

Sympathetic Nerve Traffic and Asymmetric Dimethylarginine in Chronic Kidney Disease

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Summary

Background and objectives Sympathetic overactivity and high levels of the endogenous inhibitor of NO synthase asymmetric dimethylarginine (ADMA) are prevalent risk factors in chronic kidney disease (CKD).

Design, setting, participants, & measurements In 48 stage 2 to 4 CKD patients, we investigated the relationship between efferent postganglionic muscle sympathetic nerve traffic (microneurography) and circulating ADMA and analyzed the links between these risk factors and estimated GFR (eGFR), proteinuria, and different parameters of left ventricular (LV) geometry.

Results CKD patients characterized by sympathetic nerve traffic values in the third tertile showed the highest ADMA levels, and this association was paralleled by a continuous, positive relationship between these two risk factors ($r = 0.32$, $P = 0.03$) independent of other confounders. Both sympathetic nerve traffic and ADMA were inversely related to eGFR and directly to proteinuria and LV geometry. Remarkably, the variance of eGFR, proteinuria, and LV geometry explained by sympathetic nerve traffic and ADMA largely overlapped because sympathetic nerve traffic but not ADMA was retained as a significant correlate of the eGFR ($P < 0.001$) and of the relative wall thickness or the left ventricular mass index/LV volume ratio ($P = 0.05$) in models including both risk factors. ADMA, but not sympathetic nerve traffic, emerged as an independent correlate of proteinuria ($P = 0.003$) in a model including the same covariates.

Conclusions Sympathetic activity and ADMA may share a pathway leading to renal disease progression, proteinuria, and LV concentric remodeling in CKD patients.

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Introduction

Chronic kidney disease (CKD) is a common disorder with a prevalence ranging from 3.5% to 12% that is now recognized as a major public health problem worldwide (1). This disease is associated with a high risk for cardiovascular morbidities, kidney failure, and other complications. The cardiovascular risk by CKD increases as renal function deteriorates and patients reaching the most severe stage (stage CKD-5D, patients maintained on dialysis) show a risk excess 100 times greater than that of the coevaluated general population (2). Large-scale interventions aimed at countering the CKD epidemic and the resulting cardiovascular sequelae are now held as a priority for preventing death and cardiovascular and renal complications in the CKD population. To this aim, precise knowledge of risk factors responsible for renal and cardiovascular disease at all stages of CKD, from mild dysfunction to overt kidney failure, is of major relevance.

Classic risk factors are major determinants of renal dysfunction. However, disease-specific factors and other nontraditional risk factors take place at interme-

diate and later stages of CKD (3). Among the several nontraditional risk factors identified so far, elevated sympathetic activity (4–6) and accumulation of the endogenous inhibitor of NO synthase asymmetric dimethylarginine (ADMA) (7) are much more frequent in CKD patients and independently associated with complications. In CKD-5D patients, these two factors are strictly interrelated and apparently share a common pathway leading to death and cardiovascular complications (8). These findings are in agreement with experimental data showing that sympathetic neural influences attenuate the NO-dependent vasoregulation (9) and that conversely NO inhibition by ADMA and the synthetic NO synthase inhibitor N^ω-nitro-L-arginine methyl ester (L-NAME) triggers sympathoexcitatory effects (10). However, the relationship between the sympathetic nervous system and ADMA has never been examined in patients with CKD at a predialysis stage. Furthermore, until now information on sympathetic activity in CKD patients as measured by the gold-standard technique, *i.e.*, microneurography, was limited (11–16).

To investigate the relationship between sympa-

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thetic activity and ADMA, we performed a study in a series of stable, uncomplicated patients with nondiabetic nephropathies of various severity ranging from mild to severe CKD. Patients were specifically selected to minimize the influence of factors other than CKD on sympathetic neural function and ADMA levels. We aimed at analyzing the steady-state relationship between sympathetic nerve traffic, ADMA, and the main biomarkers of renal dysfunction in CKD, namely estimated GFR (eGFR) and proteinuria. Furthermore, because high plasma norepinephrine (17) and ADMA (18) have been associated with left ventricular concentric remodeling in dialysis patients, we investigated the relationship between sympathetic nerve traffic, ADMA, and echocardiographic parameters of left ventricular geometry.

