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PERSPECTIVES IN RENAL MEDICINE

Sympathetic hyperactivity in chronic kidney disease: Pathogenesis, clinical relevance, and treatment

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Sympathetic hyperactivity in chronic kidney disease: Pathogenesis, clinical relevance, and treatment. Cardiovascular morbidity and mortality importantly influence live expectancy of patients with chronic renal disease (CKD). Traditional risk factors are usually present, but several other factors have recently been identified. There is now evidence that CKD is often characterized by an activated sympathetic nervous system. This may contribute to the pathogenesis of renal hypertension, but it may also adversely affect prognosis independently of its effect on blood pressure. The purpose of this review is to summarize available knowledge on the role of the sympathetic nervous system in the pathogenesis of renal hypertension, its clinical relevance, and the consequences of this knowledge for the choice of treatment.

Hypertension is common in patients with chronic kidney disease (CKD). Its prevalence varies between 30% and 100% depending on the target population, cause of renal disease. and level of renal function [1]. Traditionally this hypertension has been viewed as largely volume-dependent. More than three decades ago, Kim et al [2] showed that hypertensive and normotensive hemodialysis patients differ in peripheral vascular resistance and not in cardiac output. Importantly, after bilateral nephrectomy blood pressure was reduced by a decrease in resistance and not in cardiac output. This provided direct evidence that the diseased kidneys were somehow involved in the genesis of increased vascular resistance and therefore hypertension in chronic renal failure (CRF).

There is now evidence that CKD is often characterized by an activated sympathetic nervous system. This may contribute to the pathogenesis of renal hypertension, but it may also adversely affect prognosis independently of its effect on blood pressure. This could have important implications for the choice of treatment. The purpose of this review is to summarize available knowledge on the role of the sympathetic nervous system in the pathogenesis of renal hypertension, its clinical relevance, and the consequences of this knowledge for the choice of treatment.

Key words: renal hypertension, kidney disease, sympathetic activity, angiotensin II, review.

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MEASUREMENT OF SYMPATHETIC NERVOUS ACTIVITY

The sympathetic nervous system is a part of the autonomic nervous system. Its activity can be derived indirectly from sympathetic effector responses, for instance, blood pressure or heart rate. However, this is very nonspecific, because effectors may also be influenced by mechanical, chemical, and hormonal stimuli. Norepinephrine that appears in the plasma is the net result of discharge, reuptake, metabolism, and clearance, and as a consequence is not suitable as marker for activity.

Several of these limitations can be overcome by the use of sympathetic nerve recordings. True sympathetic nerve activity can be assessed by the microneurographic technique, which was developed by Vallbo et al [3]. The intraneural recording is made with a tungsten microelectrode with a shaft of 0.2 mm and a tip of a few micrometers placed in a peripheral nerve, generally the peroneal or radial nerve (muscle sympathetic nerve activity) (MSNA). Usually, nerve recordings cause minimal discomfort and negligible, transient after-effects, when studies are done by an experienced technician. However, the technique is not suitable for routine use, because it is laborious, time-consuming, and technically difficult [4]. Figure 1 shows typical examples of nerve recordings in humans.

The sympathetic nervous system is particularly relevant for the short-term regulation of blood pressure. Because the within-subject reproducibility of the basal supine MSNA signal is very good, this technique has also extensively been used to quantify chronic effects of interventions, such as medication or diet changes.

There are regional differences between sympathetic activity in the human body. MSNA represents the centrally generated postganglionic sympathetic activity to the human skeletal muscle circulation, which is an

