Plasma Norepinephrine Predicts Survival and Incident Cardiovascular Events in Patients With End-Stage Renal Disease

Carmine Zoccali, MD; Francesca Mallamaci, MD; Saverio Parlongo, MD; Sebastiano Cutrupi; Francesco Antonio Benedetto, MD; Giovanni Tripepi; Graziella Bonanno, MD; Francesco Rapisarda, MD; Pasquale Fatuzzo, MD; Giuseppe Seminara, MD; Alessandro Cateliotti; Benedetta Stancanelli, MD; Lorenzo Salvatore Malatino, MD

Background—Sympathetic tone is consistently raised in patients with end-stage renal disease (ESRD). We therefore tested the hypothesis that sympathetic activation is associated with mortality and cardiovascular events in a cohort of 228 patients undergoing chronic hemodialysis who did not have congestive heart failure at baseline and who had left ventricular ejection fraction >35%.

Methods and Results—The plasma concentration of norepinephrine (NE) was used as a measure of sympathetic activity. Plasma NE exceeded the upper limit of the normal range (cutoff 3.54 nmol/L) in 102 dialysis patients (45%). In a multivariate Cox regression model that included all univariate predictors of death as well as the use of sympathicoplegic agents and β-blockers, plasma NE proved to be an independent predictor of this outcome (hazard ratio [1-nmol/L increase in plasma NE]: 1.07, 95% CI 1.01 to 1.14, \( P=0.03 \)). Similarly, plasma NE emerged as an independent predictor of fatal and nonfatal cardiovascular events (hazard ratio [1-nmol/L increase in plasma NE] 1.08, 95% CI 1.02 to 1.15, \( P=0.01 \)) in a model that included previous cardiovascular events, pulse pressure, age, diabetes, smoking, and use of sympathicoplegic agents and β-blockers. The adjusted relative risk for cardiovascular complications in patients with plasma NE >75th percentile was 1.92 (95% CI 1.20 to 3.07) times higher than in those below this threshold (\( P=0.006 \)).

Conclusions—Sympathetic nerve overactivity is associated with mortality and cardiovascular outcomes in ESRD. Controlled trials with antiadrenergic drugs are needed to determine whether interference with the sympathetic system could reduce the high cardiovascular morbidity and mortality in dialysis patients. (Circulation. 2002;105:1354-1359.)

Key Words: nervous system, sympathetic ≠ norepinephrine ≠ kidney ≠ risk factors ≠ nervous system, autonomic

Raised sympathetic activity is now recognized as an important mechanism involved in cardiovascular complications in humans.\(^1\) Increased sympathetic activity helps raise arterial pressure, triggers arterial damage, and represents a major player in the pathogenesis of left ventricular hypertrophy. There is consistent evidence that high sympathetic tone, as measured by plasma norepinephrine (NE), predicts mortality in cardiovascular diseases such as asymptomatic left ventricular dysfunction\(^4\) and chronic congestive heart failure,\(^3\) whereas in myocardial infarction, this neurohormone is a weak predictor of adverse outcomes.\(^4\) It is unclear whether measurements of sympathetic nervous activity are associated with long-term adverse cardiovascular outcomes in chronic diseases like hypertension, diabetes, and renal failure. In theory, the measurement of sympathetic activity in these diseases may help to refine the prognosis and may be useful for patient stratification in intervention studies aimed at reducing cardiovascular complications.

The study of the relationship between sympathetic activity, survival, and incidence of cardiovascular events in end-stage renal disease (ESRD) appears to be a desirable research goal, because the high cardiovascular mortality in these patients is incompletely accounted for by traditional risk factors. Sympathetic activity is increased in patients with mild to moderate\(^5\) or end-stage renal insufficiency,\(^6\) and there is now evidence that the diseased kidneys themselves are a trigger of sympathetic overactivity.\(^6\) With this background in mind, we set out to study the predictive power of plasma NE for all-cause mortality and cardiovascular outcomes in a large cohort of patients without heart failure who were undergoing chronic hemodialysis.
Methods

The protocol conformed to the ethical guidelines of our institutions, and informed consent was obtained from each participant.