Materials and Methods

The study protocol was approved by the ethics committees of the two recruiting centers (Monza and Pisa), and all participants gave written informed consent. We excluded from the study patients affected by diseases or conditions interfering with sympathetic nerve activity recording and ADMA independently on CKD, *i.e.*, heart failure, myocardial infarction, evidence of valvular heart disease, cardiac arrhythmias, history of heavy smoking or excessive alcohol consumption, presence of diabetes, obesity, metabolic syndrome, and obstructive sleep apnea. Furthermore, we excluded patients who regularly exercise and those participating into physical training programs. From 2007 to 2010, we recruited for this specific study 48 CKD patients at various CKD stages (15 at stage 2 [eGFR 90 to 60 ml/min per 1.73 m² and either albuminuria/proteinuria or other urinary abnormalities], 11 at stage 3a [eGFR 59 to 45 ml/min per 1.73 m²], 19 at stage 3b [eGFR 44 to 30 ml/min per 1.73 m²], and 3 at stage 4 [eGFR 29 to 15 ml/min per 1.73 m²]). On the basis of data collected via kidney biopsies (carried out in 44 of the 48 patients), the etiology of renal disease was nephrosclerosis in 27 patients, chronic interstitial nephritis in six patients, chronic glomerulonephritis in six patients, nephrolithiasis in two patients, pielonephritis in two patients, low eGFR secondary to uninephrectomy (for renal neoplasia) in two patients, renal hypoplasia in one patient, and unspecified in the remaining two patients. Forty-five mild-to-moderate hypertensive patients were on antihypertensive drug treatment. Fifteen patients were on monotherapy with angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, loop diuretics, calcium antagonists, and β -blockers, and the remaining 30 were on multiple therapies with various combinations of these drugs. Drugs acting on the renin-angiotensin system and β -blocking agents were withdrawn at least 4 days before the study.

BP was monitored by a finger photoplethysmographic device (Ohmeda 2300; Finapres, Englewood, FL), and heart rate was monitored by a cardiometer triggered by the R wave of an electrocardiography lead. Respiration rate was monitored by a strain gauge pneumograph positioned at the mid-chest level. Multiunit recordings of efferent postganglionic sympathetic nerve activity to skeletal muscle (MSNA, expressed as burst frequency over time, *i.e.*, number of bursts per minute) were obtained through a

tungsten microelectrode inserted into the right or left peroneal nerve, as described (11–16). Microneurographic, echocardiographic (see below), as well as other measurements were standardized in the two recruiting centers.

Serum creatinine and 24-hour proteinuria were assessed by routine tests. Estimated GFR was calculated via the Modification of Diet in Renal Disease formula. Plasma ADMA concentration was measured by a validated ELISA (DLD Diagnostika GmbH, Hamburg, Germany) (19) in the CNR IBIM Laboratories located in Reggio Calabria (Italy). The correlation coefficient (*r*) of liquid chromatography-mass spectrometry ADMA *versus* ELISA ADMA is 0.98. Intra-assay of this ELISA ranges from 5% to 8%, and inter-assay ranges from 8% to 10%. Analytical recovery is >90%, and the assay shows no cross-reactivity (<1.5%) between ADMA and L-arginine or symmetric dimethylarginine.