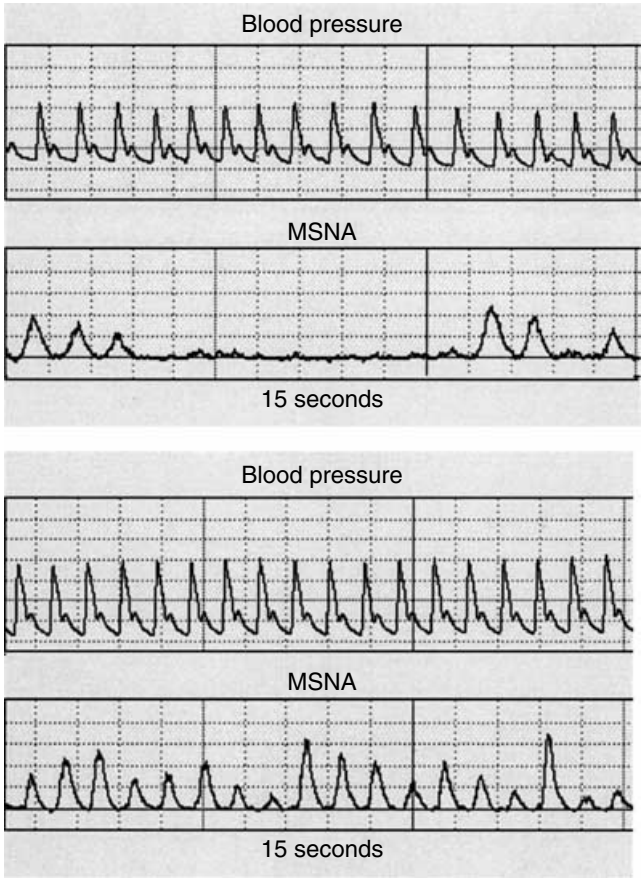

Fig. 1. Typical examples of microneurographic assessment of muscle sympathetic nerve activity (MSNA) in the peroneal nerve. The upper tracing is a recording of a normal person and the lower tracing of a patient with chronic kidney disease. Each peak represents a spontaneous burst of sympathetic nerve discharge. The rate of sympathetic nerve discharge in the patient is much higher than in the age-matched healthy control. Blood pressure curves (finger blood pressure) in the normal person and the chronic kidney disease patient are shown as well.

important determinant of blood pressure [5, 6]. It does not give information specifically about cardiac or renal sympathetic activity. Isotopic dilution method for norepinephrine spillover to plasma can be used for assessment of organ-specific sympathetic activity, for instance norepinephrine spillover into the cardiac, renal, or central nervous system vascular bed [4]. Radionucleotide imaging has been used to quantify cardiac sympathetic activity [4].

PATHOGENESIS OF SYMPATHETIC OVERACTIVITY IN CKD

Experimental studies

Renin-angiotensin system. Experimental studies have come up with several pathophysiologic mechanisms through which the diseased kidneys can be involved.

Inappropriate renin secretion in relation to the state of sodium-volume balance has long been recognized [7]. The renin output of the kidney is the sum of the production of all nephrons. If all nephrons of the diseased kidneys would have been affected equally and secrete equal amounts of renin, CRF would be characterized as a new steady-state with high blood pressure and normal renin. However, this situation is uncommon, probably due to the phenomenon of nephron heterogeneity, which stands for the hypothesis that the disease does not equally affect the nephrons. Those, which are severely affected, hypofilter, and show impaired sodium excretion and renin hypersecretion, whereas those which are less affected will adapt to the elevated blood pressure by hyperfiltering and suppressing renin secretion. Blood pressure will not be high enough to suppress renin production in all nephrons. As a result, CRF is usually characterized by high blood pressure and high renin. High circulating angiotensin II (Ang II) has a variety of effects. Ang II is a direct vasoconstrictor, it increases aldosteron production, and it has trophic effects. There is clear evidence that Ang II enhances sympathetic activity, both at peripheral and central sites. It directly stimulates MSNA, which indicates central sympathetic activation [8]. It also enhances norepinephrine release through a presynaptic effect [9]. This effect can not be assessed by MSNA measurements. On the other hand, sympathetic activation results in further activation of the renin-angiotensin system [9].

Renal injury. Renal ischemia can lead to sympathetic activation. During renal ischemia, adenosine is released. This adenosine evokes an increase in afferent renal nerve traffic, as can be shown during adenosine infusion in the renal artery of uninephrectomized dogs [10]. In rats, induction of renal artery stenosis [11], partial renal ablation by arterial ligation [12] or intrarenal phenol injection [13] cause excitation of the renal afferent nerves, which results in neurogenic hypertension. Even a small injury in one kidney caused by intrarenal injection of phenol, which does not affect glomerular filtration rate (GFR), leads to hypertension in association with an increased central sympathetic activity [14]. In these animal models, renal denervation results in a reduction or total prevention of hypertension. Additionally, in the phenol hypertension model, nephrectomy of the injured kidney several weeks after the induction of renal damage results in normalization of blood pressure [15]. Thus, renal injury in experimental conditions can lead to sympathetic hyperactivity and hypertension and this hyperactivity is associated with activation of renal afferent nerves. The signal from the diseased kidneys goes through the afferent renal nerves to the central nervous system.