Study Cohort

Two hundred twenty-eight hemodialysis patients (126 men and 102 women) who had been undergoing regular dialysis treatment for at least 6 months (median duration of regular dialysis treatment 43 months, interquartile range 21 to 110 months) were enrolled into the study. These patients represented 70% of the dialysis population of 4 dialysis units (a Clinical Research Center, an academic unit, and 2 affiliated centers). Enrollment into the study began in January 1997 and terminated in June 1998. Reasons for exclusion were history or clinical evidence of circulatory congestion (defined as dyspnea in addition to 2 of the following conditions: raised jugular pressure, bibasilar crackles, pulmonary venous hypertension, or interstitial edema on chest radiograph that required hospitalization or extra ultrafiltration) and left ventricular ejection fraction <35%, intercurrent illnesses requiring hospitalization, terminal illnesses, and dementia, and in a minority (10%) of patients, unwillingness to participate or logistical reasons. Patients were being treated thrice weekly with standard bicarbonate dialysis (Na 138 mmol/L, HCO₃ 35 mmol/L, K 1.5 mmol/L, Ca 1.25 mmol/L, Mg 0.75 mmol/L) and cuprophan or semisynthetic membranes (dialysis filter surface area 1.1 to 1.7 m²). Dry weight was targeted in each case to achieve a normotensive edema-free state. The average uraemia Kt/V in these patients was 1.21±0.27. Eighty-five patients were habitual smokers (21±16 cigarettes/d). One hundred twenty-three patients were undergoing treatment with erythropoietin, and 83 were undergoing antihypertensive therapy (58 taking monotherapy with ACE inhibitors, angiotensin II type 1 receptor antagonists, calcium channel blockers, β-blockers, or central sympatholytic agents and 25 undergoing double or triple therapy with various combinations of these drugs). Seventeen of the 83 patients taking antihypertensive drugs were being treated with central sympatholytic agents (clonidine, n=14; α-methyldopa, n=3) and 18 were taking β-blockers. After the initial assessment, patients were followed up for 34±15 months. During the follow-up, cardiovascular events (ECG-documented anginal episodes, myocardial infarction, heart failure, arrhythmia, transient ischemic attacks, stroke, and other complications; see Table 2) and death were accurately recorded. Each death was reviewed and assigned an underlying cause by a panel of 5 physicians. As part of the review process, all available medical information about each death was collected. This information always included study and hospitalization records. In the case of an out-of-hospital death, family members were interviewed by telephone to better ascertain the circumstances surrounding death.

Blood Pressure Measurements

Blood pressure was estimated by averaging all predialysis arterial blood pressure recordings during the month before the study (total of 12 measurements; ie, 3/wk). Average predialysis arterial pressure in dialysis patients is closely related to 24-hour ambulatory blood pressure monitoring and is related to left ventricular mass at least as strongly as 24-hour ambulatory blood pressure monitoring.⁹

Laboratory Measurements

Blood sampling was performed between 8 and 10 AM after an overnight fast, always during a nondialysis day. After the patient had spent 20 to 30 minutes of quiet rest in a semirecumbent position, samples were taken into chilled EDTA evacuated containers, placed immediately on ice, and centrifuged within 30 minutes at −4°C, and the plasma was stored at −80°C before assay. The plasma concentration of NE was measured by a commercially available radioimmunoassay kit (Amicyl test, Immunological Laboratories). The intra-assay coefficient of variation was 7% to 15%. The upper limit of the normal range of plasma NE in our laboratory is 3.54 nmol/L, which is very close to the value (3.38 nmol/L) reported in a previous study.¹¹

Statistical Analysis

Data are reported as mean±SD (normally distributed data) or as median and interquartile range (data which deviated from the normal distribution). Comparisons between groups were made by t test or Mann-Whitney test as appropriate. Survival curves were estimated by the Kaplan-Meier product-limit method and compared with the Mantel (log-rank) test. For patients who experienced multiple events, survival analysis was restricted to the first event. The independent prognostic power of plasma NE for all-cause mortality and cardiovascular events (fatal and nonfatal) was analyzed by the Cox proportional hazards method by introduction of all covariates that were related to all-cause mortality or cardiovascular outcome on univariate analysis. Tested covariates included traditional risk factors (previous cardiovascular events, age, sex, arterial pressure, diabetes, cholesterol, and smoking), risk factors peculiar to ESRD (hemoglobin, calcium-phosphate product, and serum albumin), and nontraditional cardiovascular risk factors (C-reactive protein and homocysteine). Because sympatholytic agents and β-blockers may interfere with sympathetic activity, we also forced them into the Cox models as the use of these drugs. The assumption of linearity for the Cox models was examined through visual inspection, and no violation of proportional hazards was found. Hazard ratios and their 95% CIs were calculated with the estimated regression coefficients and their standard errors in the Cox regression analysis. All calculations were made with a standard statistical package (SPSS for Windows version 9.0.1). All Cox proportional hazard models were of adequate statistical power (at least 9 events for each covariate in the model).

