Early Sympathetic Activation in the Initial Clinical Stages of Chronic Renal Failure

Guido Grassi, Fosca Quarti-Trevano, Gino Seravalle, Francesca Arenare, Marco Volpe, Silvia Furiani, Raffaella Dell’Oro, Giuseppe Mancia

See Editorial Commentary, pp XX-XX

Abstract—Direct and indirect indices of neuroadrenergic function have shown that end-stage renal disease is characterized by a marked sympathetic overdrive. It is unknown, however, whether this phenomenon represents a peculiar feature of end-stage renal disease or whether it is also detectable in the early clinical phases of the disease. The study has been performed in 73 hypertensive patients, of which there were 42 (age: 60.7±1.8 years, mean±SEM) with a stable moderate chronic renal failure (mean estimated glomerular filtration rate: 40.7 mL/min per 1.73 m², MDRD formula) and 31 age-matched controls with a preserved renal function. Measurements included anthropometric variables, sphygmonanometric and beat-to-beat blood pressure, heart rate (ECG), venous plasma norepinephrine (high-performance liquid chromatography), and efferent postganglionic muscle sympathetic nerve activity (microneurography, peroneal nerve). For similar anthropometric and hemodynamic values, renal failure patients displayed muscle sympathetic nerve activity values significantly and markedly greater than controls (60.0±2.1 versus 45.7±2.0 bursts per 100 heartbeats; P<0.001). Muscle sympathetic nerve activity showed a progressive and significant increase from the first to the fourth quartile of the estimated glomerular filtration rate values (first: 41.0±2.7; second: 51.9±1.7; third: 59.8±3.0; fourth: 61.9±3.3 bursts per 100 heartbeats), the statistical significance (P<0.05) between groups being maintained after adjustment for confounders. In the population as a whole, muscle sympathetic nerve activity was significantly and inversely correlated with the estimated glomerular filtration rate (r=-0.59; P<0.0001). Thus, adrenergic activation is a phenomenon not confined to advanced renal failure but already detectable in the initial phases of the disease. The sympathetic overdrive parallels the severity of the renal failure, state and, thus, it might participate, in conjunction with other factors, at the disease progression. (Hypertension. 2011;57:00-00.)

Key Words: chronic renal failure ■ microneurography ■ sympathetic nervous system

Advanced renal failure is accompanied by a marked activation of sympathetic cardiovascular influences, as documented by the increase in the circulating plasma levels of norepinephrine, the elevated number of sympathetic neural bursts recorded in the peroneal nerve via the microneurographic technique, and the augmented oscillations in the high-frequency band of the heart rate power spectra.¹⁻¹³ Whether the sympathetic activation also characterizes the earlier clinical phases of the renal failure state is not clear, however. This is because in the few studies performed so far in patients with mild renal disease, the population sample was small, and the plasma levels of norepinephrine showed inconsistent changes.¹¹⁻¹² Furthermore, in the 2 previously published studies that assessed sympathetic nerve traffic via microneurography, approximately half of the patients evaluated had a polycystic kidney, that is, a condition that is characterized, per se, by a sympathetic activation even when renal function is still in the normal range.³⁻⁵

The present study has been undertaken to determine the behavior of adrenergic cardiovascular drive in a relatively large number of patients with a renal failure of mild-to-moderate degree by assessing sympathetic tone via both plasma norepinephrine assay and efferent postganglionic muscle sympathetic nerve traffic recording without the presence of the confounding factors detectable in previous investigations. The study was also aimed at examining, in patients with a wide range of renal impairment, the relationships between adrenergic activity and glomerular filtration rate. These 2 pieces of information are clinically relevant because sympathetic neural factors might affect the disease progression, as it happens in mild hypertension and in mild conges-
tive heart failure as well. Furthermore, there is evidence that, at least in advanced renal failure, sympathetic activation is an independent predictor of cardiovascular morbidity and mortality.