Nitric oxide inhibition. In animals, the sympathoexcitatory effect of nitric oxide inhibition has been clearly demonstrated during systemic administration of nitric oxide synthesis inhibitors and is greatly attenuated by sympathectomy or by renal denervation [16, 17]. Basal activity of central sympathetic activity is inhibited by

central nitric oxide production [18]. Nitric oxide synthesis inhibition by L-arginine analog N-nitro-L-arginine methyl ester (L-NAME) results in an increase of central sympathetic activity. The overall conclusion of experimental studies is that nitric oxide has sympathoinhibitory and vagotonic effects with attenuation of cardiovascular end-organ responses, acting both on central and peripheral mechanisms (review in [19]). In vivo and ex vivo animal experiments have provided evidence that neuronal nitric oxide is a major component of the signal transduction pathway involved in the tonic restraint of central sympathetic outflow [20]. In rats with CRF some specific brain areas (i.e., posterior hypothalamic nuclei and the locus coeruleus), which are involved in blood pressure regulation by their effect sympathetic outflow, show a greater turnover rate of norepinephrine, than control rats [21].

In the phenol renal injury model neuronal nitric oxide synthase (nNOS)-mRNA expression in brain areas involved in noradrenergic control of blood pressure is decreased as compared to controls. Intravenous administration of losartan results in an increase of the abundance of nNOS-mRNA in these brain nuclei [22]. These studies suggest that stimulation of the central sympathetic nervous system activity by renal afferent impulses may be mediated by local activation of Ang II, which stimulates central sympathetic outflow by inhibition of NOS-mRNA abundance. The sympatho-inhibitory effect of intravenously administered losartan is mediated by blockage of local Ang II, resulting in an up-regulation of NOS-mRNA expression.

Clinical studies

It is long known that plasma catecholamine concentrations are approximately doubled in CRF patients [23, 24]. Application of the MSNA method has enhanced our understanding of the pathogenesis of hypertension in CKD patients. Although the MSNA technique was already available in the 1970s, the first publication showing that MSNA was increased in CRF patients appeared two decades later. Hemodialysis patients who still had their native kidneys had elevated MSNA [25]. Subsequently, we and others confirmed these observations and also showed that in hypertensive CRF patients not yet on dialysis MSNA is increased [26, 27].

Renin-angiotensin system and renal injury. Converse et al [25] studied bilaterally nephrectomized patients as well and showed that MSNA was identical to healthy controls, indicating that the signal that commands the brain to increase sympathetic outflow is generated in the diseased kidneys.

In another study, they provided data indicating that baroreceptor function was not impaired [28]. We also found no clear signs for baroreceptor dysfunction [26]. These human studies do not exclude the possibility of subtle alteration of baroreceptor function, but they definitely exclude the presence of any relevant sino-aortic or cardiopulmonary baroreceptor denervation (i.e., the traditional notion of clinically important autonomic neuropathy in CRF). Therefore, based on these studies, sympathetic hyperactivity in CRF patients cannot by explained on the basis of baroreceptor function impairment.

Renal transplant patients with good renal graft function exhibit MSNA identical to hemodialysis patients [27]. Bilateral nephrectomy in these transplant patients resulted in a MSNA level not different from controls. Furthermore, in human renovascular hypertension, angioplasty resulted in a decrease of MSNA [29]. Unilateral nephrectomy for transplantation purpose did not affect MSNA [30]. All these data together indicate that in humans the diseased kidneys are also the key players in the pathogenesis of increased MSNA.

Based on the experimental data outlined above, which indicate that renal injury without affecting GFR can result in sympathetic hyperactivity, we hypothesized that this would be also the case in humans. Normotensive and hypertensive polycystic kidney disease (PKD) patients were investigated, either with normal renal function or with CRF. MSNA in hypertensive PKD patients was increased regardless of renal function, whereas in normotensive PKD patients MSNA was identical to controls [31]. In this population, the MSNA correlated with blood pressure, suggesting that the increased sympathetic activity contributes to the pathogenesis.

