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Editorial Comment

Sympathetic hyperactivity in chronic kidney disease

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Introduction

There is clear evidence that chronic kidney disease (CKD) is often characterized by the presence of sympathetic hyperactivity. Importantly, data are accumulating that this sympathetic hyperactivity is indeed important, because it may influence cardiovascular and renal prognosis. Comprehensive reviews have been published elsewhere [1,2]. The purpose of this Editorial Comment is to briefly summarize available knowledge on the pathogenesis of sympathetic hyperactivity and to discuss its clinical relevance, the consequences of this knowledge for the choice of treatment and as yet unresolved issues.

Pathogenesis

Already in the 1970s, increased catecholamine levels, as an index for sympathetic activity, were reported in CKD patients. With the microneurographic technique, true sympathetic nerve activity can be measured, usually as muscle sympathetic nerve activity (MSNA). This MSNA, for instance measured in the peroneal nerve, represents the centrally generated sympathetic nerve activity directed to resistance vasculature. Sympathetic activity is not uniform in all parts of the body. Therefore, techniques have been developed to assess sympathetic activity of a specific organ, for instance by measuring noradrenaline spillover (using tracer-labelled noradrenaline) or by imaging using ^{123}I-metaiodobenzylguanidine.

The application of microneurography has enhanced our knowledge. Haemodialysis patients who still have their native kidneys have elevated MSNA [3]. Also, hypertensive CKD patients not yet on dialysis have increased MSNA [4,5], independent of age [6]. However, bilaterally nephrectomized patients have MSNA identical to healthy controls, indicating that the signal that commands the brain to increase sympathetic outflow is generated in the diseased kidneys [3]. Hypertensive polycystic kidney disease (PKD) patients with normal renal function already have higher MSNA than normotensive PKD patients and controls [7]. Renal transplant patients with good renal graft function exhibit MSNA identical to haemodialysis patients [5]. Bilateral nephrectomy in these transplant patients resulted in a MSNA level not different from controls. Unilateral nephrectomy for transplantation purpose did not affect MSNA [6].

In experimental studies it was found that even a limited renal lesion, not affecting glomerular filtration rate, results in neurogenic hypertension, which is reduced or prevented by renal denervation [1,2]. It is also well established that circulating angiotensin II (AngII), which is usually increased in CKD patients, can increase sympathetic activity. In human renovascular hypertension, angioplasty resulted in a decrease of MSNA. Both angiotensin-converting enzyme (ACE) inhibitors and AngII antagonists reduced MSNA [4,8]. These data collectively indicate that in humans the diseased kidneys are the key players in the pathogenesis of increased MSNA. The data also indicate that centrally located AngII is important and that ACE inhibition and AngII-receptor antagonism can reduce sympathetic nerve activity. The main factor is probably renal ischaemia.

There is evidence that yet other mechanisms are involved. Nitric oxide (NO) availability is clearly decreased in CKD patients as a combined result of two factors: inhibition by asymmetrical dimethylarginine (ADMA), an endogenous inhibitor of NO synthase, and NO scavenging by reactive oxygen species. The NO system is a natural antagonist of catecholamines. Inhibition of centrally located NO results in sympathetic activation. ADMA causes an increase in vascular resistance and blood pressure [9]. ADMA also appears to be a strong and independent

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predictor of overall mortality and cardiovascular outcome in haemodialysis patients [10] and is associated with left ventricular dimensions [11]. Recent data in dialysis patients show a relationship between noradrenaline and ADMA levels, suggesting a cause and effect relation [12].

Increasing the frequency of haemodialysis from three to six times weekly results in a decrease in MSNA, accompanied by a decrease in peripheral resistance, in the absence of changes in renin activity [13]. MSNA returned to its initial level when after 6 months the patients returned to the initial thrice weekly regimen. Apparently, the intensification of the dialysis regimen results in a reduction of sympathostimulating factor(s) or in an increase in sympathoinhibiting factor(s). ADMA levels are reduced by haemodialysis treatment [14]. It is very possible that through an increased dialysis dose more ADMA and possibly other inhibitors of the NO system are removed, ultimately resulting in an inhibition of sympathetic activity.

Additional factors, which have been documented to be able to increase sympathetic activity, include sleep apnoea, smoking and obesity. Dialysis patients often suffer from sleep apnoea. Long nocturnal haemodialysis has been shown to reduce the number of sleep apnoea periods [15]. Whether nocturnal haemodialysis also reduces MSNA remains to be shown.

Clinical relevance

There is increasing evidence that sympathetic hyperactivity is harmful.

Hypertension

Already 3 decades ago, a profound decline in blood pressure was reported in hypertensive haemodialysis patients with the ganglion blocker debrisoquine, whereas an only moderate effect occurred in normotensive patients [16]. Blood pressure in CKD patients correlated with MSNA and blood pressure reduction during chronic ACE inhibition or AngII-receptor antagonism correlated with the decrease of MSNA [7,8]. These data support the idea that sympathetic hyperactivity contributes to the hypertension in CKD patients.

Cardiovascular outcome

In essential hypertension, indices of sympathetic activity are related to left ventricular hypertrophy. Also, in CKD patients there is a positive relation between plasma noradrenaline and left ventricular dimensions [17] and patients with left ventricular hypertrophy generally have poorer prognosis. Sympathetic activity contributes to the development of other forms of organ damage independent of its effect on blood pressure [18]. It is associated with heart failure, arrhythmias and, in experimental conditions, with atherogenesis. Plasma noradrenaline was an independent predictor for all-cause mortality and cardiovascular event in haemodialysis patients without overt heart failure [19].