Methods

Study Population

Our study was performed in 73 hypertensive patients of both sexes (60 men and 13 women, with an age ranging from 31 to 78 years) recruited for this specific study between 2005 and 2010. Forty-two subjects displayed a renal failure state of a moderate degree (average estimated glomerular filtration rate: 40.7 mL/min per 1.73 m²). Modification of Diet in Renal Disease formula,17 belonging to stage 3 to 4 of National Kidney Foundation Classification.18 The renal failure state was clinically stable during the 3 months before the recruitment. The remaining 31 hypertensive patients, without evidence of renal damage (average estimated glomerular filtration rate: 85 mL/min per 1.73 m²) and belonging to a group of individuals followed in the outpatient clinic of our hospital for periodical routine examinations, served as a control group. Based on data collected via renal biopsies, causes of renal failure were nephrosclerosis (n=19), chronic glomerulonephritis (n=9), and chronic interstitial nephritis (n=14). The subjects were selected for the study if they had no history or laboratory evidence of secondary forms of hypertension, diabetes mellitus, obesity, metabolic syndrome, cardiac rhythm abnormalities, myocardial infarction, congestive heart failure, or other cardiovascular or noncardiovascular disorders known to affect sympathetic function. Subjects were enrolled in the study if they had the following characteristics: (1) if they had no evidence of polycystic kidney as cause of the renal failure state; (2) if they were not treated with immunosuppressive drugs and/or steroids; (3) if they were not on hemodialytic treatment; (4) if they had hemoglobin values within the normal range; and (5) if they did not show any clinical evidence of alterations in the volanic state, as suggested by the absence of peripheral edema. Both nephropathic and control patients were only occasionally alcohol drinkers. They were under antihypertensive treatment with various drugs, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, loop diuretics, β-blockers, and calcium channels blockers. The distribution of the different antihypertensive drug classes was almost superimposable in the 2 groups of patients. In the patients with renal disease, angiotensin-converting enzyme inhibitors were used in 26 patients, angiotensin II antagonists in 23, diuretics in 38, calcium channels blockers in 22, and β-blockers in 10. β-Blockers were withdrawn 1 week before the study. No patient was treated with α-adrenergic receptor blockers or central sympatholytic agents. Eight patients and 5 controls smoked between 5 and 15 cigarettes per day. They were asked to refrain from smoking during the 24 hours before the study. All of the participants gave their informed written consent to the study, for which the protocol was approved by the ethics committee of one of the institutions involved.

Measurements

Blood pressure (BP) was measured by a mercury sphygmomanometer, taking the first and fifth Korotkoff sounds to identify systolic and diastolic values, respectively, and by a finger photoplethysmographic device (Finapres 2300, Ohmeda) capable of providing accurate and reproducible beat-to-beat systolic and diastolic values.14,15 Heart rate was continuously monitored by a cardiometer triggered by the R wave of an ECG lead. Waist and hip circumferences were determined using a nonstretchable tape. Waist measurements were made at the natural waist midpoint between the lowest edge of the rib cage and the highest point of the iliac crest. Hip circumference was measured at the point of maximum circumference over the buttocks. Body mass index was obtained by dividing body weight in kilograms by the square of the height in meters. M-mode, 2D, and Doppler echocardiographic examinations were performed using commercially available instruments (HDI 3000 and 5000, ATL) equipped with a 2.25-MHz imaging transducer. Measurements included end-diastolic left ventricular internal diameters, left ventricular ejection fraction, interventricular septum thickness, posterior wall thickness, and calculation of left ventricular mass index normalized to body surface area.19,20 Multifrequency recording of elferent postganglionic sympathetic nerve activity to the skeletal muscle (muscle sympathetic nerve activity [MSNA]) district was obtained through a tungsten microelectrode inserted into the right or left peroneal nerve, as described previously.2-6,13-15 The nerve signal was amplified ×70 000, fed through a bandpass filter (700 to 2000 Hz), and integrated with a custom nerve traffic analyzer (Bioengineering Department, University of Iowa). Integrated nerve activity was monitored by a loudspeaker, displayed on a storage oscilloscope (model 511A, Tektronix), and recorded with BP and heart rate on thermic paper by an ink polygraph (Gould 3800, Gould Instruments). The muscle nature of sympathetic nerve activity was assessed by the criteria detailed in previous studies.2-6,13-15 MSNA was quantified over a 30-minute recording period as burst incidence over time (bursts per minute) and as number of bursts corrected for heart rate values (bursts per 100 heartbeats). Plasma norepinephrine was measured by high-performance liquid chromatography21 from a venous blood sample. The same blood sample was used to assess biochemical parameters, including hemoglobin and estimated glomerular filtration rate. Glomerular filtration rate was estimated by the Modification of Diet in Renal Disease formula.17 Proteinuria was evaluated by 24-hour home urine collection in all of the patients.