A subsequent study was aimed to unravel the mechanisms affecting the sympathetic nervous system in CKD patients [30]. It has long been recognized that sympathetic activity increases with age [32] and is feedback-regulated by baroreflex control and volume status [33]. In CKD patients, volume status may vary substantially. Therefore, it is critical that this should be taken into account when assessing sympathetic activity in individual patients. We studied a large group of CKD patients with various renal parenchymal diseases when in normovolemic condition, which was evidenced by assessment of extracellular fluid volume (ECFV). On average MSNA was higher in normovolemic patients than in controls. Multiple regression analysis revealed age and plasma renin activity as significant predictors for MSNA [30]. Figure 2 shows the relation between age and MSNA. Additionally, both patients and controls were studied in two different volume states (i.e., in patients when on and off diuretics and in controls on high and low salt diet). The relation between changes in volume and MSNA in patients parallels that in healthy subjects, but is shifted to a higher level of MSNA (Fig. 3). This relation is very similar to that for volume and plasma renin activity. This similarity suggests a cause-effect relation or a common origin.

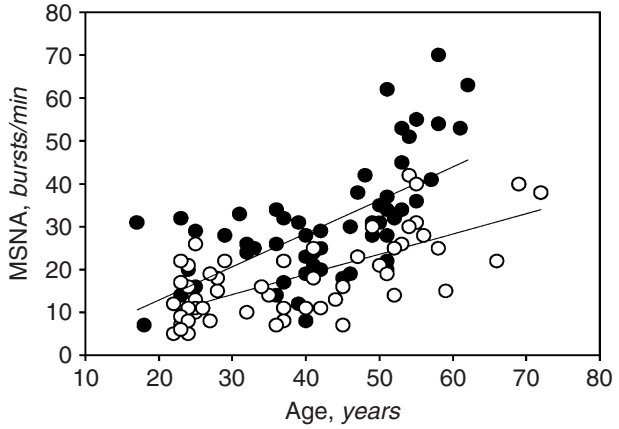

Fig. 2. Relation between age and muscle sympathetic nerve activity (MSNA) (○; controls, $N = 57$) (●; chronic kidney disease patients, $N = 57$). In controls and in patients age correlated with MSNA ($r = 0.69$ and $r = 0.62$). The regression line of the patients was steeper than that of controls ($P < 0.01$) (adapted with permission from [30]).