Results

The main demographic and clinical characteristics of the study population are detailed in Table 1. The prevalence of

### Table 1. Clinical Data in Dialysis Patients

<table>
<thead>
<tr>
<th>Demographic data</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>59.9±15.0</td>
</tr>
<tr>
<td>Males/females</td>
<td>126/102</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemodynamic data and cardiovascular risk factors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic pressure, mm Hg</td>
<td>139.7±25.0</td>
</tr>
<tr>
<td>Diastolic pressure, mm Hg</td>
<td>76.0±12.8</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>63.7±18.8</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>78.3±10.1</td>
</tr>
<tr>
<td>Diabetics</td>
<td>15%</td>
</tr>
<tr>
<td>Smokers</td>
<td>37%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biochemical data</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin, g/L</td>
<td>108±19</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L</td>
<td>5.37±1.49</td>
</tr>
<tr>
<td>Serum albumin, g/L</td>
<td>42±5</td>
</tr>
<tr>
<td>Serum calcium, mmol/L</td>
<td>2.3±0.2</td>
</tr>
<tr>
<td>Serum phosphate, mmol/L</td>
<td>2.0±0.4</td>
</tr>
<tr>
<td>Serum CRP, mg/L</td>
<td>7.4 (3.4–16.0)</td>
</tr>
<tr>
<td>Plasma homocysteine, μmol/L</td>
<td>27.0 (19.8–42.6)</td>
</tr>
<tr>
<td>Plasma norepinephrine, nmol/L</td>
<td>2.92 (1.72–6.57)</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD or as median (interquartile range), as appropriate.
diabetes mellitus in this cohort was 15% (ie, 35 of 228 patients). Eight-four patients had a history of ECG-documented anginal episodes or myocardial infarction, and 33 had experienced transient ischemic attacks or strokes.

Median plasma NE was 2.92 nmol/L (interquartile range 1.72 to 5.57 nmol/L), and individual plasma NE exceeded the upper limit of the normal range (cutoff 3.54 nmol/L) in 102 cases (45%). No relationship was found between plasma NE and Kt/V ($P = 0.31$) and serum creatinine ($P = 0.47$).

**NE, All-Cause Mortality, and Cardiovascular Outcomes**

During the follow-up period (34±15 months), 124 fatal and nonfatal cardiovascular events occurred in 85 patients. Eighty-seven patients died; 57 deaths (ie, 66% of all deaths) were attributable to cardiovascular causes (Table 2). Plasma NE was significantly higher ($P = 0.04$) in patients who died during follow-up (3.97 nmol/L, range 1.76 to 7.06 nmol/L) than in those who survived (2.70 nmol/L, range 1.68 to 4.63 nmol/L). Similarly, plasma NE was higher ($P = 0.03$) in patients with incident cardiovascular events (3.99 nmol/L, range 1.88 to 6.69 nmol/L) than in those who did not have such events (2.70 nmol/L, range 1.66 to 4.63 nmol/L). Event-free survival curves in patients subdivided on the basis of the 75th percentile of plasma NE are reported in the Figure. Cumulative mortality and cumulative cardiovascular events in patients with values above this threshold were consistently higher than in those showing values below this threshold.

**Cox Proportional Hazards Models**

On univariate Cox regression analysis, plasma NE (hazard ratio [1-nmol/L increase in plasma NE] 1.10, 95% CI 1.04 to 1.17, $P = 0.001$) as a continuous variable was significantly related to all-cause mortality. In addition, age ($P = 0.001$), male sex ($P = 0.02$), diabetes ($P = 0.002$), previous cardiovascular events ($P < 0.001$), serum albumin ($P = 0.006$), and C-reactive protein ($P = 0.01$) were associated with death. In a multivariate Cox regression model that included all univariate predictors of survival and the use of sympathicoplegic agents and β-blockers, plasma NE proved to be an independent predictor of this outcome (Table 3).