M-mode, two-dimensional, and Doppler echocardiographic examinations were performed using commercially available instruments (HDI 3000 and 5000; ATL, Bothell, WA) equipped with a 2.25-MHz imaging transducer. Measurements included end-diastolic left ventricular internal diameters (LVEDDs), left ventricular ejection fraction, interventricular septum thickness, posterior wall thickness, and calculation of LV mass index normalized to body surface area (20). Left ventricular hypertrophy was defined as an LV mass index >131 g/m² in men and >100 g/m² in women. The relative wall thickness (RWT; 2*posterior wall thickness/LVEDD) and the LV mass-to-volume ratio (21) were also calculated as indexes of the left ventricular geometric pattern. Left ventricular end-diastolic volume was calculated by the standard formula ($[1.047 \times \text{LVEDD}^3] / \text{body surface area}$). Values indicative of concentric and eccentric left ventricular geometry were established on the basis of an RWT >0.45. Mean wall thickness was calculated by the standard formula: mean wall thickness = (interventricular septum + posterior wall thickness)/2. The data are expressed as the means \pm SD, median and interquartile range, or as a percentage of frequency, as appropriate, and comparisons among groups were made by *P* for trend. Variables showing a positively skewed distribution were log transformed (\lg_{10}) before the correlation study.

The interrelationships between MSNA, ADMA, eGFR, proteinuria, and left ventricular geometry were investigated by univariate and multiple linear regression analysis. To maintain adequate statistical power, all statistical adjustments were performed in restricted models including at most three covariates. To infer the involvement of the sympathetic nervous system and ADMA in the pathophysiological pathway leading to renal dysfunction (low eGFR, proteinuria) and left ventricular concentric remodeling, we applied the analytical approach by Kraemer *et al.* (22). We introduced MSNA and ADMA values simultaneously into separate models aimed at predicting the eGFR and proteinuria and then performed further adjustments for other risk factors, always in restricted models including three covariates at most. This approach allowed us to maintain adequate statistical power, and all of the models included at least 15 patients for each variable into the same models. The data are expressed as standardized regression coefficients (β) and 95% confidence intervals and *P* values.

All of the calculations were made by a standard statistical package (SPSS for Windows Version 9.0.1, 11 Mar-1999; SPSS, Chicago, IL).

Results

The study population as stratified according to tertiles of MSNA is shown in Table 1. Patients in the third MSNA tertile displayed higher heart rate and lower diastolic pressure values than in the patients belonging to the other two tertiles. Furthermore, they also displayed lower eGFR and higher proteinuria along with raised ADMA levels. Similarly, the RWT was higher and the LVEDD was shorter in patients in the third tertile as compared with those in the other tertiles. These categorical associations were confirmed by correlation analysis (Table 1, right column). Correlation analysis also showed a parallel inverse relationship between ADMA and eGFR and a direct association between the same biomarkers and proteinuria (Figure 1). These relationships were accompanied by a similar relationship between MSNA and the same parameters of renal dysfunction. The association between MSNA and eGFR was particularly close ($r = -0.62$), with a 38% shared variability of the two parameters. In addition, both MSNA and ADMA were directly associated with RWT and inversely with LVEDD (Table 1), a pattern suggesting that high sympathetic and ADMA may identify patients with LV concentric remodeling.

To determine whether the association between MSNA and ADMA was dependent on other factors, we performed restricted multiple regression (three covariates) analyses by adding age, gender, body mass index, BP, cholesterol, and antihypertensive drug treatment (one factor at a time) to the MSNA-ADMA relationship. These analyses showed minimal or no effect of these risk factors on the strength of the MSNA-ADMA association (all $P \leq 0.05$). Furthermore, smoking status was not a modifier of the MSNA-ADMA relationship (P for interaction = 0.15). Overall, such analyses suggest that sympathetic activity is an independent determinant of ADMA or *vice versa*.

Because both MSNA and ADMA were associated with the eGFR and proteinuria, we further analyzed these relationships by multiple regression. In a basic, two-covariate model testing the association between MSNA and ADMA with the eGFR, MSNA retained a close, independent relationship with the eGFR, whereas ADMA almost entirely lost its explanatory power for the eGFR variability (Figure 2). Further adjustments for proteinuria, age, gender, diagnosis of renal disease, BP, serum cholesterol, anti-hypertensive treatment, and other risk factors in restricted (three-covariate) models (see Methods) did not modify the strength of the link between MSNA and the eGFR. This analysis suggests that the link between high adrenergic activity and CKD is largely independent of other risk factors and that ADMA and sympathetic overactivity largely overlap in explaining the variability of the eGFR in CKD patients. Conversely, in a model testing the association between the same biomarkers with proteinuria, ADMA emerged as the strongest correlate of proteinuria, whereas MSNA failed to retain an independent explanatory power for proteinuria (Figure 2), and these links were unaffected by adjustments for the eGFR and other risk factors considered in the previous analysis.

