Sympathetic activity in chronic kidney disease patients is related to left ventricular mass despite antihypertensive treatment

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Abstract
Background. Chronic kidney disease (CKD) patients often have sympathetic hyperactivity, which contributes to the pathogenesis of hypertension and cardiovascular organ damage. Angiotensin-converting enzyme (ACE) inhibitors (ACEi) and angiotensin II receptor blockers (ARB) reduce sympathetic hyperactivity. Ideally, treatment should eliminate the relation between sympathetic activity and organ damage. The aim of the present study is firstly to compare left ventricular mass (LVM) of CKD patients using chronic ACEi or an ARB with LVM of controls. Secondly, we determine whether previously found muscle sympathetic nerve activity (MSNA) and arterial blood pressure during follow-up are predictive for the presence of increased LVM.

Methods. We restudied 20 CKD patients and 30 healthy volunteers matched for age. Sympathetic nerve activity was quantified by the microneurography (MSNA). Arterial blood pressure was the mean of office blood pressure measurements. LVM was quantified by magnetic resonance imaging (MRI) without contrast.

Results. The period between MSNA and MRI measurements was 9 ± 3 years. All patients were treated according to guidelines with an ACEi or an ARB. In CKD patients, mean systolic and diastolic arterial pressure were 129 ± 10 and 84 ± 5 mmHg, respectively, during follow-up. In patients, as compared to controls, LVM was 93 ± 16 versus 76 ± 18 g, LVM index 30 ± 5 versus 24 ± 4 g/m² and mean wall thickness 11 ± 2 versus 9.0 ± 1 mm (all P < 0.01). Moreover, MSNA was related to LVM (r = 0.65, P < 0.002), LVM index (r = 0.46, P < 0.03) and LV mean wall thickness (r = 0.84, P < 0.001).

Conclusions. In conclusion, the present study demonstrates that measures of LVM in CKD patients are greater than in healthy controls, despite a well-controlled blood pressure in the patients. Moreover, there is a positive relationship between these measures of LVM and MSNA, assessed years before, despite a standard antihypertensive treatment. These results support the notion that additional sympatholytic therapy could be beneficial.

Keywords: antihypertensive treatment; cardiovascular damage; chronic kidney disease; left ventricular mass; muscle sympathetic nerve activity

Introduction
Chronic kidney disease (CKD) is often accompanied by sympathetic hyperactivity [1–6]. Sympathetic nerve activity is related to left ventricular mass (LVM) and poor clinical outcome in patients with hypertension and in patients with chronic heart failure [2,7–11]. This effect is at least partially independent of its effect on blood pressure. Reduction of sympathetic hyperactivity may improve prognosis.

Zoccali and co-workers were the first to show that, also in end-stage renal disease (ESRD), sympathetic activity is related to clinical outcome [11]. In another study, they reported in a cohort of dialysis patients that plasma noradrenaline levels were related to the risk of having increased LVM [12]. Campese and co-workers showed in experimental settings that kidney injury is central in the
Sympathetic activity and cardiovascular damage in CKD patients

pathogenesis of sympathetic hyperactivity [13]. Recently, we summarized that kidney ischaemia may be the mechanism of the parallel activation of the renin and sympathetic system [14]. Previously, we have shown that angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) reduce sympathetic nerve activity, quantified by assessing muscle sympathetic nerve activity (MSNA), by 20–25% [15–18]. Ideally, such treatment would eliminate the influence of sympathetic activity on clinical outcome. However, there are no data to substantiate that notion [19]. Therefore, the aim of the present study was firstly to compare LVM obtained by magnetic resonance imaging (MRI) of CKD patients who are on chronic ACEi or ARB with LVM of healthy controls. Secondly, we determine whether previously quantified sympathetic nerve activity (MSNA: 9 ± 3 years before) and arterial blood pressure during the years prior to LVM assessment are predictive for the presence and severity of increased LVM.

Materials and methods

Study population

We re-evaluated all our CKD patients who had undergone MSNA measurement longer than 6 years ago. Inclusion criteria at the time of MSNA study were stable CKD and hypertension (i.e. using antihypertensive drugs or blood pressure >145/95 mmHg without medication). Diabetics and dialysis and transplant patients were excluded. We identified 70 patients. MSNA measurement was done between 1996 and 2002. Patients had various primary renal diagnoses, including polycystic kidney disease (32), interstitial nephritis (6), glomerulonephritis (12), congenital (3), reflux nephropathy (3), vascular disease (2) and CKD of unknown aetiology (12) [19].