Protocol and Data Analysis

All of the participants were studied in the morning after a light breakfast and an overnight abstinence from alcohol and coffee consumption. They were placed supine and fitted with the intravenous cannula and the devices to measure sphygmomanometric BP, finger BP, and heart rate. Blood samples were taken 30 minutes after positioning the venous cannula. BP was then measured 3 times by a mercury sphygmomanometer, and then the microelectrode was inserted into the peroneal nerve to obtain MSNA, which was recorded together with finger BP and heart rate during a 30-minute period. Data were collected in a semidark and quiet room kept at a constant temperature of 20°C to 21°C. Calculations of the various variables were made by a single independent observer unaware of the belonging of the patients to the different groups and quartiles (see below). Values from individual participants were averaged for the renal failure and the control group and expressed as mean±SEM. The entire population sample was subdivided into 4 groups according to the quartiles of the estimated glomerular filtration rate values (Modification of Diet in Renal Disease formula). Comparisons between the different quartiles were made by ANOVA using the Bonferroni correction for multiple comparisons, after adjustments for age, sex, waist circumference, waist:hip ratio, and systolic and diastolic BPs. The Pearson correlation coefficient was used to determine the relationship among MSNA, plasma norepinephrine, heart rate, and estimated glomerular filtration rate. A value of P<0.05 was taken as the minimal level of statistical significance.

Results

Table 1 shows the demographic, anthropometric, hemodynamic, echocardiographic, and neurohumoral data in renal failure patients and the corresponding values detected in control subjects. The 2 groups of individuals displayed almost superimposable age, hemoglobin, body mass index, and waist:hip ratio values, whereas estimated glomerular filtration rate was, as expected, significantly reduced in the renal failure group as compared with the control group. Patients with renal failure also showed, on average, a significant
Our study provides 2 new major findings. First, adrenergic activation is a phenomenon not confined to end-stage renal failure, as documented by previous studies.1–4 but already detectable in the initial clinical phases of the disease. Second, the magnitude of the adrenergic overdrive parallels the severity of the renal failure state, becoming more and more pronounced as the renal function progressively deteriorates. Taken together, these 2 pieces of information suggest that, along with other factors, sympathetic overdrive may participate in the progression of the disease, as it has been reported in hypertension and congestive heart failure, that is, 2 conditions also characterized by an adrenergic overdrive.14,15

Several other findings of our study deserve to be discussed. In our patients, the progressive increase in MSNA seen in the different groups of patients characterized by a progressively greater impairment in renal function was not paralleled by a similar behavior of plasma norepinephrine, which showed, with the exception of the third quartile, values almost superimposable in the different groups. A similar behavior of plasma norepinephrine has also been reported in congestive heart failure of mild to moderate degree, characterized by a marked increase in MSNA with only a modest and not significant increase in the circulating plasma levels of the adrenergic neurotransmitter.15 This finding may be interpreted as a further demonstration that plasma norepinephrine, although capable of detecting increases in sympathetic tone of a marked degree, such as those characterizing a heart failure or renal failure state to a severe degree, does not allow us to reflect on the increase of adrenergic drive seen in both renal failure and heart failure when the severity of the disease is much less pronounced. The above-mentioned conclusion is supported, in the case of the renal failure state, by the evidence that, at variance from MSNA, plasma norepinephrine did not bear any significant relationship with estimated glomerular filtration rate values. A more sensitive approach for assessing sympathetic function in renal failure might be represented by the norepinephrine spillover technique, as has been shown in other cardiovascular disease characterized by sympathetic activation, such as congestive heart failure and hypertension.22