The direct relationship between MSNA, ADMA, and RWT as well as the inverse relationship of the same variables with end-diastolic diameter (Table 1, right column) suggests that elevated sympathetic activity and ADMA values may underlie left ventricular concentric remodeling. To confirm that higher levels of these risk factors denote progressively severe concentric geometry, we tested the association with left ventricular volume ratio (a tridimensional parameter of left ventricular geometry). These analyses showed that it was indeed the case both for sympathetic nerve traffic and ADMA (Figure 3). Of note, among all of the variables listed in Table 1, only these two factors were associated with concentric remodeling as assessed by left ventricular mass to volume ratio. Accordingly, both MSNA (median: 50 bursts/min, interquartile range [IQR]: 42 to 56 bursts/min *versus* 40 bursts/min, IQR 33 to 43 bursts/min, $P = 0.02$) and ADMA (median: 0.80 $\mu\text{mol/L}$, IQR: 0.64 to 0.88 $\mu\text{mol/L}$ *versus* 0.58 $\mu\text{mol/L}$, IQR 0.50 to 0.68 $\mu\text{mol/L}$, $P = 0.005$) values were significantly higher in patients with left ventricular concentric hypertrophy or remodeling than in those with normal left ventricular mass or eccentric hypertrophy.

In keeping with the eGFR and proteinuria models, MSNA and ADMA overlapped also in explaining the variability of concentric remodeling, because the strength of the correlation coefficient of the ADMA-left ventricular mass to volume ratio became substantially weaker (-32%) and NS after adjustment for MSNA, whereas the correlation coefficient of MSNA with this same outcome measure showed a less pronounced attenuation (-19%) and retained marginal statistical significance ($P = 0.05$).

Discussion

There are three new major findings of this study. First, our data show that in a selected series of nondiabetic patients with stage 2 to 4 CKD, there is a direct and independent relationship between MSNA and plasma levels of ADMA. Second, our results show that both sympathetic neural drive and ADMA are consistently associated with markers of renal dysfunction (eGFR, proteinuria), as well as with left ventricular concentric geometry. Finally, our data show that MSNA and ADMA largely overlap in explaining the variability of eGFR, proteinuria, and left ventricular concentric geometry. This suggests that these risk factors may share a causal pathway leading to renal damage and left ventricular concentric remodeling in CKD patients. These three sets of data will be discussed as follows.

Sympathetic overactivity (11–16) and elevated ADMA (23–25) are prevalent disturbances in patients with CKD well before the stage where dialysis is needed, but the link between these two risk factors has never been investigated in patients at early and intermediate stages of CKD. In this study, we document for the first time an independent association between MSNA and circulating ADMA in patients with stage 2 to 4 CKD. Although residual confounding by unmeasured risk factors cannot be excluded, the extensive multiple regression analyses make this possibility fairly unlikely. Overall, our data are compatible with the hypothesis that the link between sympathetic activity and ADMA unraveled in this survey truly underlies a

Table 1. Main clinical, biochemical, microneurographic, and echocardiographic data of the study population