Kidney damage

There is experimental evidence that catecholamines are involved in the development of kidney damage also independent of their effect on blood pressure [20]. These effects include vascular and glomerular injury. Catecholamines induce not only renal vasoconstriction, but also proliferation of smooth muscle cells and adventitial fibroblasts in the vascular wall. Podocyte injury is a pivotal step in the development of glomerulosclerosis. Podocytes have adrenergic as well as AngII receptors. Adrenergic blockade has been tested in experimental CKD models [20]. In subtotally nephrectomized rats, a low dose of moxonidine, but also of alpha- and beta-blockers, ameliorates renal damage without affecting blood pressure [21,22]. In normotensive diabetic humans, moxonidine reduced albuminuria without affecting blood pressure [23].

Treatment

Based on the pathophysiological mechanisms outlined above, it seems logical that treatment should include an ACE inhibitor or an AngII-receptor antagonist, combined with diuretics (or ultrafiltration for haemodialysis patients) to maintain normovolaemia.

ACE inhibition and AngII-receptor antagonism reduce MSNA [4,6,24]. They also reduce cardiac sympathetic activity in essential hypertension, whereas a calcium channel blocker does not [25]. Addition of an AngII-receptor antagonist or spironolactone to an ACE inhibitor was even more effective [26,27]. However, sympathetic hyperactivity (at least MSNA) is not normalized [4,6,24]. The addition of a beta-blocker or a centrally acting sympatholytic agent might be beneficial to the patient. Recently, we showed that moxonidine normalized MSNA in CKD patients chronically treated with an AngII-receptor antagonist [24]. Carvedilol reduced cardiac noradrenaline spillover in heart failure, whereas metoprolol did not [28]. In CKD patients, ACE inhibition appeared more effective in reducing left ventricular hypertrophy than calcium channel blockade [29]. Also, in other studies in CKD patients, whether or not on dialysis, ACE inhibitors appear to be most effective in reducing left ventricular hypertrophy [30–32]. In various CKD populations, ACE inhibitor use was associated with improved survival independently of its effect on blood pressure [33,34]. In dialysis patients with dilated cardiomyopathy, addition of carvedilol to the standard therapy regimen reduced cardiovascular morbidity and mortality as compared with placebo [35]. All these data

support the notion that mechanisms that are affected by ACE inhibitor use are important in determining cardiovascular prognosis in CKD patients.

In CKD patients, ACE inhibitors and AngII-receptor antagonists have been accepted as the first choice therapy. Registry data suggest that only a minority of patients receive anti-adrenergic treatment. In the USRDS survey, only 14% of patients were on an ACE inhibitor and 8.5% were on a beta-blocker [36]. DOPPS data were not much different [37]. In Canada, 34% of a CKD population received a beta-blocker and 64.5% an ACE inhibitor or AngII-receptor antagonist [38]. In a recent study from Germany, >90% of a CKD population was on an ACE inhibitor or an AngII-receptor antagonist [39]. Finally, in patients admitted to hospital because of myocardial infarction, patients with various degrees of CKD were less likely to be treated with an ACE inhibitor or beta-blocker than patients with normal renal function [40]. Therefore, although sympathetic hyperactivity can be effectively reduced in CKD patients and this is beneficial to the patient, apparently not all patients receive appropriate medication.

Unresolved issues

Although sympathetic hyperactivity has been recognized as a cardiovascular and/or renal risk factor in kidney disease patients also by others [41,42], many issues remain unclear. Certainly, MSNA is increased in hypertensive CKD patients. Studies on cardiac and on renal sympathetic activity in CKD patients are, however, lacking. Such studies are eagerly needed to define optimal treatment strategies. There seems to be enough rationale to conduct studies addressing the hypothesis that the combination of an ACE inhibitor or an AngII-receptor antagonist with a beta-blocker or a centrally acting sympatholytic agent, such as moxonidine, would result in an improvement in clinically relevant (that is, cardiovascular and/or renal) endpoints, as compared with treatment with an ACE inhibitor or an AngII-receptor antagonist alone. To date, no such study exists. Future investigations need to identify patients who are particularly at risk, to answer, for instance, the question whether there is a relation between renal diagnosis and risk. Are newer beta-blockers, such as carvedilol and nebivolol, more protective than the traditional ones, possibly by their stimulation of NO release? Experimental evidence suggests that not all AngII-receptor antagonists are equally effective in reducing sympathetic activity at central and peripheral levels. Whether these differences are clinically relevant is unknown. Do normotensive CKD patients also benefit from this kind of therapy? If the state of NO deficiency characteristic for CKD indeed means that even normal sympathetic activity may cause harm to patients, these patients might benefit from such a treatment as well.

Conclusion

CKD is often associated with sympathetic hyperactivity, which contributes to the development of cardiovascular and, possibly, also renal damage. This occurs through its effect on blood pressure, but, probably, is also independent of blood pressure. Properly designed clinical trials are needed to establish the effects of specific anti-adrenergic therapy on cardiovascular and renal endpoints in CKD patients.

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Conflict of interest statement. None declared.

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