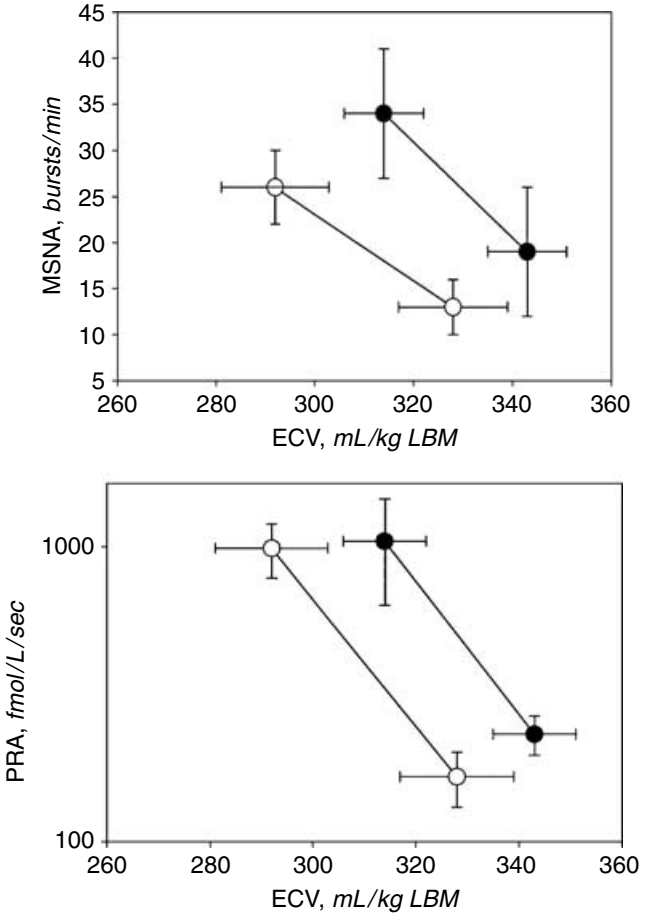

Fig. 3. Plots of extracellular fluid volume (ECV) and muscle sympathetic nerve activity (MSNA) and ECV and plasma renin activity (PRA) in chronic renal failure patients (●; $N = 7$) in normovolemic and hypervolemic condition and in healthy volunteers (○; $N = 8$) during low and high sodium diet (adapted with permission from [30]).

Based on the pathophysiologic considerations outlined above it seems logical that an angiotensin-converting enzyme (ACE) inhibitor or an Ang II receptor antagonist reduce MSNA. Indeed, enalapril and losartan lower blood pressure and MSNA in CRF patients [26, 34] (Fig. 4). In the dosages used in our study, the two drugs are equally effective in their blood pressure lowering and MSNA-inhibiting effect [34]. This is in contrast to amlodipine, which reduces blood pressure but increases MSNA [26]. These studies provide evidence in humans that centrally located Ang II importantly contributes in the pathogenesis of this form of hypertension, thereby confirming the experimental data outlined above.

In both studies, MSNA was only partially suppressed [26, 34]. Addition of the centrally acting sympatholytic drug moxonidine to the treatment with an Ang II antagonist resulted in a normalization of blood pressure and MSNA [abstract; Neumann J et al, *J Am Soc Nephrol* 14:20A, 2003].

Nitric oxide inhibition. Nitric oxide availability is clearly decreased in humans with advanced CRF, but also in early renal failure [35, 36]. If this is also the case for central nervous system nitric oxide, it could result in a limitation of the central inhibition of sympathetic outflow. However, the acute effects of a systemic infusion of N-monomethyl-L-arginine (L-NMMA), which is a NOS inhibitor, in humans were an increase in blood pressure and decrease in MSNA [37], while others found a dose-dependent effect, sympatho-excitatory at low dosage and inhibitory at higher dosage [38]. Effects on sympathetic activity of chronic administration in humans have not been assessed. However, asymmetrical dimethylarginine (ADMA), which is an endogenous inhibitor of NOS, appeared to be a strong and independent predictor of overall mortality and cardiovascular outcome in hemodialysis patients [39], and is associated with left ventricular dimensions [40]. Interestingly, recent data in dialysis patients show a relationship between norepinephrine and ADMA levels, suggesting a cause and effect relation [41].

Dialysis regimen. It was already shown that intensifying the dialysis regimen has a profound impact on blood pressure, presumably by its effect on peripheral vascular resistance [42–45]. It also results in regression of left ventricular hypertrophy (LVH) [42]. We have recently shown that increasing the frequency of hemodialysis from three to six times weekly results in a decrease in MSNA, accompanied by a decrease in peripheral resistance [abstract; Zilch O et al, *J Am Soc Nephrol* 12:280A, 2001]. The MSNA returned to its initial level after the patients returned after 6 months to the three weekly regimen. This important finding points to an additional mechanism for the pathogenesis of sympathetic hyperactivity. Apparently, the intensification of the dialysis regimen results in the reduction of sympatho-stimulating factor(s) or in an increase in sympatho-inhibiting factor(s). ADMA, an

