Sympathetic overactivity in renal failure controlled by ACE inhibition: clinical significance

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Introduction

We have recently shown that sympathetic activity is increased in patients with chronic renal failure (CRF), and that this can be controlled by enalapril, but not by amlodipine [1]. What can we learn from these data and do they affect our daily clinical practice?

Sympathetic overactivity in CRF

Is it news that sympathetic activity is high in patients with CRF? Certainly not. The subject was recently reviewed in this journal and elsewhere [2,3], although the information that we had until recently was quite indirect. It was known for a long time that plasma catecholamine concentrations are approximately doubled in CRF patients [4,5], but this could also be due to the reduced clearance of catecholamines by the kidney. Although the method of measuring muscle sympathetic nerve activity (MSNA) directly in humans was available in the late seventies, the first publication showing that MSNA was increased in CRF patients did not appear until the early nineties [6]. Converse et al. demonstrated that haemodialysis patients with their native kidneys still present had elevated MSNA. In contrast, in bilaterally nephrectomized patients, MSNA was identical to that in healthy controls [6]. This suggests strongly that the signal commanding the brain to increase sympathetic outflow is generated in the diseased kidneys. We confirmed this observation in a larger group of hypertensive CRF patients not yet on dialysis, and were able to add that baroreflex sensitivity was not altered in these patients [1]. We also found recently that MSNA is elevated in hypertensive patients with polycystic kidney disease but still normal renal function [7].

Pathophysiology of sympathetic overactivity in CRF

Is it surprising that sympathetic activity is increased in CRF? No. Experimental studies have come up with at least two pathophysiological mechanisms. Inappropriate renin secretion in relation to the state of sodium-volume balance has long been recognized [8,9]. The renin output of the kidney is the sum of the production of all nephrons. If all nephrons of the diseased kidneys were affected equally and secrete
equal amounts of renin, CRF would be characterized as a new steady state with high blood pressure and normal renin. The concept of ‘nephron heterogeneity’ stands for the hypothesis that the nephrons are not equally affected by the disease. Those that are severely affected hypofilter, showing impaired sodium excretion and renin hypersecretion, whereas those less affected will adapt to the elevated blood pressure by hyperfiltration and suppression of 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 concentrations have a variety of effects. Angiotensin II has direct vasoconstricting properties, increases aldosterone production, and has trophic effects. There is clear evidence that angiotensin II stimulates central sympathetic outflow by a direct effect on the vasomotor centres in the brain stem [10], which can be picked up as increased MSNA [11]. Angiotensin II enhances sympathetic activity also at peripheral sites. Angiotensin II enhances noradrenaline release through a presynaptic effect on peripheral nerves [12]. This cannot be picked up by MSNA.

A second way by which the kidneys can command the brain to increase sympathetic outflow is increased renal afferent nerve activity. This is started by renal ischaemia. During renal ischaemia, 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 [13]. Such infusion also causes an increase in blood pressure, which is prevented by renal denervation [13]. In rats, induction of renal artery stenosis [14], partial renal ablation by arterial ligation [15], or intrarenal phenol injection [16], cause excitation of the renal afferent nerves. This results in an increase in central sympathetic outflow and hypertension. In these animal models, bilateral renal afferent denervation prevents the increase in blood pressure.

Since both mechanisms underlying the sympathetic stimulation, i.e. increased angiotensin II levels and renal afferent nerve traffic, are related to intrarenal ischaemia, it is difficult to differentiate between contribution of these two mechanisms in human disease. For example, in patients with renovascular hypertension MSNA is also high, and restored by arterial recanalization [17]. In such cases it is likely that both ischaemia-induced renal afferent nerve activity and angiotensin II release are relevant. Whether this also holds good for more complex renal disease states such as glomerulonephritis or polycystic kidney disease is unclear.

How can ACE inhibition lower sympathetic activity?