A further result of our study that deserves to be discussed refers to the behavior of heart rate, taken as an index, although indirect, of adrenergic cardiovascular drive. The results of the present study show that, whereas heart rate values are significantly increased in the whole group of renal failure patients, as compared with those of healthy

### Table 1. Demographic, Anthropometric, Biochemical, Hemodynamic, Echocardiographic, Neurohumoral, and Microneurographic Characteristics of Control Patients and Patients With Renal Failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Patients (n=31)</th>
<th>Renal Failure Patients (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, men/women</td>
<td>28/3</td>
<td>32/10</td>
</tr>
<tr>
<td>Age, y</td>
<td>56.6±1.3</td>
<td>60.7±1.8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.1±0.6</td>
<td>27.2±0.6</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>91.1±1.8</td>
<td>94.8±1.9</td>
</tr>
<tr>
<td>Waist:hip ratio</td>
<td>0.93±0.02</td>
<td>0.96±0.02</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, mL/min per 1.73 m²</td>
<td>85.2±2.4</td>
<td>40.7±1.7*</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14.0±0.9</td>
<td>13.9±1.3</td>
</tr>
<tr>
<td>Sphygmomanometric BP, S/D, mm Hg</td>
<td>142.3±2.1/77.7±1.8</td>
<td>143.6±2.5/73.2±1.4</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>69.1±1.3</td>
<td>74.4±2.0*</td>
</tr>
<tr>
<td>Plasma NE, pg/mL</td>
<td>259.3±21.3</td>
<td>350.8±47.7*</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>50.9±1.0</td>
<td>49.8±0.5</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>111.4±2.4</td>
<td>117.4±1.8</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>61.3±1.0</td>
<td>59.6±0.8</td>
</tr>
<tr>
<td>Proteinuria, g/24 h</td>
<td>0.04±0.01</td>
<td>1.6±0.2†</td>
</tr>
<tr>
<td>MSNA, bursts per minute</td>
<td>31.5±1.4</td>
<td>43.8±1.4‡</td>
</tr>
<tr>
<td>MSNA, bursts per 100 heartbeats</td>
<td>45.7±2.0</td>
<td>60.0±2.1‡</td>
</tr>
</tbody>
</table>

Data are shown as mean±SEM unless otherwise indicated. BMI indicates body mass index; S, systolic; D, diastolic; NE, norepinephrine. *P<0.05 refers to the statistical significance between renal failure patients and controls. †P<0.001 refers to the statistical significance between renal failure patients and controls.

increase in 24-hour urinary protein excretion. Heart rate was significantly greater in patients with renal failure than in controls, whereas systolic BP, diastolic BP, left ventricular ejection fraction, left ventricular diastolic diameter, and left ventricular mass index values were almost superimposable in the 2 groups. MSNA values, both when expressed as burst incidence over time and corrected for heart rate, were significantly greater in patients with renal failure than in controls. A significant increase in plasma norepinephrine was detected in renal failure patients when they were compared with controls.

Figures 1 and 2 show the same variables as Table 1 but grouped according to the quartiles of estimated glomerular filtration rate values (Table 2). Age and hemoglobin values were almost superimposable in the 4 groups, whereas body mass index and waist:hip ratio showed a nonsignificant tendency to be greater in the highest quartiles. This was the case also for systolic BP, heart rate, and plasma norepinephrine. On the other hand, MSNA, both when expressed as burst incidence over time and when corrected for heart rate values, showed a progressive and significant increase from the first to the fourth quartiles of estimated glomerular filtration rate values (Figure 2). MSNA differences between groups maintained statistical significance also after data adjustment for confounders, that is, age, sex, systolic BP, diastolic BP, waist circumference, and waist:hip ratio. MSNA values were almost superimposable in the different subgroups of nephropathic patients, classified according to the etiology of the disease. In the population as a whole, MSNA, but not heart rate and plasma norepinephrine, was significantly and inversely correlated with estimated glomerular filtration rate (r=−0.59; P<0.0001; Figure 3), whereas it was significantly and directly correlated with heart rate (r=0.55; P<0.02) but not with plasma norepinephrine (r=0.06; P value not significant).

