Sympathetic Hyperactivity in Chronic Renal Failure: A Wakeup Call

HEIN A. KOOMANS, PETER J. BLANKESTIJN, and JAAP A. JOLES
Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, The Netherlands

Abstract. Sympathetic hyperactivity plays an important and distinct role in hypertension associated with chronic renal failure (CRF). Renal ischemia, elevated angiotensin II, and suppressed brain nitric oxide (NO) all stimulate sympathetic activity. Evidence is accumulating for a role of sympathetic hyperactivity in renal and cardiac damage in patients with CRF. Decreased NO availability and increased oxidative stress, characteristic in CRF patients, seem to sensitize target organs for damaging actions of sympathetic hyperactivity. Fortunately, sympatholytic agents can slow down progression of renal and cardiac dysfunction. Angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists suppress sympathetic activity, but complete elimination of the effect of sympathetic hyperactivity can be obtained only with specific adrenergic blockers. However, this important therapeutic option is grossly neglected, painfully illustrated by the unwillingness to treat CRF patients with β-blockers, even if they have had a myocardial infarction. After discussion of mechanisms and effects of the sympathetic hyperactivity, a case is made for increased application of specific adrenergic blockers in patients with CRF.

Sympathetic Activity in Patients with CRF

Hypertension remains an important issue in patients with chronic renal failure (CRF). It plays a key role in progression of renal failure and forms the basis for the cardiovascular complications and mortality. Although this point is widely recognized, BP control in patients with CRF, whether in an early or advanced stage or when on dialysis, is often poor (1, 2).

Hypervolemia and activated renin angiotensin system (RAS) have long been acknowledged as major determinants of hypertension in CRF, and in most patients, both need to be controlled to normalize BP. Besides, it has been shown in several trials that the renoprotective effect of RAS suppression extends beyond BP lowering only. This applies particularly to patients with diabetic (3–6) or nondiabetic (3, 5, 7) glomerulopathy. It has also become clear that many other factors cause renal hypertension. These include elevated levels of endothelin, sympathetic activity, and oxidant stress and reduced levels of NO and medullary vasodilating factors (8–10). As is the case for angiotensin II, many of these factors probably damage the kidney and the cardiovascular system independent of their hypertensive effect. However, as long as their pathogenic role has not been proved in large clinical trials, it is understandable that these factors are still regarded as foot-soldiers compared with the well-accepted nobility of volume and RAS—understandable, but probably not right. Already several Cinderellas have been identified that relate CRF to cardiovascular disease, i.e., the underestimated role of renal dysfunction in cardiovascular risk profile (11) and of cardiac systolic dysfunction in dialysis patients (12). We can do without one more. In this review, we highlight the pathogenesis of sympathetic hyperactivity in CRF and the evidence for its role in organ damage and give suggestions for the approach of this problem.

Correspondence to Dr. Hein A. Koomans, Department of Nephrology and Hypertension, University Medical Center Utrecht, Room F03.223, P.O. Box 85500, 3508 GA Utrecht, The Netherlands. Phone: 31-30-2507329; Fax: 31-30-2543492; E-mail: H.A.Koomans@azu.nl

1046-6673/1503-0524; E-mail: H.A.Koomans@azu.nl
85500, 3508 GA Utrecht, The Netherlands. Phone: 31-30-2543492; Fax: 31-30-2507329; E-mail: H.A.Koomans@azu.nl

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previously for resting levels of plasma noradrenaline (14, 16, 17). Existence of increased MSNA apparent in dialysis patients was also established in less advanced renal failure (23, 24). Although few studies have addressed this question, it is likely that sympathetic hyperactivity is not present in patients who are (spontaneously) normotensive. In patients with early polycystic kidney disease, high MSNA was limited to patients with hypertension (23).

Increased MSNA has also been found in many other types of hypertension: renovascular hypertension (25), malignant hypertension (26), pre-eclampsia (27), and hypertension associated with obesity (28), and hypercapnia (29). Modestly increased MSNA has also been found in essential hypertension (30) and white-coat hypertension (31). Although the intensity of increased sympathetic activity will vary among these conditions, the message seems to be that there is no hypertension without increased vasoconstrictor action, i.e., sympathetic hyperactivity.

MSNA also increases with age (32, 33). The background for this phenomenon is unclear (see below) but should be taken into account when judging MSNA in individual patients. Other items that should be taken into account are, of course, medication that can interfere with sympathetic activity, and the volume state. After elimination of these factors, we found that MSNA is indeed increased in patients with moderate renal failure (Figure 1). We also found that baroreflex function, tested by acutely manipulating BP with phenylephrine or sodium nitroprusside, is normal in patients with CRF (Figure 2), disproving the older concept of diminished sympathetic function in CRF (34, 35).

At which stage sympathetic activity starts to rise in patients with progressing renal failure is still unclear. Because, as discussed later, sympathetic activity in itself contributes to the progression, this is a relevant question. Renal ischemia is probably an important factor causing the sympathetic hyperactivity in patients with CRF. Therefore, one can predict that in patients in whom renal ischemia occurs early in renal failure, sympathetic activity (and BP) will be high. This is evidently the case in patients with polycystic kidney disease (23) (Figure 3) and patients with renovascular disease (25), but whether this can be extrapolated to hypertensive patients with early renal disease as a result of other causes remains to be resolved.