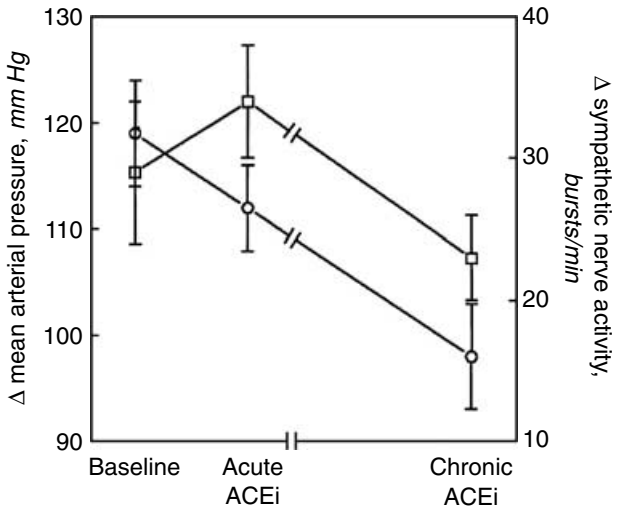

Fig. 4. Changes in mean arterial pressure and muscle sympathetic nerve activity (MSNA) during intravenous infusion of enalaprilat and during long-term (approximately 6 weeks) treatment with enalapril in patients with chronic renal failure (CRF). Blood pressure was decreased by both long-term treatment with enalapril ($P < 0.001$) and a short-term infusion of enalaprilat ($P = 0.007$). MSNA was decreased by long-term treatment with enalapril ($P < 0.001$) and increased by a short-term infusion of enalaprilat ($P = 0.005$) (with permission from [26]). ACEi is angiotensin-converting enzyme inhibitor.

inhibitor of NOS, concentrations are increased in hemodialysis patients, but reduced by hemodialysis treatment [41, 46]. It is very well possible that by increasing the dosage of hemodialysis more ADMA and possibly other inhibitors of the nitric oxide system are removed, ultimately resulting in an inhibition of sympathetic activity, as outlined above. One study suggested that during hemodiafiltration ADMA removal was more effective than during standard hemodialysis [47].

Sleep apnea is a condition associated with sympathetic hyperactivity. Dialysis patients also often suffer from this condition. Interestingly, nocturnal hemodialysis has been shown to reduce the number of sleep apnea periods [48]. The mechanism for this effect is unclear. Whether nocturnal hemodialysis reduces MSNA remains to be shown.

Clinical relevance

Is the sympathetic hyperactivity harmful? There is substantial evidence that it is!

Blood pressure. The importance of sympathetic hyperactivity for elevated blood pressure in CRF was already demonstrated by Schohn et al [49], who found a profound decline in blood pressure after the ganglion blocker debrisoquine in hypertensive hemodialysis patients, whereas it had moderate effect in normotensive patients. We also found an enhanced blood pressure response to the sympatholytic drug clonidine [26]. In PKD patients, blood pressure correlated with MSNA [31]. In a group of CRF patients with various primary diseases, blood pressure reduction during chronic ACE inhibitor or Ang II antagonist correlated with the decrease of MSNA [34]. These data support the idea that sympathetic hyperactivity contributes to the hypertension in CKD patients.

Cardiovascular outcomes. Sympathetic activity is related to LVH. Indexes of left ventricular mass correlate with plasma norepinephrine levels [50]. The presence of LVH is associated with higher MSNA [51], and cardiac norepinephrine spill over [52]. CRF patients also show a positive relation between norepinephrine and LVH [53]. Both CRF patients not yet on dialysis and those on dialysis often have LVH, and in end-stage renal disease (ESRD) patients LVH is associated with poor prognosis [54–57].

Additionally, sympathetic activity contributes to the development of other forms of organ damage independent of its effect on blood pressure (reviewed in [58, 59]). It is associated with heart failure, arrhythmias, and, in experimental conditions, with atherogenesis [58, 59]. Plasma norepinephrine was an independent predictor for all-cause mortality and cardiovascular event in hemodialysis patients without overt heart failure [60] (Fig. 5). It is likely that sympathetic activation is associated with an even greater cardiovascular risk in renal patients with heart failure.

Kidney. Sympathetic nervous system may also be important in determining rate of progression of kidney function in CKD patients. Catecholamines have direct effects that may be relevant for renal damage, including proliferative effects mediated by beta-adrenoceptors or effects on the function of podocytes, the key cells in the genesis of glomerular injury. Interestingly, in subtotally nephrectomized rats a low dose of moxonidine but also of α and β blockers ameliorates renal damage without affecting blood pressure [61, 62]. These results are compatible with the notion that sympathetic activation via release of catecholamines promotes progression of kidney damage independently of systemic blood pressure, at least in this animal model. In normotensive diabetic humans, moxonidine reduced albuminuria without affecting blood pressure [63].