Similarly, on univariate Cox regression analysis, plasma NE (hazard ratio [1-nmol/L increase in plasma NE] 1.09, 95% CI 1.02 to 1.15, $P = 0.006$), age ($P < 0.001$), diabetes ($P = 0.005$), previous cardiovascular events ($P < 0.001$), pulse pressure ($P < 0.001$), and smoking ($P = 0.03$) were significantly associated with fatal and nonfatal cardiovascular events, and plasma NE again emerged as an independent predictor of cardiovascular outcomes in a multivariate Cox regression model that included these covariates and the use of sympathicoplegic agents and β-blockers (Table 4). The adjusted relative risk for cardiovascular complications in patients with plasma NE >75th percentile was 1.92 (95% CI 1.20 to 3.07) times higher than in those with normal NE concentration ($P = 0.006$).
Discussion
This study shows for the first time that sympathetic activity as assessed by the measurement of plasma NE is an independent predictor of all-cause mortality and cardiovascular morbid events in patients with ESRD without heart failure.

Sympathetic Activity in ESRD
Plasma NE measurement represents a useful guide to assess sympathetic neural activity. However, the amount of NE in the plasma is only a fraction of the amount released into the synaptic clefts and may be influenced by several factors, such as the rate of reuptake into the nerve endings or into extraneuronal cells, the density of neuroeffector junctions, and the metabolic clearance rate. Measurement of plasma catecholamines as an indicator of sympathetic neural activity demands caution in ESRD because of the complex metabolic alterations that are present in these patients. Plasma NE concentration in ESRD patients undergoing dialysis has been reported to be high or normal. Sympathetic microneurography is presently the golden standard for measuring sympathetic activity.

In the sole study in which sympathetic activity was assessed by this technique, sympathetic nerve discharge was substantially higher in patients with ESRD than in healthy subjects.

Although less reliable than sympathetic microneurography, the measurement of plasma NE is regarded as an adequate method to estimate sympathetic activity in prognostic studies. We found that plasma NE level was frankly elevated in a substantial proportion of patients, which confirms that sympathetic tone is markedly raised in ESRD. We enrolled the population without symptoms of heart failure or intercurrent illnesses from 4 dialysis units that shared common policies and clinical practices. Thus, our cohort represented a valid sample of the dialysis population without advanced cardiac complications.

### TABLE 3. Survival Analysis: All-Cause Death

<table>
<thead>
<tr>
<th>Units of Increase</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 1 year</td>
<td>1.04</td>
<td>1.02–1.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous cardiovascular events</td>
<td>2.23</td>
<td>1.39–3.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.24</td>
<td>1.34–3.75</td>
<td>0.002</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.24</td>
<td>1.41–3.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Norepinephrine 1 nmol/L</td>
<td>1.07</td>
<td>1.01–1.14</td>
<td>0.03</td>
</tr>
<tr>
<td>CRP 10 mg/L</td>
<td>1.08</td>
<td>1.01–1.16</td>
<td>0.02</td>
</tr>
<tr>
<td>Albumin 1 g/L</td>
<td>0.96</td>
<td>0.92–1.00</td>
<td>0.06</td>
</tr>
<tr>
<td>Pulse pressure 10 mm Hg</td>
<td>0.97</td>
<td>0.86–1.10</td>
<td>0.67</td>
</tr>
<tr>
<td>Use of central sympathicoplegic agents</td>
<td>1.13</td>
<td>0.49–2.59</td>
<td>0.77</td>
</tr>
<tr>
<td>Use of β-blockers</td>
<td>1.24</td>
<td>0.50–3.07</td>
<td>0.64</td>
</tr>
</tbody>
</table>

**Cox’s model for all-cause mortality. As described in detail in Methods, multivariate Cox’s models were constructed by selecting variables which resulted to be related to outcome (death, cardiovascular events) on univariate Cox’s regression analysis. Because sympathicoplegic agents and β-blockers may interfere with sympathetic activity, we always forced into the Cox’s models the use of these drugs. The full list of tested variables is given in Methods.**

### TABLE 4. Survival Analysis: Cardiovascular Events (Fatal and Nonfatal)

<table>
<thead>
<tr>
<th>Units of Increase</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine 1 nmol/L</td>
<td>1.08</td>
<td>1.02–1.15</td>
<td>0.01</td>
</tr>
<tr>
<td>Previous cardiovascular events</td>
<td>1.83</td>
<td>1.15–2.91</td>
<td>0.01</td>
</tr>
<tr>
<td>Pulse pressure 10 mm Hg</td>
<td>1.10</td>
<td>0.97–1.24</td>
<td>0.12</td>
</tr>
<tr>
<td>Age 1 year</td>
<td>1.02</td>
<td>1.00–1.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.64</td>
<td>0.96–2.80</td>
<td>0.07</td>
</tr>
<tr>
<td>Smoking 1 packet of cigarettes/month</td>
<td>1.01</td>
<td>0.99–1.02</td>
<td>0.11</td>
</tr>
</tbody>
</table>