Mechanism of Increased Sympathetic Activity

The possible mechanisms involved in the increased sympathetic activity of CRF are illustrated in Figure 4. The main factor is probably renal ischemia. That ischemia of the kidney elevates sympathetic activity is well known from a study of experimental renal artery stenosis (36). It seems that unilateral renal ischemia causes an acute rise in sympathetic activity, which is mediated through increased renal afferent activity from that kidney. De-afferentation of the ischemic kidney prevents the vasoconstriction in the contralateral kidney and the rise in BP (37). In established 2K-1C hypertension, de-afferentation of the clipped kidney restores BP almost to normal (38). These experiments also show that the increased
sympathetic activity generated by renal ischemia is an important hypertensive mechanism. It is interesting that humans with renovascular hypertension exhibit increased MSNA, which normalizes after angioplasty along with normalization of BP and the elevated concentrations of angiotensin II (25).

The afferent signal probably starts with intrarenal accumulation of adenosine as a result of decreased oxygen supply (39, 40). This seems to be a common principle: Ischemia-induced local accumulation of adenosine in any tissue or organ will direct sympathetic activity toward other regions to improve its own perfusion. In the (contralateral) kidney, sympathetic activity leads to sodium retention, presumably also serving to restore the circulation in the hypoperfused tissue (or kidney). Indeed, adenosine infusion in rats causes renal sodium retention that is prevented by renal denervation (41). In humans, arterial infusion of adenosine into the forearm immediately elevates MSNA in the leg (42). Administration of dipyridamole, which increases the availability of adenosine, also acutely increases MSNA (43).

Renal ischemia will, of course, also stimulate the RAS. It is well established that angiotensin II can stimulate sympathetic nerve activity by a direct effect on the vasomotor center in the brain stem. It seems that angiotensin II from the blood can easily reach the area postrema of the medulla oblongata, which contains a high density of angiotensin II receptors and has direct connections with cardiovascular control centers (see for review (44)). Conversely, angiotensin II decreases sympathetic nervous activity indirectly by its effect on BP, via the baroreflex (Figure 2). This has to be kept in mind when looking at the interactions of angiotensin II with sympathetic activity. Indeed, in humans, angiotensin II infusion decreases MSNA but less so than an equivalent pressor dose of phenylephrine (45). Conversely, angiotensin-converting enzyme (ACE) inhibition increases MSNA less than an equivalent dose of sodium nitroprusside (24). As a consequence of these dual actions, chronic elevation of angiotensin II resets sympathetic activity (and the baroreflex) to a higher BP level (46). Angiotensin II also facilitates sympathetic neurotransmission at the adrenergic nerve terminal by increased release and decreased uptake of norepinephrine (44).

Campese et al. (47–50) also consistently found elevation of sympathetic activity in rats with CRF as a result of 5/6 nephrectomy. Selective renal de-afferentation (dorsal rhizotomy) prevents hypertension and the increased norepinephrine turnover rate in hypothalamic nuclei (47). Because renal ablation in their model is obtained through arterial ligation, it is likely that renal ischemia is the proximal cause of sympathetic hyperactivity. In the excision model of 5/6 nephrectomy as practiced by Amann et al. (51–53), BP is hardly elevated, and renal norepinephrine concentration is low (52).

Adult dominant polycystic kidney disease (ADPKD) is another (probable) condition of intrarenal ischemia. Many patients with ADPKD are already hypertensive when kidney function is still largely normal (54). These patients have increased MSNA (23). It is very well possible that this is related to local intrarenal ischemia caused by the growing cysts. This option is underscored by the finding that kidney volume in
patients with early ADPKD is larger when they are hypertensive than when they are normotensive (55).

It is unclear whether decreased nitric oxide (NO) availability in CRF contributes to sympathetic hyperactivity. Infusion of an NO synthase (NOS) inhibitor in humans is followed by an acute decrease in MSNA, probably as a result of baroreflex activation induced by the BP rise (36). In rats, plasma noradrenaline was decreased at 24 h after starting an infusion of NOS inhibitor that induced hypertension (57). However, the same study showed elevated plasma noradrenaline concentrations after 4 wk (57). Suggesting that progressive organ damage may be involved after such a period, others repeated the experiment and found no change in plasma noradrenaline after 1 wk of NOS inhibition (58). A large number of studies devoted to direct interactions of NO with sympathetic output have shown that infusion of NO (donor) or NOS blocker into the rostral ventrolateral medulla, respectively, inhibits and stimulates sympathetic output (for review, see (59, 60)). Downregulation of neuronal NOS was also shown to mediate sympathetic stimulation induced by intracerebral administration of angiotensin II (61). However, little is known about central NO activity in CRF. Increased neuronal NOS (nNOS) mRNA and NO metabolites were found in posterior hypothalamic and paraventricular nuclei in rats with CRF as a result of 5/6 renal ablation. This led to the idea that upregulation of NO production in the brain mitigates sympathetic output and the severity of hypertension in CRF (49).