Variable	MSNA (Tertiles)			P for Trend	MSNA (lg ₁₀ versus r (P))
	I (<35.83 bursts/min)	II (35.83–43.00 bursts/min)	III (>43.00 bursts/min)		
Age (years)	58 ± 9	60 ± 11	58 ± 12	0.99	0.11 (0.45)
Male gender, n (%)	13 (81%)	15 (88%)	9 (60%)	0.17	–0.31 (0.03)
BMI (kg/m ²)	26.9 ± 3.3	28.3 ± 2.9	26.8 ± 5.2	0.99	–0.07 (0.62)
Smokers, n (%) ^a	6 (40%)	5 (29%)	8 (53%)	0.46	0.14 (0.34)
Systolic BP (mmHg)	146 ± 9	143 ± 18	141 ± 18	0.43	–0.09 (0.55)
Diastolic BP (mmHg)	81 ± 11	76 ± 9	72 ± 11	0.03	–0.45 (0.001)
Heart rate (beats/min)	66 ± 9	76 ± 8	76 ± 14	0.01	0.34 (0.02)
Total cholesterol (mg/dl)	203 ± 25	208 ± 30	204 ± 28	0.88	0.06 (0.70)
HDL cholesterol (mg/dl)	54 ± 14	50 ± 10	55 ± 15	0.94	0.06 (0.67)
Triglycerides (mg/dl)	126 ± 44	121 ± 37	150 ± 95	0.28	0.04 (0.77)
Creatinine (mg/dl)	1.21 ± 0.25	1.49 ± 0.36	1.83 ± 0.50	<0.001	0.50 (<0.001)
GFR (MDRD, ml/min per 1.73 m ²)	64 ± 17	53 ± 13	40 ± 14	<0.001	–0.62 (<0.001)
Urinary protein (g/24 h)	0.09 (0.03 to 0.26)	0.40 (0.09 to 1.25)	1.50 (0.18 to 1.95)	0.001	0.35 (0.02)
ADMA (μmol/L)	0.57 (0.48 to 0.62)	0.64 (0.50 to 0.69)	0.67 (0.58 to 0.77)	0.04	0.32 (0.03)
HS-CRP (mg/L)	0.21 (0.15 to 0.25)	0.35 (0.19 to 0.50)	0.26 (0.20 to 0.38)	0.17	0.26 (0.07)
MSNA (bursts/min)	32.2 (24.4 to 35.2)	41.0 (39.6 to 42.8)	48.5 (45.5 to 56.0)	<0.001	0.82 (<0.001)
LVMI (g/m ²)	113 ± 5	116 ± 15	115 ± 18	0.77	0.01 (0.93)
EF (%)	62 ± 3	61 ± 2	63 ± 4	0.37	0.15 (0.32)
LVEDD (cm)	5.1 ± 0.3	5.1 ± 0.4	4.8 ± 0.5	0.03	–0.47 (0.002)
PWT (cm)	1.04 ± 0.08	1.01 ± 0.09	1.05 ± 0.09	0.95	–0.06 (0.69)
IVST (cm)	1.09 ± 0.09	1.08 ± 0.13	1.11 ± 0.11	0.76	–0.03 (0.83)
MWT (cm)	1.07 ± 0.08	1.04 ± 0.11	1.08 ± 0.10	0.84	0.05 (0.76)
LV mass to volume ratio (g/ml)	1.47 ± 0.16	1.45 ± 0.28	1.64 ± 0.17	0.04	0.35 (0.01)
RWT (cm)	0.41 ± 0.03	0.39 ± 0.05	0.44 ± 0.03	0.03	0.38 (0.008)

The data are shown as means ± standard deviation, median, and interquartile range, as appropriate. BMI, body mass index; MDRD, Modification of Diet in Renal Disease; ADMA, asymmetric dimethylarginine; HS-CRP, high-sensitivity C-reactive protein; MSNA, muscle sympathetic nerve activity; LVMI, left ventricular mass index; EF, ejection fraction; LVEDD, end-diastolic left ventricular internal diameter; PWT, posterior wall thickness; IVST, interventricular septum thickness; LV, left ventricular; RWT, relative wall thickness.

^aFor the variable “smokers,” there is one missing value.