**Cox’s model for cardiovascular outcomes. See Table 3 footnote and Methods for detail.**
NE, Survival, and Cardiovascular Outcomes

Approximately one third of patients enrolled in the present study had 1 or more cardiovascular complications. The annual death rate was 12.5%, which is similar to that of the Italian registry of dialysis and transplantation and of other European registries,26 and during the follow-up, as many as 66% of patients died of cardiovascular causes. The incidence of stroke in the present cohort was higher than that reported in the United States Renal Data System,27 and this difference should be taken into account when generalizing the results of the present study. Such high cardiovascular morbidity and mortality in large part depends on the fact that atherosclerosis and diabetes, ie, the major causes of ESRD, are risk factors for the cardiovascular system and the kidney as well. However, traditional (ie, Framingham) risk factors do not fully explain the exceedingly high cardiovascular mortality of these patients.28 Anemia, hyperhomocysteinemia, inflammation, malnutrition and hypoalbuminemia, and hyperphosphatemia28–30 have now emerged as primary cardiovascular risk factors in patients with advanced renal disease. The need for observational studies to better characterize the risk profile of dialysis patients and to identify new risk factors has been set recently as a research priority by an expert panel of the National Kidney Foundation in the United States.31

Sympathetic factors are involved in the progression of cardiovascular structural alterations such as left ventricular hypertrophy and arterial remodeling,1 and high sympathetic activity may promote atherosclerosis.32 The importance of high sympathetic tone in cardiovascular complications has a solid scientific basis that is also supported by intervention studies.33 We found by multiple forms of analysis that NE was associated with death and cardiovascular outcomes. Importantly, the relationship between this marker of sympathetic activity and outcomes remained significant on multivariate analysis that controlled for other significant risk factors, including previous cardiovascular complications, as well as use of sympathicoplegic agents and β-blockers. Plasma NE concentration above the 75th percentile of the distribution in the present study population was associated with a 20-mm Hg increase in diastolic pressure, and a 1-g/L increase in the serum concentration of fibrinogen or that associated with a 20-mm Hg increase in diastolic pressure.29 However, measurement of plasma NE is a much less reproducible marker of sympathetic function than direct sympathetic nerve discharge measurement.25 Therefore, due to regression dilution bias, plasma NE may substantially underestimate the true link between sympathetic activity and cardiovascular risk in dialysis patients.

Factors responsible for sympathetic activation in ESRD are still incompletely understood, and augmented sympathetic activity in dialysis patients may depend, at least in part, on compromised cardiac function. Although we cannot exclude that mild degrees of asymptomatic left ventricular dysfunction might have contributed to raised plasma NE in our patients, it is unlikely that this factor is a major component, because we excluded from the study patients with EF <35% and those with clinical evidence of congestive heart failure. The cardiovascular risk associated with plasma NE that we observed in ESRD was less than that reported in the SOLVD (Studies of Left Ventricular Dysfunction) trial2 in patients with asymptomatic heart failure. It appears likely but remains to be proved that in the dialysis population as a whole, the risk conveyed by sympathetic activation is much higher than that demonstrated from the present study, because clinical manifestations of congestive heart failure and systolic dysfunction are present in ~30% of patients.35

High NE predicts cardiovascular complications in ESRD. Increased sympathetic nerve traffic and circulating catecholamines might render uremic patients susceptible to a series of cardiovascular complications ranging from left ventricular hypertrophy to arrhythmia.36 Controlled trials with antiadrenergic drugs are needed to establish whether interference with the sympathetic system reduces the high cardiovascular morbidity and mortality of dialysis patients.

Acknowledgments

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References


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In the article “Plasma Norepinephrine Predicts Survival and Incident Cardiovascular Events in Patients With End-Stage Renal Disease,” by Zoccali et al that appeared in the March 19, 2002, issue of the journal (Circulation. 2002;105:1354–1359), an error appeared in the byline. Alessandro Cataliotti’s last name was spelled incorrectly. The corrected byline appears below.

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