Of the 70 patients, 11 patients had died, 17 were lost to follow-up and 2 had a contraindication for MRI. Patients who had started dialysis or had received a kidney transplant (n = 5), or who had aorta stenosis (n = 4) were excluded, and 11 patients were invited but refused MRI, mainly because of claustrophobia. Twenty patients were available for MRI study 9 ± 3 years after the MSNA measurement, 12 had polycystic kidney disease, 3 reflux nephropathy, 3 vascular disease, 1 interstitial nephritis and 1 CKD of unknown aetiology.

In addition, an age-matched control group of 30 controls was selected from the database of the Department of Radiology of the University Medical Center Utrecht.

The study protocol was carried out with the approval of the Ethics Committee of the University Medical Center Utrecht, and all patients gave a written informed consent.

Baseline measurement

The study protocol was described in more detail elsewhere [15–18]. Briefly summarized, all CKD patients were studied after having been taken off antihypertensive medication for more than 2 weeks. Diuretics were continued in 12 patients to maintain normovolaemia. This was evidenced by assessing extracellular fluid volume by measuring bromide distribution [20]. All patients underwent an identical set of MSNA measurement. Baseline arterial blood pressure was measured in supine position by an automatic oscillometric device (Accuror Plus with mean error ≤ ± 5 mmHg,Datascope Corp, Paramus, NJ, USA) [21,22]. MSNA was recorded with a unipolar tungsten microelectrode placed in a muscle nerve <± 5 mmHg, Datascope Corp, Paramus, NJ, USA) [21,22]. MSNA was recorded with a unipolar tungsten microelectrode placed in a muscle nerve [23]. The neural signal was filtered (bandwidth, 500–2000 Hz), rectified and integrated (time constant, 0.1 s). Sympathetic bursts were identified by their characteristic morphology and relationship to R waves on the electrocardiograph (ECG). 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. We have previously reported that intra-observer and inter-observer reproducibility are 4.5 ± 0.5% and 6.2 ± 0.7% [15]. After instrumentation, the subjects rested for 20 min. The nerve activity was monitored online (software: Poly 5, Inspectors Research Systems, Amsterdam, the Netherlands) and stored on disc for offline analysis. Means of three measurements are presented, 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. Glomerular filtration rate (eGFR) was estimated using the plasma creatinine (at the day of MSNA measurement) by the Modification of Diet in Renal Disease (MDRD) equation [24].

Measurements during follow-up

All patients visited our outpatient clinic regularly (at least four times a year). During follow-up, they were treated according to current guidelines with an ACEi or an ARB (and a diuretic in case of volume overload), targeting office blood pressure levels of 135/85 mmHg [25]. Arterial blood pressure was measured in sitting position using standard equipment. The mean of at least four measurements was registered into the patient file. We have taken the first available arterial blood pressure results of each individual patient of each calendar year of the follow-up period registered in the patient file. The means of all these annual mean arterial blood pressures were taken as representing the ‘arterial blood pressure burden’ in a particular patient. The presented arterial blood pressures are the means of these blood pressure burdens. Mean arterial pressure was calculated using systolic and diastolic arterial blood pressure according to the formula [MAP = DAP + 1/3 (SAP – DAP)], whereas SAP and DAP are systolic and diastolic arterial pressure, respectively [26]. eGFR was assessed using the MDRD equation. We have taken the first three available creatinine results of each individual patient of each calendar year of the follow-up period registered in the patient file. Most patients were also on statins, some were on phosphate binders and vitamin D derivatives, and four patients were on erythropoiesis-stimulating agents. Laboratory values were the mean of every first value obtained in a calendar year.

Medical history was taken from the patients files. Kidney function and urinalysis were done regularly. Standard laboratory methods were used. LVM is indexed to height$^{-2}$ [27].

Arterial blood pressure of the control group was also measured in sitting position using standard equipment.

MRI studies at follow-up

Acquisition protocol. Cardiac MRI was performed with a 1.5-T Philips Achieva MRI scanner (Philips Medical Systems, Best, the Netherlands) using a five-element phased array cardiac coil for signal reception and a vector ECG for ECG triggering. The protocol included steady-state free precession (SSFP) cine images [two-chamber left ventricle (LV); four-chamber, short-axis LV outflow tract (LVOT)] and quantitative flow measurement over the aortic valve. ECG-gated breath-hold two-chamber left and 4-chamber cine images were used to identify the cardiac short axis. The LV was imaged in the short-axis plane, from ventricular apex to base, using contiguous 10-mm slices of 50 frames per cardiac cycle, matrix $256 \times 256$ and field of view (FOV) $350–400$. Sequence parameters included repetition time/echo time of 3.2/1.6 ms, in-plane pixel size of 1.4 mm, flip angle 55°, and acquisition time of 18 heartbeats during breath-holds of 10–15 s [28]. All images were stored digitally for offline analysis of cardiac mass.