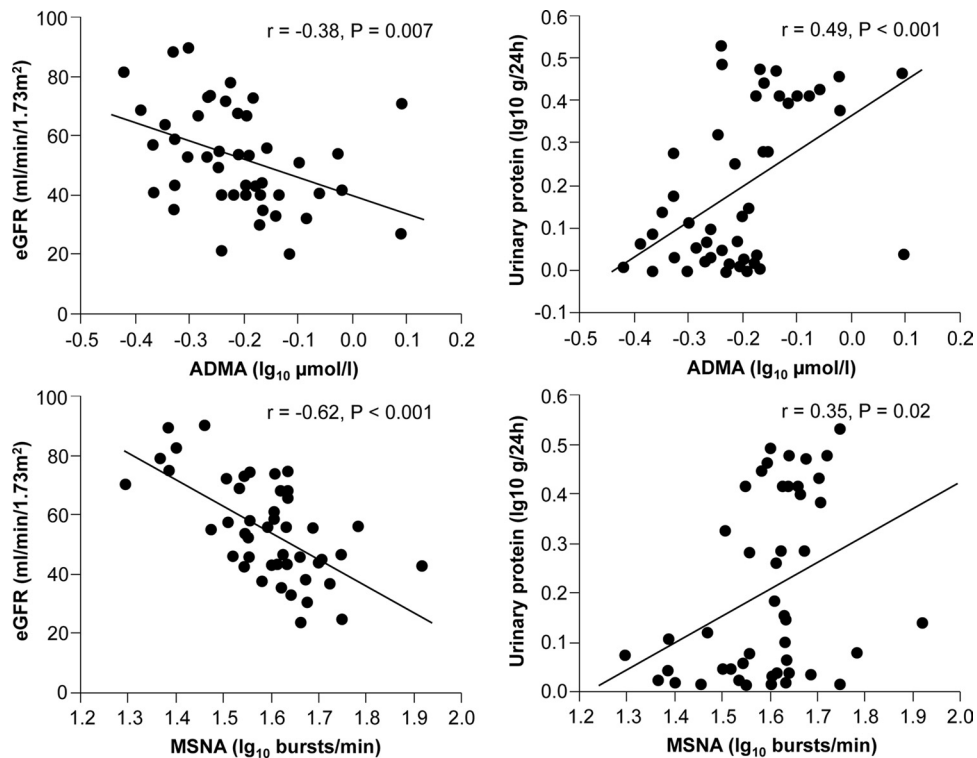


Figure 1. | Relationships between muscle sympathetic nerve activity (MSNA), NO synthase asymmetric dimethylarginine (ADMA), and estimated GFR (eGFR) or proteinuria in the study population. The data are Pearson product moment correlation coefficient (r) and P values. Because proteinuria allows 0 values, we added 1 to each patient's value before log transformation.

causal, probably bidirectional, association that develops during the evolution of renal diseases.

To the best of our knowledge, the relationship between MSNA and biomarkers of renal dysfunction has never been analyzed in detail. Intriguingly, we found a close, direct relationship between sympathetic activity directly assessed via microneurography and the eGFR and an opposite one with proteinuria. On the other hand, in agreement with previous data by some authors of this study (24) and by Fliser *et al.* (25), we found coherent, parallel relationships between ADMA, eGFR, and proteinuria. Thus, sympathetic activity and ADMA are not only associated each other but also show parallel links with biomarkers of renal dysfunction. The close relationship between sympathetic activity and the eGFR (shared variability 38%) suggests that activation of this system is a progressive phenomenon in CKD set possibly in motion by progressive renal ischemia, disturbed control of afferent neural inputs in diseased kidneys, and nocturnal hypoxemia (26). Experiments in animals indicate that the sympathetic nervous system may heavily impinge upon renal disease progression (27,28). Overall, both high sympathetic activity and high ADMA were associated with reduced eGFR, but on multiple regression analysis, only high sympathetic activity emerged as an independent correlate of the eGFR considering the two risk factors simultaneously. On the other hand ADMA was the sole independent correlate of proteinuria in a similar multiple regression analysis including sympathetic activity. Thus, MSNA and ADMA may at least in part share a common pathway conducive to eGFR

loss and proteinuria. Sympathetic overactivity may be a main driving force of eGFR loss, whereas ADMA is a prevailing mechanism in proteinuria. This hypothesis is in agreement with recent observations showing that the eGFR decline over time in a nonproteinuric nephropathy like hypertensive nephrosclerosis is accelerated by adrenergic genetic influences (29), whereas proteinuria is strongly associated with high ADMA in CKD patients with normal eGFR (25). Angiotensin-converting enzyme inhibition, an intervention that markedly inhibits the sympathetic system in CKD patients (30,31), determines a parallel decline in proteinuria and ADMA levels in patients with diabetic nephropathy and preserved eGFR (32).