Treatment

Sympathetic hyperactivity in CKD can be reduced by several types of antihypertensive medications. We have shown that both an ACE inhibitor and an Ang II antagonist can reduce but not normalize MSNA in CRF patients [26, 34]. Addition of a centrally acting sympatholytic agent moxonidine to chronic treatment with an Ang II receptor antagonist normalizes blood pressure and MSNA [abstract; Neumann J et al, *J Am Soc Nephrol* 14:20A, 2003].

The ^{123}I-metaiodobenzylguanidine technique has been used to show that an ACE inhibitor reduced cardiac

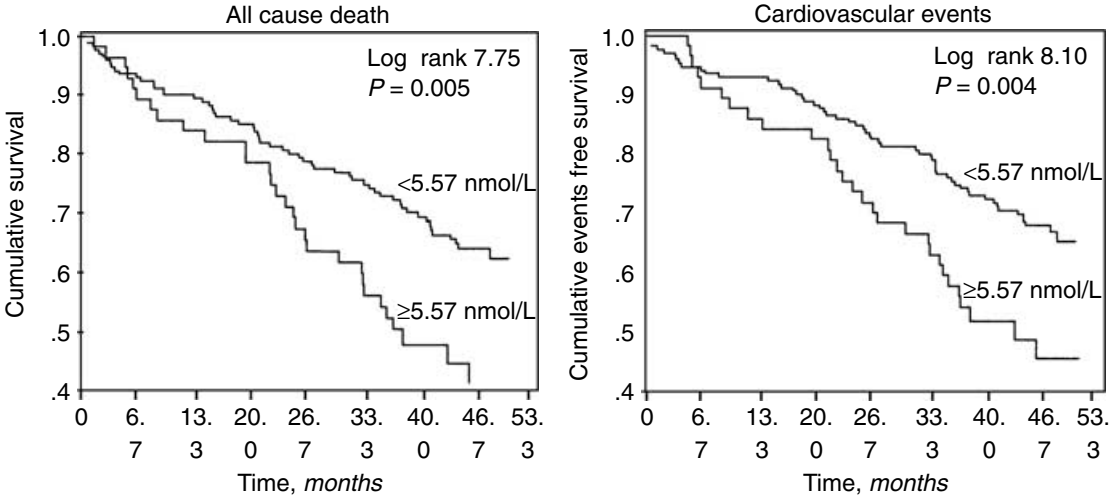

Fig. 5. Kaplan-Meier survival curves for all-cause death and cardiovascular events (fatal and nonfatal) in hemodialysis patients below and above the 75th percentile of plasma norepinephrine. Patients in the highest quartile of plasma norepinephrine showed significant greater mortality and cardiovascular events (with permission from [60]).

sympathetic activity in essential hypertension, whereas a calcium channel blocker did not [64]. This parallels our previous findings in CRF patients that enalapril reduced MSNA and amlodipine did not [26]. The combination of an ACE inhibitor and an Ang II antagonist or the addition of spironolacton to ACE inhibitor may be even more effective [65, 66]. Carvedilol, but not metoprolol, also reduces cardiac norepinephrine spill over in heart failure patients [67]. Cardiac sympathetic activity and the effects of treatment have yet to be studied in CKD patients.

Antiadrenergic therapy may be beneficial to hypertensive patients, and also in CKD patients. Treatment aimed at regression of LVH in essential hypertension is particularly successful when this includes reduction of sympathetic activity (reviewed in [68]). In CRF patients, ACE inhibition appeared more effective than calcium channel blockade in reducing LVH [69]. Conceivably, this difference is explained by the fact that, in contrast to ACE inhibition, chronic calcium channel blockade increases MSNA and cardiac sympathetic activity [26, 64]. Also, in other studies in CRF patients whether or not on dialysis, ACE inhibitors appear to be most effective in reducing LVH [70–72].

ACE inhibition improves prognosis in heart failure. It is particularly superior to traditional vasodilator therapy in patients with the highest plasma norepinephrine levels at baseline [73]. In a retrospective analysis in hemodialysis patients ACE inhibitor use, independently of its effect on blood pressure, seems to be associated with a dramatic reduction in mortality [74]. In CRF patients not on dialysis, ACE inhibitor therapy also improved survival rates independently of its effect on blood pressure [75]. A recent study shows that in dialysis patients with dilated cardiomyopathy addition of carvedilol to the standard therapy regimen reduces cardiovascular morbidity and mortality as compared to placebo [76]. All these effects may be mediated by a reduction of sympathetic activity, although the reduction of Ang II and aldosterone may also be important.