### Discussion

Several other findings of our study deserve to be discussed. In our patients, the progressive increase in MSNA seen in the different groups of patients characterized by a progressively greater impairment in renal function was not paralleled by a similar behavior of plasma norepinephrine, which showed, with the exception of the third quartile, values almost superimposable in the different groups. A similar behavior of plasma norepinephrine has also been reported in congestive heart failure of mild to moderate degree, characterized by a marked increase in MSNA with only a modest and not significant increase in the circulating plasma levels of the adrenergic neurotransmitter.15 This finding may be interpreted as a further demonstration that plasma norepinephrine, although capable of detecting increases in sympathetic tone of a marked degree, such as those characterizing a heart failure or renal failure state to a severe degree, does not allow us to reflect on the increase of adrenergic drive seen in both renal failure and heart failure when the severity of the disease is much less pronounced. The above-mentioned conclusion is supported, in the case of the renal failure state, by the evidence that, at variance from MSNA, plasma norepinephrine did not bear any significant relationship with estimated glomerular filtration rate values. A more sensitive approach for assessing sympathetic function in renal failure might be represented by the norepinephrine spillover technique, as has been shown in other cardiovascular disease characterized by sympathetic activation, such as congestive heart failure and hypertension.22

A further result of our study that deserves to be discussed refers to the behavior of heart rate, taken as an index, although indirect, of adrenergic cardiovascular drive. The results of the present study show that, whereas heart rate values are significantly increased in the whole group of renal failure patients, as compared with those of healthy
subjects, no significant trend for a heart rate increase was detected in the different quartiles of renal failure patients, despite the evidence of a progressive and significant increase in MSNA. Several sound hypotheses can be advanced for explaining this finding. It is possible that heart rate represents an insensitive marker of adrenergic drive unable to detect an increase in adrenergic drive of not-so-pronounced magnitude, such as that seen in mild-to-moderate renal failure. It is also possible, however, to hypothesize that, in the early phases of renal failure, the sympathetic overdrive does not homogeneously affect the cardiovascular system, being more pronounced at peripheral vascular rather than at the cardiac level. Indeed, in favor of the heterogeneous behavior of the sympathetic activation between various cardiovascular districts stands the observation that, in renal failure, although MSNA is markedly increased, skin sympathetic nerve traffic is almost normal.24-25 This phenomenon, however, does not appear to be specific for chronic renal failure, with a similar behavior of the adrenergic neural function being detectable in hypertension, heart failure, obesity, metabolic syndrome, and hepatic cirrhosis as well.26-28

Our study was not designed to clarify the mechanisms responsible for the adrenergic overdrive seen in the renal failure state of a mild-to-moderate degree. A number of not mutually exclusive hypotheses can be advanced, however. We can speculate that the sympathetic activation seen in our mild renal failure patients has a reflex origin, namely that it depends on a reduction of the restraint physiologically exerted by arterial baroreceptors on the sympathetic nervous system.14,29 This hypothesis, however, is not supported by the finding that arterial baroreceptor modulation

Figure 1. Hemoglobin (HB), waist:hip ratio (WHR), systolic BP (SBP), diastolic BP (DBP), heart rate (HR), and plasma norepinephrine (NE) values in the subjects of the study grouped according to quartiles of estimated glomerular filtration rate (Modification of Diet in Renal Disease formula). The age values of the groups were 57.5±1.7, 58.1±1.7, 60.2±3.0, and 59.8±2.5 years, respectively. No statistical differences of the values of the different parameters were detected in the different quartiles. Data are shown as mean±SEM.

