Sympathetic Nerve Activity in End-Stage Renal Disease

Martin Hausberg, MD; Markus Kosch, MD; Patrick Harmelink, MS; Michael Barenbrock, MD; Helge Hohage, MD; Klaus Kisters, MD; Karl Heinz Dietl, MD; Karl Heinz Rahn, MD

Background—Uremia is proposed to increase sympathetic nerve activity (SNA) in hemodialysis patients. The aims of the present study were to determine whether reversal of uremia by successful kidney transplantation (RTX) eliminates the increased SNA and whether signals arising in the diseased kidneys contribute to the increased SNA in renal failure.

Methods and Results—We compared muscle sympathetic nerve activity (MSNA) in 13 hemodialysis patients wait-listed for RTX and in renal transplantation patients with excellent graft function treated with cyclosporine (RTX-CSA, n=13), tacrolimus (RTX-FK, n=13), or without calcineurin inhibitors (RTX-Ø, n=6), as well as in healthy volunteers (CON, n=15). In addition to the above patients with present diseased native kidneys, we studied 16 RTX patients who had undergone bilateral nephrectomy (RTX-NE). Data are mean±SEM. MSNA was significantly elevated in hemodialysis patients (43±4 bursts/min), RTX-CSA (44±5 bursts/min), RTX-FK (34±3 bursts/min), and RTX-Ø (44±5 bursts/min) as compared with CON (21±3 bursts/min), despite excellent graft function after RTX. RTX-NE had significantly reduced MSNA (20±3 bursts/min) when compared with RTX patients. MSNA did not change significantly with RTX in 4 hemodialysis patients studied before and after RTX (44±6 versus 43±5 bursts/min, P=NS). In contrast, nephrectomy resulted in reduced MSNA in all 6 RTX patients studied before and after removal of the second native kidney.

Conclusions—Despite correction of uremia, increased SNA is observed in renal transplant recipients with diseased native kidneys at a level not significantly different from chronic hemodialysis patients. The increased SNA seems to be mediated by signals arising in the native kidneys that are independent of circulating uremia related toxins. (Circulation. 2002;106:1974-1979.)

Key Words: nervous system, sympathetic ▪ kidney ▪ kidney failure, chronic ▪ cyclosporine ▪ tacrolimus

Patients with chronic renal failure, and particularly patients with end-stage renal disease, are characterized by an excessive cardiovascular morbidity and mortality.1 It has been convincingly shown that patients with compensated renal failure2 and patients undergoing hemodialysis treatment3 exhibit sustained activation of the sympathetic nervous system, which contributes to hypertension and increased cardiovascular morbidity and mortality.4

Signals arising in the failing kidneys seem to mediate sympathetic activation in chronic renal failure.5 Animal studies suggest that circulating uremia-related toxins, which are present in compensated renal failure and even more strikingly in patients with end-stage renal disease despite effective dialysis therapy, cause excitation of renal afferent nerves6 and thus may produce sustained activation of the sympathetic nervous system. Whereas dialysis treatment does not eliminate uremia, kidney transplantation can. The activity of the sympathetic nervous system has not yet been assessed in patients after renal transplantation.

Sympathetic overactivity in renal failure may be caused by circulating uremia-related toxins stimulating renal afferent signals but may also result from stimuli independent of uremia arising in the diseased kidneys. Also, the currently generally used calcineurin-dependent immunosuppressants cyclosporine and tacrolimus may cause sympathetic activation.7 The latter, though, has been reported equivocally,8–10 and sympathetic nerve activity has not yet been described in humans treated with tacrolimus.

There were therefore 3 aims of the present study. The first was to assess the level of sympathetic nerve activity in patients after renal transplantation as compared with dialysis patients, using healthy volunteers and essential hypertensive patients with normal kidney function as control groups to address a potential influence of antihypertensive drugs. Second, we sought to assess whether the presence of the diseased native kidneys in renal transplant recipients influences sympathetic nervous system activity in the absence of uremia. Third, we wanted to compare sympathetic nerve activity in renal allograft recipients treated with cyclosporine, tacrolimus, or calcineurin-independent immunosuppressants.
TABLE 1. Clinical Characteristics of Patients and Healthy Subjects

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Displayed are clinical characteristics of patients with renal disease, essential hypertensive patients (HYP), and healthy subjects (CON). The number of patients treated with antihypertensive drugs, causes of renal failure among renal transplant patients receiving cyclosporine (RTX-CSA), tacrolimus (RTX-FK), no calcineurin inhibitors (RTX-Ø), and hemodialysis patients (HD), and daily doses of immunosuppressive medication in the renal transplant recipients.