Our data also provide information on the relationship between sympathetic activity, ADMA, and left ventricular structural and functional changes occurring in CKD patients. Previous studies have shown that sustained sympathetic activation favors myocardial hypertrophy by mechanisms only in part dependent on raised arterial pressure (5) and that MSNA is by far more strongly related with LV mass than BP in patients with essential hypertension (33). Elevated plasma norepinephrine values are a hallmark of concentric left ventricular hypertrophy (LVH) in dialysis patients (17) and an elevated sympathetic activity predicts LVH in moderate to severe CKD (34). By the same token, high ADMA characterizes dialysis patients with concentric LVH or remodeling (18), and a link between high ADMA and LVH has been recently described also in CKD patients in the predialysis phase (35). This study is the first considering the two risk factors simultaneously. In line with

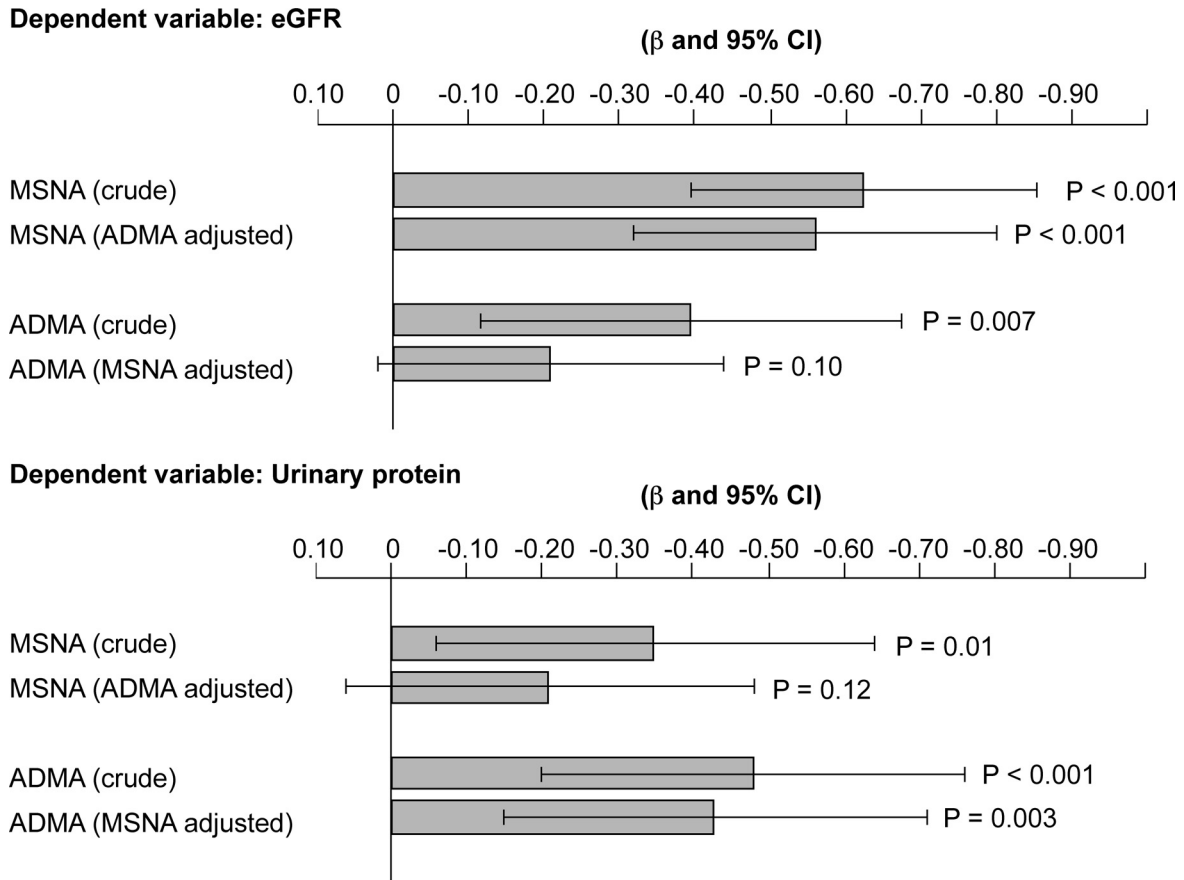


Figure 2. | Crude and adjusted relationships of muscle sympathetic nerve activity (MSNA) and asymmetric dimethylarginine (ADMA) with estimated GFR (eGFR) and proteinuria. The data are standardized regression coefficients (β), 95% confidence intervals [CIs], and P values. See text for more details.

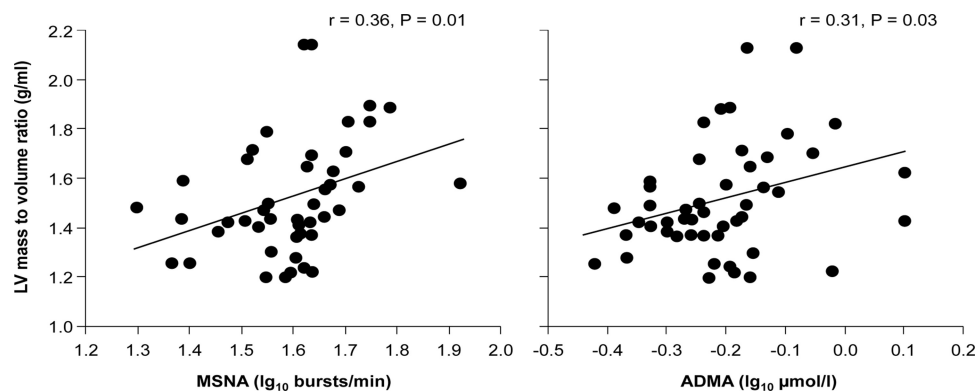


Figure 3. | Relationships between muscle sympathetic nerve activity (MSNA), asymmetric dimethylarginine (ADMA), and left ventricular (LV) mass to volume ratio in the study population. The data are Pearson product moment correlation coefficients (r) and P values.