Figure 2. MSNA expressed as burst incidence over time (bursts per minute, left) or as burst incidence corrected for heart rate (bursts per 100 heartbeats, right) in the subjects of the study grouped according to quartiles of estimated glomerular filtration rate. Asterisks (*P<0.05) refer to the statistical significance between quartiles. Data are shown as mean±SEM.
of adrenergic outflow is preserved in renal failure, at variance from arterial baroreflex modulation of heart rate, which depends on the vagus and is markedly impaired in this condition. It is, on the other hand, possible that other reflex mechanisms modulating adrenergic drive are involved. This may be the case for the reflex influences stemming from volume-sensitive receptors located within the cardiac chambers, of which the inhibitory function on sympathetic drive is drastically impaired in chronic renal failure. This may be also the case for the arterial chemoreceptor reflex, of which the tonic activation (leading to an adrenergic stimulation) has been reported to occur in severe renal failure. This may be finally the case for renal afferent fibers, of which activation in experimental animals has been shown to trigger sustained reflex sympathoexcitatory effects. Interestingly, in these animal models renal afferent nerve ablation is accompanied by an improvement in renal function, suggesting that renal afferents may definitely play a role in the occurrence and/or in the progression of the renal disease. Alterations in reflex cardiovascular control, however, cannot be regarded as the exclusive mechanisms involved in the mild renal failure–related sympathetic activation. Evidence indeed exists that several humoral/metabolic factors with central sympathoexcitatory effects may participate. The first one is angiotensin II, of which circulating levels are increased in renal failure. The second one is represented by asymmetrical dimethylarginine, of which plasma levels are also increased in patients with renal disease. The third one is insulin, of which circulating plasma levels have been found frequently elevated in patients with a reduced glomerular filtration rate. The final one is a decreased brain NO availability reported in renal failure and potentially responsible for the renal disease–related sympathetic activation.

Our study has some limitations but also a clinical implication. The first limitation refers to the fact that we evaluated our renal failure patients under treatment with different antihypertensive drugs known to affect sympathetic function. However, this limitation is counterbalanced by the evidence that our control hypertensive patients were also under a similar pharmacological treatment. Furthermore, the majority of our nephropathic patients were treated with either angiotensin-converting enzyme inhibitors or angiotensin II receptors blockers, that is, drugs known to exert, particularly in renal failure, sympathoinhibitory effects. This would have led us, if anything, to underestimate the degree of sympathetic activation seen in the early stages of the disease. A second limitation is represented by the fact that, in our patients, the evidence of a normovolemic state was based on clinical findings and not on direct volume measurements. However, the absence of peripheral edema, the mild-to-moderate nature of the disease itself, and the use of diuretics should make unlikely the occurrence of substantial modifications of the fluid volume balance in our patients.

The clinical implication is represented by the possibility that, given the prognostic relevance that the sympathetic activation carries in advanced renal failure, pharmacological sympatho-inhibition should represent a treatment goal even in the earlier clinical phases of the renal failure state. This will presumably allow the disease progression to slow down throughout the adrenergic deactivation, as shown by the evidence that, in patients with advanced renal failure, the addition of a central sympatholytic agent, such as moxonidine, to standard treatment may allow for the improvement of renal function and for the exertion of nephroprotective effects in the 2-year follow-up period of the study.

**Perspectives**

Our study has been carried out in mild-to-moderate renal failure patients with clinical evidence of a BP elevation. Although in our study we recruited as controls patients with hypertension in order to minimize the effects of high BP on sympathetic function, we have to recognize that a normal BP state should represent a better clinical model to investigate the effects of renal failure, per se, on the neuroadrenergic

### Table 2. Subgroups of Patients According to Estimated Glomerular Filtration Rate (Modification of Diet in Renal Disease Quartiles)

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Subjects (n)</th>
<th>Mean±SEM</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>18</td>
<td>95.4±1.6</td>
<td>106–75</td>
</tr>
<tr>
<td>II</td>
<td>17</td>
<td>67.6±1.7</td>
<td>74–55</td>
</tr>
<tr>
<td>III</td>
<td>18</td>
<td>47.5±1.2</td>
<td>54–41</td>
</tr>
<tr>
<td>IV</td>
<td>20</td>
<td>31.4±1.8</td>
<td>40–17</td>
</tr>
</tbody>
</table>

Figure 3. Relationship between estimated glomerular filtration rate (eGFR) and various markers of adrenergic function in the whole study population. Only MSNA showed a significant relationship with eGFR.
profile. Future studies, however difficult to perform given the frequent association between high BP and renal dysfunction, will thus be needed to address this specific issue.

Disclosures
None.

References


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