*P<0.05 vs HD; †P<0.05 vs CON.

Methods

Patients and Subjects

All patients and subjects gave their written informed consent. The Review Board on Human Investigation of the University of Muenster approved the studies.

Fifteen healthy volunteers not receiving any medication served as controls. Six essential hypertensive patients with otherwise normal physical examination, ECG, and routine laboratory tests served as additional control group (Table 1).

A total of 32 renal transplantation patients with preserved diseased native kidneys were recruited, 13 of whom were receiving cyclosporine (dose adjusted to maintain trough levels between 80 and 150 ng/mL) and prednisolone, 13 of whom were receiving tacrolimus (dose adjusted to maintain trough levels between 4 and 10 ng/mL) and prednisolone, and 6 of whom had never received a calcineurin inhibitor. Inclusion criteria were stable graft function and prednisolone, and 6 of whom who had never received a calcineurin inhibitor. Inclusion criteria were stable graft function and prednisolone, 13 of whom were receiving tacrolimus (dose adjusted to maintain trough levels between 4 and 10 ng/mL) and prednisolone, 13 of whom were receiving cyclosporine (dose adjusted to maintain trough levels between 80 and 150 ng/mL) and prednisolone, 13 of whom were receiving RTX-CSA, tacrolimus (RTX-FK), no calcineurin inhibitors (RTX-Ø), and hemodialysis patients (HD), and daily doses of immunosuppressive medication in the renal transplant recipients.

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Nephropathy due to analgesic drugs in 5 cases, polycystic kidney disease in 8 cases, and chronic pyelonephritis in 3 cases. In 10 patients, bilateral nephrectomy was performed before transplantation; in the remaining 6, the second native kidney was removed shortly after transplantation and measurements were obtained before and 3 months after removal of the second native kidney. All patients received calcineurin inhibitors. Antihypertensive treatment consisted of angiotensin-converting enzyme inhibitors in 5 patients, calcium antagonists in 11 patients, loop diuretics in 9 patients, β-blockers in 8 patients, and α-blockers in 1 patient.

Measurements

Heart rate was measured continuously by an ECG. Blood pressure was measured using an automatic sphygmomanometer (Dinamap XL, Johnson & Johnson) during the last half of each minute. Calf blood flow (CBF) was measured by venous occlusion plethysmography using an air plethysmograph as described previously.11 Respiration was monitored by a strain gauge respiration transducer (Pneumotrace, UFI).

Microneurography

Intraneural recording techniques were used to obtain multifiber recordings of postganglionic muscle sympathetic nerve activity (MSNA) from the peroneal nerve as described in more detail elsewhere.12 13

Protocol

All studies were performed between 8 and 12 AM, after an overnight fast with the subject in the supine position. Immunosuppressive drugs were withheld for at least 12 hours before the study, and antihypertensive medication was withheld for at least 36 hours before the study. Subjects were instrumented for ECG, blood
pressure (in the arm without an arteriovenous fistula), CBF, and sympathetic nerve and Pneumotrace recordings. A catheter was placed into a cubital vein for blood sampling.

After 30 minutes of quiet rest, blood samples were drawn, and ECG and sympathetic neurograms were recorded continuously for 30 minutes, CBF was measured every 15 seconds, and blood pressure was measured every minute for 5 of every 10 minutes throughout the 30-minute recording period.

Analyses
Tracings of sympathetic neurograms, electrocardiograms, respiration, and CBF were recorded with a MacLab data acquisition system (AD Instruments, Wisseth GmbH) on a Macintosh computer (Apple Inc).

Sympathetic bursts were identified by inspection of the mean voltage neurogram by an investigator blinded to the patients’ group assignment. Only bursts with a minimal signal-to-noise ratio of 2.5:1 were counted. Interobserver and intraobserver variabilities in identifying bursts were 5.4±0.5% and 4.3±0.3%, respectively.14 The rate of sympathetic nerve discharge was expressed as number of sympathetic bursts per minute; the coefficient of variation for this measure was 8.8±1.5% in 15 subjects and patients studied twice within 8 weeks.