Do our patients receive any and enough antiadrenergic medication? Recent United States Renal Dialysis System (USRDS) data of more than 11,000 hemodialysis patients indicate that only half of the population was prescribed antihypertensive drugs (an average of 0.76 drugs per patient), most frequently calcium channel blockers (35%), followed by ACE inhibitors (14%), centrally acting drugs (10%), and β blockers in 8.5% [77]. The use of β blockers was associated with improved survival. A CRF population in Germany received a median of three antihypertensive drugs per patient, most often diuretics (77%), followed by ACE inhibitors/Ang II receptor antagonists (64%), calcium channel blockers (58%), β blockers (40%), and centrally acting agents (29%) [78]. In a more recent study, more than 90% of patients were on an ACE inhibitor or Ang II receptor antagonist [79]. In a CRF population in Canada 34% received a β blocker and 64.5% an ACE inhibitor or an Ang II receptor antagonist [80]. In the Dialysis Outcomes and Practice Patterns Study (DOPPS) population only a minority of patients were on an ACE inhibitor, Ang II antagonist or β blocker [81]. Finally, in patients admitted to the hospital because of myocardial infarction, patients with various degree of CRF were less likely to be treated with an ACE inhibitor or β blocker than patients with normal renal function [82].

So, it is clear that there are therapies available to reduce sympathetic activity in CKD patients, but that not all patients receive antiadrenergic agents. It seems safe to say that based on the pathophysiology outlined above that an ACE inhibitor or an Ang II receptor antagonist

should be the cornerstone of treatment, combined with diuretics (or ultrafiltration in dialysis patients) to maintain normovolemia. Because sympathetic hyperactivity is not normalized in this way, the addition of a β blocker or a centrally acting sympatholytic agent may be beneficial to the patient. Indeed, in CRF patients the ACE inhibitors and Ang II receptor antagonists have been accepted as first-choice therapy both in Europe and the United States [83, 84]. Both Guidelines Committees recognized that in CRF patients often a third agent is necessary to obtain normotension. A recent study in CRF patients (mean creatinine clearance 28 ± 12 mL/min) showed that adding of the centrally acting agent moxonidine to standard therapy (including an ACE inhibitor or Ang II receptor antagonist) was safe [79].

Presently, many issues need to be resolved. For instance, it is not known which class or combination of classes is most effective in reducing sympathetic hyperactivity and has the greatest effect on cardiovascular and renal prognosis. Experimental evidence suggests that not all Ang II receptor antagonists are equally effective in reducing sympathetic activity at the central and peripheral level [85]. Third generation beta-blockers, such as carvedilol and nebivolol, seem to have more protective effects than traditional β blockers, possibly by their stimulation of nitric oxide release [67, 86]. Further, in a recent study in an animal model of heart failure, simvastatine appears to have a sympatholytic effect [87]. Whether this class of agents also reduces sympathetic activity in humans has not been investigated. It is not known whether agents that reduce MSNA also reduce cardiac sympathetic activity to the same extent. Which patients have the highest risks? For instance, is there a relation between a specific renal diagnosis and risk? Do normotensive CKD patients also benefit from this kind of therapy? If the state of nitric oxide deficiency characteristic for CRF indeed means that even normal sympathetic activity may cause harm to our patients, these patients might benefit from this treatment as well. In anephric patients, who have undetectable plasma renin levels, normal MSNA and usually normal blood pressure, an ACE inhibitor also reduced blood pressure [25, 88]. All these issues need to be addressed in clinical trials.

CONCLUSION

Sympathetic activity is increased in hypertensive patients with renal parenchymal disease. It is "inappropriately" increased for the volume status. Recent data indicate that sympathetic activity is associated with mortality and poor cardiovascular outcomes in CRF patients. It may also affect the progression of renal failure. Some authors consider it a cardiovascular and renal risk factor [89, 90]. We support this view. However, properly designed clinical trials are needed to establish the effects of specific antiadrenergic therapy in CRF patients on cardiovascular and renal end points.

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