Is it surprising that ACE inhibition can decrease the sympathetic overactivity in renal failure? We think not. With the two pathophysiological mechanisms described in the previous paragraph in mind, it is in fact logical that ACE inhibition reduces central sympathetic outflow. ACE inhibition eliminates angiotensin II stimulatory effects on the central nervous system by blocking its generation. By improving renal perfusion and decreasing ischaemia, it can also lessen the stimulatory effects of the renal afferent nerves. However, our finding that amlodipine, which can also increase renal perfusion, did not reduce MSNA, suggests major importance for the former mechanism.

In chronic heart failure, a disease state also characterized by high renin levels and high MSNA, chronic ACE inhibition also reduces sympathetic overactivity [18]. In this patient group baroreceptor sensitivity, which is impaired, improves during ACE inhibition treatment. The mechanism is unclear. In CRF patients, baroreceptor sensitivity is not different from controls and is not affected by ACE inhibition [1]. Traditional sympatholytic drugs often reduce baroreceptor sensitivity, resulting in orthostatic hypotension.

In patients with essential hypertension and normal renin activity, chronic ACE inhibition reduces blood pressure but does not affect MSNA [19]. Apparently, sympathetic suppression by ACE inhibition occurs only if the renin–angiotensin system is stimulated. Put together, these observations indicate that ACE inhibitors are not sympatholytic drugs per se, but modulate basal activity of the brain centres responsible for the regulation of central sympathetic outflow.

Whether angiotensin II receptor antagonists can also control sympathetic overactivity has not yet been studied. Crucial is that such drugs can penetrate into the brain centres involved in regulating sympathetic outflow. As recently put forward in this journal, the net effect of these drugs on peripheral sympathetic activity may be even larger than that of ACE inhibition [12]. First, ACE inhibition cannot completely prevent formation of angiotensin II, whereas receptor antagonists may completely block the actions of angiotensin II. Second, stimulation of bradykinin formation by ACE inhibition may facilitate noradrenaline release by sympathetic nerves [12]. However, the clinical relevance of such a difference may be difficult to prove.

Clinical importance of control of sympathetic overactivity

Is it important to control sympathetic overactivity in patients with renal failure? Yes, we think so. First, sympathetic overactivity contributes to the hypertension in CRF patients. This was clearly demonstrated by Schohn et al. [20], who found a profound decline in blood pressure after the ganglion blocker debrisoquine in hypertensive haemodialysis patients, but only a moderate effect in normotensive patients. We also found an exaggerated blood pressure response to the sympatholytic drug clonidine in CRF patients [1]. Second, sympathetic overactivity may increase the risk of developing cardiovascular disease. There is evidence that sympathetic activity contributes to the genesis of structural changes, including left ventricular hypertrophy and arteriolar remodelling, independent of its
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Future directions

The finding that ACE inhibition can effectively reduce sympathetic overactivity in hypertensive patients with CRF forms an additional argument for ACE inhibition in CRF. Whether sympathetic activity is normal in normotensive (and normovolaemic) patients with CRF has not been studied yet. Further, neither our study in CRF patients [1], nor that by others in patients with chronic heart failure [18], showed complete normalization of sympathetic overactivity by ACE inhibition. Whether angiotensin II receptor antagonists can do this better, remains to be seen. In addition, the place of recently introduced centrally acting drugs has still to be studied.

From a clinical as well as a pathophysiological viewpoint it is interesting to investigate whether ACE inhibition is also effective in other conditions associated with increased sympathetic activity (obesity, pre-eclampsia, sleep apnoea syndrome, chronic inflammation). This is to be expected when the signals to the CNS inducing enhanced sympathetic outflow involve the renin–angiotensin system. In obesity and sleep apnoea at least this seems an option [25,26].

Conclusion

Hypertensive patients with CRF are characterized, apart from their overhydration and enhanced activity of the renin–angiotensin system, by sympathetic overactivity. Angiotensin II plays a role in the enhancement of sympathetic activity. ACE inhibition appears to reduce the sympathetic overactivity quite effectively. This may contribute to the beneficial properties of this class of drugs, including anti-atherosclerotic and anti-hypertrophic effects, and forms an additional argument for the use of such drugs in patients with CRF.

References

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