CBF was expressed as mL/min per 100 mL calf volume. Calf vascular resistance (CVR) was calculated by dividing mean arterial pressure by flow and was expressed in arbitrary units (a.U.).

For statistical analysis, χ² test, ANOVA with post-hoc tests (Fisher’s protected least significant differences), and least-squares linear regression analysis were used where applicable. Statistical significance was assumed at P<0.05. NS means statistically not significant. Data are presented as mean±SEM.

Results
Comparison of Healthy Volunteers, Essential Hypertensive Patients, Hemodialysis Patients, and Renal Transplant Recipients With Native Kidneys
Patient groups and healthy volunteers did not differ significantly in their demographic characteristics. Kidney function was normal in essential hypertensive patients. Renal transplantation patients had serum creatinine concentrations not significantly different from healthy volunteers, and their concentrations of blood urea nitrogen were within the laboratory’s reference range (Table 1).

Measures of Sympathetic Nerve Activity and Hemodynamic Parameters in Patients and Healthy Volunteers
Representative recordings of sympathetic neurograms of a hemodialysis patient, the same patient after successful kidney transplantation (receiving cyclosporine), a renal transplantation patient receiving tacrolimus before and after native kidney nephrectomy, a renal transplantation patient without calcineurin inhibitor treatment, and a healthy volunteer are depicted in Figure 1. The hemodialysis patient and all renal allograft recipients with present native kidneys had a more than 2-fold elevated rate of sympathetic nerve discharge as compared with the healthy subject. Kidney transplantation did not change MSNA. In contrast, after native kidney nephrectomy, MSNA decreased substantially as discussed in the following section.

Summary data of muscle sympathetic nerve activity and plasma norepinephrine concentrations are shown in Table 2. All groups of renal transplantation patients, as well as the small group of patients not receiving a calcineurin inhibitor, and the hemodialysis patients had significantly elevated MSNA when compared with both healthy volunteers and patients with essential hypertension but normal kidney function. Despite elimination of uremia, MSNA was indistinguishable in renal transplantation patients treated with cyclosporine, renal transplantation patients not receiving calcineurin inhibitors, and hemodialysis patients. These results were supported by the small subgroup of 4 hemodialysis patients studied before and after kidney transplantation. In these patients, there was no significant change in MSNA with transplantation (44±6 bursts/min before versus 43±5 bursts/min after kidney transplantation, P=NS). MSNA tended to be somewhat lower in tacrolimus-treated transplant recipients, but this did not reach statistical significance (P=0.09).

Plasma norepinephrine concentrations showed higher variation than MSNA, but plasma norepinephrine concentrations...
were also significantly elevated in hemodialysis patients and cyclosporine-treated renal transplantation patients as compared with healthy volunteers and essential hypertensive patients. Average plasma norepinephrine concentrations of renal allograft recipients receiving tacrolimus or no calcineurin inhibitor tended to be lower than in the other patient groups with renal disease and higher than in hypertensives and healthy subjects; however, these differences did not reach statistical significance. There was a significant correlation between plasma norepinephrine concentrations and MSNA when all groups were analyzed together (r=0.49, P<0.001). On separate analysis of each group, however, regression analysis reached statistical significance only for patients treated with cyclosporine (r=0.56, P<0.05).

Systolic, diastolic, and mean arterial pressure did not differ significantly across the patient groups but were, except for diastolic blood pressure in the patients not receiving calcineurin inhibitors, significantly higher as compared with healthy volunteers. (Table 2).

Comparison of Renal Transplant Recipients With Native Kidneys and Renal Transplant Recipients Who Had Undergone Bilateral Nephrectomy

Table 3 shows demographic parameters, hemodynamic measures, MSNA, and plasma norepinephrine concentrations in 10 renal transplant recipients who had undergone bilateral nephrectomy. These patients were matched for sex, age, and immunosuppressive treatment with 10 kidney transplantation patients with preserved native kidneys and 10 healthy controls. Both patient groups had excellent graft function. MSNA was significantly lower in renal transplant recipients who had undergone bilateral nephrectomy and was similar to that observed in healthy volunteers. Consistent with the differences in MSNA, CVR was lower in patients who had undergone bilateral nephrectomy than in patients with preserved native kidneys.