Image analysis, measurements and validation. Analysis was performed on a workstation with semi-automated contour-tracing software (View Forum, Philips Medical Systems, Best, the Netherlands). LVM was measured by an experienced blinded observer on the contiguous short-axis slices of the LV. The epicardial contour was traced in end-diastolic phase for LV mean wall mass. The LV was traced from the most apical slice to the most basal short-axis slice where ventricular wall was visible for at least 50% of the circumference [29]. Papillary muscles were excluded from the wall mass. Masses were calculated by adding the areas for each slice per ventricle, multiplied by the slice thickness using the Simpson’s rule [30]. We measured LV wall thickness at the left ventricular short-axis cine view. Data were analysed according to a standard protocol at our hospital [29]. Reproducibility is considered to be very high with a maximum intra-observer and inter-observer disagreement of 58% and 55% ($R^2 = 0.93–0.99$), respectively [29].

Data analysis and statistics. One-way ANOVA tests were used to compare mean LVM index and other parameters between CKD patients and healthy volunteers. Values of $P < 0.05$ were considered significant, and
Data are presented as mean ± standard deviation. LVM, assessed by MRI without contrast, was related to the previously measured MSNA. MSNA is expressed in number of bursts of sympathetic activity per minute. Univariate relation between MSNA and other variables was tested by Spearman’s correlation analysis and further examined with multiple regression analysis procedure.

**Results**

Patient characteristics at the time of MSNA measurement are given in Table 1. None of the patients had electrocardiographic signs of LV hypertrophy (measured according to the Sokolow–Lyon index [31]). At the time of cardiac MRI, patients were 47 ± 10 years old; they had an eGFR of 39 ± 29 mL/min/1.73 m², BMI of 26.2 ± 3.8 kg/m², non-fasting serum glucose of 5.2 ± 0.3 mmol/L and haemoglobin of 8.1 ± 0.9 mmol/L. MSNA of CKD patients was 27 ± 7 bursts/min, and MSNA of an age-matched control population was 20 ± 11 burst/min (n = 20) (P < 0.02).

Mean systolic and diastolic arterial pressure during follow-up were 129 ± 10 and 84 ± 5 mmHg, respectively, with a calculated MAP of 100 ± 7 mmHg (Table 2). Average heart rate during follow-up taken from periodic ECG registrations was 72 ± 13 per minute.

LVM, LVM index and mean wall thickness in patients were greater than in controls (P < 0.009) (Table 2). These differences remained significant after adjusting for gender.

MSNA expressed in number of bursts per minute was related with LVM (r = 0.65 and P < 0.002) and to LVM index (r = 0.46 and P < 0.03) and to the mean wall thickness (r = 0.84, P < 0.001) (Figure 1). Moreover, MSNA expressed in number of bursts per 100 heart beats was significantly related with mean wall thickness (r = 0.6, P < 0.01). Interestingly, MSNA correlated with change in eGFR during follow-up (r = 0.45, P < 0.05). Blood pressure and LV parameters did not correlate with the change in eGFR.

Importantly, there was no relation between MAP and LVM (P = 0.2). Also, there was no relation between MSNA and MAP (P = 0.7) in CKD subjects. Moreover, LVM is not significantly correlated to blood haemoglobin, calcium and phosphate levels.

**Discussion**

The present study shows that LVM in CKD patients is greater than in healthy controls, despite the fact that arterial blood pressure in the patients was reasonably well controlled over a long period of time. Secondly, we find a positive relationship between LVM measurements and sympathetic nerve activity assessed as MSNA years ago, despite the fact that all patients are on standard antihypertensive treatment which reduces sympathetic activity.

Guidelines committees have indicated clearly defined arterial blood pressure goals [25]. In CKD patients, ACEi and ARB, often combined with diuretics, are the preferred agents to obtain these goals. In the present study, we show that, despite the fact that arterial blood pressure is on average reasonably well controlled, measures of LVM are about 20% greater in patients than in healthy volunteers. LVM of healthy volunteers obtained in our study is in agreement with LVM measured by others applying comparable techniques [29,32]. Of note, mean wall thickness is comparable to that found in dialysis patients [12]. LVM is a strong predictor for cardiovascular morbidity and mortal-

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**Table 1.** Baseline characteristics of patients with CKD at the time of MSNA measurement

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40 ± 10</td>
</tr>
<tr>
<td>Female</td>
<td>30%</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>157 ± 19</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mmHg)</td>
<td>94 ± 10</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>48 ± 24</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.9 ± 1.0</td>
</tr>
<tr>
<td>Haemoglobin (mmol/L)</td>
<td>8.9 ± 0.9</td>
</tr>
<tr>
<td>MSNA (bursts/minute)</td>
<td>27 ± 7</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.3 ± 2.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81 ± 12</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.2 ± 0.3</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation. eGFR, estimated glomerular filtration rate calculated by Modification of Diet in Renal Disease (MDRD) equation.