analyses related with biomarkers of renal dysfunction, multiple regression analyses of LV geometry parameters suggest that muscle sympathetic nerve traffic and ADMA share a common pathway conducive to concentric LVH in CKD patients. This finding is in keeping with experimental data in the rat. Indeed β -adrenergic blockade by celiprolol prevents LVH induced by aortic banding, but such a beneficial effect of β -blockade is almost completely abolished

by NO inhibition (36). Carvedilol, a β -adrenergic blocker with anti-oxidant properties, increases survival and decreases plasma ADMA in patients with heart failure (37) and reduces mortality in stage 5D-CKD patients with cardiomyopathy (38).

Our study has some limitations that concern the cross-sectional design of our study and its relatively small sample size. Cross-sectional studies cannot establish causality

but can just generate hypotheses. Furthermore, residual confounding by risk factors not considered in this study cannot be excluded. Measurement of MSNA by microneurography is time consuming and technically difficult, and therefore it cannot be regarded as suitable for routine use. In this regard, this study is one of the largest applying this technique in CKD patients. The main findings in this study, namely the MSNA-ADMA association and the overlapping contribution of these risk factors to explain the variability in eGFR, proteinuria, and concentric remodeling, are in line with biologic knowledge and with longitudinal observations in patients with end-stage renal disease (8).

Finally, given the cross-sectional nature of our study, it cannot be determined whether therapeutic interventions aimed at reducing sympathetic activity exert beneficial renal and cardiovascular effects in renal patients also via a reduction in plasma ADMA and *vice versa*. Future studies will be needed to clarify this issue.

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Disclosures

None.

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