Figure 2 shows data from 6 renal transplantation patients before and 3 months after removal of the second native kidney. MSNA decreased in all 6 patients after nephrectomy (left panel, P<0.05). Five patients also had a decrease in CVR (middle panel, P<0.05). Antihypertensive medications (loop diuretics in 5, calcium antagonist in 5, β-blockers in 4, α-blockers in 1, and angiotensin-converting enzyme inhibitors in 2 patients) were not changed between the measurements, except for a decrease of medication dose in 2 patients. Mean arterial pressure decreased in 4 of the 6 patients, which did not reach statistical significance (right panel, P=NS).

Discussion

We present several major findings. First, as compared with healthy volunteers, sympathetic nerve discharge to the skeletal muscle vascular bed was considerably elevated in both patients with end-stage renal disease on maintenance hemodialysis and renal transplant patients with preserved native kidneys (RTX—native kidneys), and healthy volunteers (CON).
in renal transplantation patients, despite excellent graft function. Second, the diseased native kidneys contribute substantially to elevated sympathetic nerve activity in renal transplant recipients, because MSNA measured in renal transplantation patients who underwent bilateral native kidney nephrectomy is not significantly different from that measured in healthy volunteers. Third, MSNA does not differ significantly in renal transplant recipients treated with cyclosporine, tacrolimus, or calcineurin-independent immunosuppressants.

Several studies in animal models of renal failure suggest that excitation of renal afferent nerves results in increased efferent sympathetic nerve discharge, with resulting increases in blood pressure. Campese and coworkers\(^5\) observed increased sympathetic nerve activity of central origin in an ablation model of renal failure that could be prevented by dorsal rhizotomy, a procedure that selectively blocks subdiaphragmatic afferent nerves. Also, the development of hypertension in the 5/6 nephrectomized rats could be prevented by dorsal rhizotomy. The same group showed that acute renal injury by intrarenal injection of phenol caused an immediate rise in blood pressure and in norepinephrine secretion from the posterior hypothalamus that could be prevented by renal denervation.\(^5\) Thus, afferent impulses from the diseased kidney to central integrative structures in the brain may cause increased sympathetic nerve discharge and contribute to hypertension in chronic renal failure.

Recordati and coworkers\(^6\) showed that uremia-related toxins may be responsible for afferent sympathetic nerve discharge in the kidneys. Uremia-related toxins accumulate in chronic renal failure and cannot be completely cleared by dialysis treatment. Consistent with our findings, Converse and coworkers also observed that patients undergoing chronic hemodialysis treatment had increased MSNA as compared with healthy subjects.\(^3\) In contrast, MSNA was not significantly different from healthy humans in hemodialysis patients who had undergone bilateral nephrectomy. These studies suggest that uremia-related toxins present in patients with end-stage renal disease despite effective dialysis treatment may elicit afferent impulses in the failing kidneys that cause an increase in efferent sympathetic nerve activity mediated by central integrative structures.

Thus, we hypothesized that in patients with excellent graft function and absence of uremic toxins after renal transplantation, sympathetic nerve discharge would be reduced. Our results did not confirm this. Sympathetic nerve activity did not differ significantly between hemodialysis patients and patients after renal transplantation, despite correction of uremia in the latter. This was true even in a small group of renal transplant recipients who have never received calcineurin-dependent immunosuppressants.

Our results cannot be explained by recruitment of patients from different populations because all studied dialysis patients were wait-listed for renal transplantation and met the same medical criteria as the renal transplantation patients. The groups of patients were comparable with respect to age, sex, and time since onset of end-stage renal failure. Moreover, in a subgroup of hemodialysis patients studied before and after kidney transplantation, MSNA did not change with transplantation.