**Table 2.** Characteristics of patients with CKD and control group at follow-up

<table>
<thead>
<tr>
<th>Parameters</th>
<th>CKD (n = 20)</th>
<th>Control (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47 ± 10</td>
<td>47 ± 10</td>
</tr>
<tr>
<td>Female</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>129 ± 10</td>
<td>126 ± 12</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mmHg)</td>
<td>84 ± 5*</td>
<td>76 ± 10</td>
</tr>
<tr>
<td>Left ventricular mass (g)</td>
<td>93 ± 16*</td>
<td>76 ± 18</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>30 ± 5*</td>
<td>24 ± 4</td>
</tr>
<tr>
<td>Left ventricular mean wall thickness (mm)</td>
<td>11 ± 2*</td>
<td>9 ± 1</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation. *P < 0.005 versus controls.
blood pressure.

In this study, we find no relation between arterial blood pressure and LVM, and LVM index and mean wall thickness. The arterial blood pressure results represent the average of every first set of office blood pressure readings of each calendar year. So, for each patient on average, nine sets of arterial blood pressure readings are available for analysis. This is taken as a representation of the arterial blood pressure ‘burden’ in the time period between the MSNA measurement and the MRI, which is 9 ± 3 (range 6–11) years. Obviously, we cannot exclude the possibility that a more detailed analysis of blood pressure (for instance by using 24 h or home blood pressure measurements) would have shown a positive relation. However, it is important to realize that the present study, in which medication dosage is based on office arterial blood pressure readings, most likely reflects everyday practice in most clinics.

The present data suggest relationships between sympathetic activity and LVM, and LVM index and LV mean wall thickness, independent of blood pressure. Indeed, experimental evidence suggests that noradrenaline may be involved in the development of LV hypertrophy [35]. We have quantified sympathetic activity by assessing MSNA using microneurography technique. This technique is considered one of the most reliable techniques to quantify sympathetic nerve activity [36].

Although MSNA level in our patients is not very much increased, it is ~30% higher than in age-matched healthy volunteers. At baseline, we selected the patients based on having CKD and hypertension, and the patients willing to undergo MSNA. At follow-up, several have died, and they were the patients with the highest MSNA as published earlier [19]. So, this is the selected population, which is also relatively young. However, despite this limitation, we found the relationships. It is very likely that, in a more general CKD population, mean age would be higher, age range would be larger and also the range of MSNA results would be larger. Potentially, the relation with LV mass would even be stronger.

We also found that MSNA (expressed in bursts per 100 heart beats) correlated with change in eGFR during follow-up, independent of blood pressure. This subject was not the primary aim of this study. However, it supports the idea that sympathetic activity is of relevance in the process of kidney failure progression.

We have previously shown that ACEi and ARB reduce sympathetic nerve activity, quantified by microneurography, by 20–25% [15–18]. Recently, we summarized that agents that interfere with the renin-angiotensin system (RAS) are particularly effective in reducing sympathetic hyperactivity and that kidney ischaemia could be the key factor in the pathogenesis, not only in CKD, but also in heart failure, essential hypertension and metabolic syndrome [14]. Indeed, agents that interfere with the RAS seem to be more effective in reducing LV hypertrophy than other antihypertensives [37,38]. Despite the fact that arterial blood pressure level is reasonably well controlled and all patients were on an ACEi or an ARB, we show that MSNA assessed years before is positively related to LVM. Such a positive correlation between sympathetic nerve activity and LVM is also reported in cross-sectional studies in patients with essential hypertension [8,39,40]. Zoccali et al. demonstrated a strong association between noradrenaline and LVM in patients with end-stage kidney disease independent of other risk factors [12]. Strand et al. showed that arterial plasma noradrenaline as index of sympathetic nerve activity predicts LVM at 20 years of follow-up independent of systolic arterial blood pressure [41]. Our results suggest that, despite the RAS blockage in presently advised and commercially licenced dosage, MSNA still contributes to the increase in LVM in CKD patients. A possible explanation for this finding is that the dosages of ACEi or ARB used are not high enough to fully suppress sympathetic nerve activity, despite their antihypertensive effect. Experimental evidence shows that the intrarenal RAS is compartmentalized from the systemic RAS. Tissue ACE, and therefore the intrarenal RAS, may not be adequately inhibited by plasma concentrations of ACEi in currently used dosages [42].

