parallel to PRA. 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, >80% of patients had an 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 the baroreceptor set point was set at a lower level. 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 an effect on blood pressure. ACEi and Ang II receptor blocker treatment are the cornerstones of treatment of CKD patients. A recent study shows that in dialysis patients with dilated cardiomyopathy, the addition of carvedilol to the standard therapy regimen, which included an ACEi or Ang II receptor blocker, reduces cardiovascular morbidity and mortality as compared with placebo. Another study in CKD patients, who were almost all on an ACEi or an ARB, suggests that the addition of moxonidine may help to slow progression of kidney failure. Recently, we have shown that such combination results in normalization of sympathetic hyperactivity in CKD patients. Also, in heart failure, a condition characterized by high activity of the renin and sympathetic system, the addition of a β-blocker to standard therapy improves prognosis.

This study is limited in the sense that we have not tested higher dosages of ACEi or ARB treatment or the combination of these 2 types of treatment. The fact that the 3 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 the renin and sympathetic system, MSNA was only normalized after adding clonidine to chronic treatment with an ACEi or ARB.

Perspectives

The present data may help to understand why ACEi or ARB treatment results in a substantial blood pressure reduction in hypertensive CKD patients and why these agents are particularly effective in reducing the high cardiovascular risk in CKD patients. The data give further support to the notion that these agents should be considered the first-line choice of treatment in CKD patients. Furthermore, the data support the rationale to study the questions of whether higher dosages of ACEi or ARB treatment or the combination of these agents not only suppress sympathetic hyperactivity more effectively but also are more effective in improving the cardiovascular prognosis than either agent alone. It seems worth studying, whether adding a sympatholytic agent, such as moxonidine or a (newer) β-blocker, to standard treatment reduces cardiovascular risk. In this respect, it is also important to investigate whether orally active renin inhibitors, such as aliskiren, which will soon be available and which are likely to be able to block the renin cascade more effectively, really mean an improvement in treatment.

In conclusion, sympathetic hyperactivity occurs in a substantial proportion of CKD patients, which, in dialysis patients, is associated with increased cardiovascular risk. Decreasing the activity of the renin–angiotensin system by ACEi or ARB treatment reduces sympathetic activity, suggesting a cause and effect relationship between these 2 effects or a common origin, which could be kidney ischemia.

Sources of Funding

Studies were supported by the Dutch Kidney Foundation (grants C95.1489, C97.1684, and KC 24). P.J.B. received significant support via research grants of the Dutch Kidney Foundation, Solvay Pharmaceuticals, and Merck Sharp & Dohme.

Disclosures

None.

References


Sympathetic Hyperactivity in Hypertensive Chronic Kidney Disease Patients Is Reduced During Standard Treatment

Jutta Neumann, Gerry Ligtenberg, Inge H.T. Klein, Peter Boer, P. Liam Oey, Hein A. Koomans and Peter J. Blankestijn

Hypertension. 2007;49:506-510; originally published online January 15, 2007; doi: 10.1161/01.HYP.0000256530.39695.a3

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/49/3/506

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/