It may be argued that a potential sympathoinhibitory effect of correction of uremia in transplantation patients may be overridden by sympathoexcitatory effects of calcineurin-dependent immunosuppressants. Indeed, animal studies demonstrate that both cyclosporine and tacrolimus acutely increase sympathetic nerve activity.\(^7\) To our knowledge, however, sympathetic nerve activity has not yet been assessed in patients treated with tacrolimus, and it is controversial whether chronic treatment with cyclosporine causes activation of the sympathetic nervous system in humans.\(^8\)–\(^10\) It is to be noted that the doses and blood levels of cyclosporine in the present study are considerably lower than those in the above cited studies involving heart transplantation patients. Recent animal studies suggest that the calcineurin inhibitors cyclosporine and tacrolimus cause activation of the sympathetic nervous system via activation of renal afferent nerves;\(^11\) synapsin in renal sensory nerve endings is involved.\(^12\) This may contribute to but not fully explain our findings of normal MSNA in cyclosporine- or tacrolimus-treated renal transplantation patients after bilateral native kidney nephrectomy, because MSNA was also elevated in a group of renal transplant recipients not receiving any calcineurin inhibitors. It may be hypothesized that a potential sympathoexcitatory effect of calcineurin inhibitors is attenuated in patients with diseased native kidneys because in these patients other factors already cause a tonic activation of renal afferent nerves.

Importantly, our study demonstrated that the elevated sympathetic nerve discharge observed in renal transplant recipients is mediated by signals arising from the native

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**Figure 2.** The left panel shows MSNA, the middle panel CVR, and the right panel mean arterial pressure (MAP) in 6 renal transplantation patients who were studied before and 3 months after removal of the second native kidney. Means before and after nephrectomy are displayed in horizontal bars. All 6 patients had a substantial decrease in MSNA after nephrectomy, 5 a decrease in CVR, and 4 a decrease in MAP.
kidneys independent of correction of uremia. The present study excludes uremic toxins as the signals, but cannot otherwise disclose their nature. Underlying causes may be tonic excitation of renal afferent nerves by fibroproliferative scarring in the failing native kidneys with local ischemia and possible release of chemical mediators, eg, adenosine. Activation of the renin-angiotensin system in the failing kidneys may be responsible for the increased sympathetic nerve discharge. Lichtenberg and coworkers reported improvement of elevated muscle sympathetic nerve activity in patients with chronic renal failure after angiotensin-converting enzyme inhibitor treatment. Further studies are needed to determine if blockade of the renin-angiotensin system can reduce elevated sympathetic nerve activity in renal transplantation patients and decrease their excess cardiovascular morbidity and mortality.

A further limitation of the study is that we did not assess the time course of sympathetic nerve activity after transplantation. It is conceivable that sympathetic nerve activity could change with more time after transplantation. However, patients were studied several months after transplantation, those patients not receiving a calcineurin inhibitor even longer after transplantation. Patients had reached stable graft function and no symptoms of uremia were present. At that time, patients with native kidneys in place had significantly increased MSNA, whereas patients who had their native kidneys removed had MSNA that was not different from that of healthy subjects.

The present study does not allow us to determine to what extent elevated sympathetic nerve activity in renal transplantation patients contributes to hypertension. Although after bilateral native kidney nephrectomy renal transplantation patients had reduced MSNA and CVR, the decline in blood pressure did not reach statistical significance, and patients continued to require antihypertensive medication. In renal transplantation patients, many other factors, eg, immunosuppressive drugs, cause hypertension and may mask an effect of reduced sympathetic outflow on blood pressure. Moreover, the effect of native kidney nephrectomy on MSNA may appear earlier than a potential effect on blood pressure.

We doubt that antihypertensive treatment interfered with the conclusions of the study for 3 reasons. First, sympathetic nerve activity was elevated and not significantly different in patients receiving antihypertensive medication likely to decrease sympathetic nerve activity (ie, angiotensin-converting enzyme inhibitors and β-blockers) and in patients receiving antihypertensive medication likely to increase sympathetic nerve activity (ie, calcium channel blockers). Second, renal transplantation patients who have undergone bilateral nephrectomy showed reduced muscle sympathetic nerve activity as compared with patients with native kidneys, despite similar antihypertensive medication. Third, essential hypertensive patients with normal kidney function on similar antihypertensive medication as the patients with renal disease had significantly lower MSNA than patients with renal disease and preserved native kidneys but did not differ significantly in MSNA from healthy volunteers.

Conclusions

Despite excellent graft function with correction of uremia, increased sympathetic nerve activity is observed in renal transplant recipients at a level not significantly different from chronic hemodialysis patients. The increased sympathetic nerve activity seems to be mediated by signals arising in the native kidneys that are independent of circulating uremia-related toxins.

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