**Strength and limitations**

The strength of the study is that we have used a state-of-the-art methodology. Both MSNA and MRI are considered gold standard methods. The study was performed in the same population in which we have previously shown that MSNA was decreased by ACEi and ARB [15–18]. So, we are certain not only that all patients were on the preferred medication, but also that the medication actually had reduced sympathetic activity. This study adds to the earlier one by Zoccali et al. in that it shows, not only in ESRD patients but also in CKD patients not on dialysis, that the relationship between sympathetic activity and LVM exists. This may not be surprising because there is both experimental and clinical evidence that sympathetic hyperactivity is a feature of kidney injury and not of kidney failure [13,43]. As a consequence, it is likely that it already existed in our patients for a considerable period of time.

Possible limitations are the fact that we have no baseline assessment of LVM by MRI. At that time, there was virtually no experience with this method. The fact that we miss baseline MRI data only limits us to define the change in LVM over time. Furthermore, one might consider the lack of repeated MSNA as a limitation. The within-subject reproducibility of MSNA is very high, up to more than a decade between measurements. Performing a repeated MSNA at the time of MRI would inform us on the reproducibility within subjects. This information is already convincingly available in the literature [44]. Therefore, we considered the balance of scientific novelty versus burden to the patient not very favourable. Furthermore, the fact that we found the present results suggests that the relationship is very strong. The correlation between MSNA and LVM is so striking that it is hard to believe that it is caused by change. Finally, as mentioned above,
we cannot exclude the possibility that a more detailed analysis of blood pressure would have shown a relation with LVM indices. Such a finding would not affect the overall suggestion that comes with our study that additional sympatholytic therapy could be beneficial in CKD patients. In fact, this idea has already been suggested by experts in the field, but we cannot exclude the possibility that a more detailed analysis of the blood pressure would have shown a (positive) relation. In both cases, the findings support the notion that additional sympatholytic treatment may be beneficial in CKD patients, as has been suggested by some experts in the field. This requires further investigation.

**Conclusion**

In conclusion, we find that, despite of the fact that CKD patients were on ACEI or ARB, LVM, LVM index and LV mean wall thickness are greater than in controls and that these variables are related to sympathetic activity. We find no relationship with blood pressure. We cannot exclude the possibility that a more detailed analysis of the blood pressure would have shown a (positive) relation. In both cases, the findings support the notion that additional sympatholytic treatment may be beneficial in CKD patients, as has been suggested by some experts in the field. This requires further investigation.

**Conflict of interest statement.** None declared.

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Ga-67 scintigraphy in the differential diagnosis between AIN and ATN

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Abstract

Background. The differentiation between acute interstitial nephritis (AIN) and acute tubular necrosis (ATN) is crucial in patients with acute kidney injury. Gallium-67 citrate (Ga-67) has been used clinically in the differential diagnosis between these entities, but its efficacy is disputed. The aim of this study was to evaluate Ga-67 scintigraphy efficacy in the differentiation between experimental models of drug-induced AIN and ATN.

Methods. Animals were divided into three groups: AIN (n = 8), ATN (n = 8) and control (NL, n = 10). The AIN group received intraperitoneal puromycin aminonucleoside (single dose, 150 mg/kg). The ATN group received a single intraperitoneal injection of cisplatin (6 mg/kg). The NL group did not receive active drugs. All of the animals were submitted to Ga-67 scintigraphy, serum creatinine (Cr) and urinary osmolality assessment, and blinded renal histology evaluation.

Results. Renal Ga-67 uptake was strikingly more intense in the AIN group when compared to the ATN (P < 0.0001) and NL (P < 0.001) groups. The ATN group had increased Cr when compared to the NL group (P < 0.001) and lower urinary osmolality vs the NL (P < 0.001) and AIN (P < 0.01) groups. Renal histology showed severe acute tubular injury in the ATN group and intense interstitial inflammation in the AIN group, and was normal in control animals.

Conclusion. Ga-67 scintigraphy was extremely effective in the differentiation between experimental drug-induced ATN and AIN.

Keywords: acute interstitial nephritis; acute kidney injury; acute tubular necrosis; experimental study; Ga-67 scintigraphy

Introduction

The correct differentiation between acute tubular necrosis (ATN), the major cause of acute kidney injury (AKI) in hospitalized patients [1], and drug-induced acute interstitial nephritis (AIN) is extremely important. AIN represents ~3% of all renal biopsies [2,3]. Drug-induced AIN is the