Convincing evidence has become available that superoxide has a direct stimulatory effect on sympathetic nerve activity. Tempol, a superoxide dismutase (SOD) mimetic, lowers both renal sympathetic neural activity (RSNA) and BP in normotensive rats (SHR) (64). Moreover, the effects on RSNA were not inhibitory decreases sympathetic hyperactivity (24, 95), which is known to stimulate sympathetic tone, and sympathetic hyperactivity has been found in patients with sleep apnea associated with pulmonary disease (29).

As mentioned above, sympathetic activity increases with aging (32, 33, 77), but the background is unclear. Because RAS activity tends to decrease with age (78), one can speculate that slowly progressing ischemia in nonrenal tissues forms the basis for the “physiologic” increase in sympathetic activity. Because many patients with CRF have widespread and progressive peripheral vascular insufficiency, it is not unlikely that nonrenal ischemia also contributes to their sympathetic hyperactivity.

**Sympathetic Hyperactivity and Kidney Damage**

Infusion of noradrenaline for 7 d did not induce proteinuria or decrease GFR, in contrast to angiotensin II, despite similar development of marked hypertension (79). Nonetheless, attenuation of progression of renal failure by inhibition of sympathetic action, by either renal denervation or pharmacologic agents, has been found in diverse rat models of CRF, such as subtotal nephrectomy by surgical excision (52, 80), or by infarction (81–84), NOS inhibition (85–88), streptozotocin-induced diabetes (89), and type 2 diabetes in corpulent SHR (90, 91) and in salt-loaded stroke-prone SHR (92, 93). When studied, the efficacy was comparable to that of interference with the RAS (52, 82, 90) or with a calcium antagonist (94). Both α-adrenergic blockade (51, 85, 87, 88, 90, 91) and β-adrenergic blockade (51, 80, 83, 84, 92, 93) have protective action, and summation of their effects occurs (51). In a model of type 2 diabetes, combining adrenergic blockade with RAS blockade offered only slightly better protection (90), which may not be surprising because there is probably much overlap in downstream pathways leading to renal damage. However, this issue needs to be studied in other models.

In humans with CRF, information on renoprotective effects of adrenergic blockers is limited, and studies on the combination of α + β blockade are lacking, in contrast with the huge number of studies addressing ACE inhibitors and angiotensin receptor blockers. Renoprotection by the latter classes of drugs, especially in proteinuric patients with hypertension, has been proved without doubt, as shown in a number of meta-analyses in both diabetic (4) and nondiabetic nephropathy (7).

Generally, the effects of α and β blockade on albuminuria and glomerular disease in hypertensive patients seem less promising than RAS inhibition. It should be realized that RAS inhibition decreases sympathetic hyperactivity (24, 95), which may be one of mechanisms through which it causes renoprotection. However, the recently published trial in black individuals with hypertensive kidney disease showed no clear long-term difference in chronic decline of GFR in patients who were treated with ACE inhibition or β blockade. A study in 65 patients with moderate renal failure comparing an α-β blocker...
versus an ACE inhibitor added on a calcium antagonist also showed similar decline in kidney function in the two study arms (96). Regarding halting of proteinuria, a meta-analysis in both diabetic and nondiabetic renal disease showed that β-blockade is approximately half as effective as ACE inhibition (5). Similarly, a meta-analysis in diabetic patients showed a 45% decrease in proteinuria by ACE inhibitors, as compared with 23% on conventional therapy (diuretics and/or β blocker) (6). Importantly, this analysis also revealed that BP reduction correlated with improvement of renal function for ACE inhibitors but not for other antihypertensive drugs (6).

A separate meta-analysis of studies with normotensive microalbuminuric diabetic subjects is available for ACE inhibition and shows consistent antiproteinuric effects (97). In normotensive IDDM patients, renal biopsies were taken before and after 3 to 4 yr of treatment (98). An untreated group who had also had renal biopsies twice in a previous study (99) was used as a reference. Although there were no differences in renal function, both ACE inhibition and β blockade halted the progression of diabetic glomerulopathy and basement membrane thickening, whereas this progressed in the untreated reference group (98). However, it takes many years before renal function starts to decline in normotensive patients with diabetes (100), so the duration of most studies is probably too short to make a statement to this effect.

The mere fact that sympathetic activity contributes to high BP means that it will also contribute to glomerulosclerosis (101). Sympathetic hyperactivity also promotes atherosclerosis by decreasing arterial compliance (102–104). Progressive atherosclerosis is a hallmark of patients with CRF and no doubt contributes to progression of renal damage irrespective of the original diagnosis. Besides vasoconstriction, there is growing evidence that catecholamines induce proliferation of smooth muscle cells and adventitial fibroblasts in the vascular wall (105, 106). α1-Adrenoceptors mediate these effects (105). In vivo, however, such effects are difficult to prove because of the concomitant hemodynamic effects that also have trophic effects. However, in recent experiments, suffusion of rat carotid arteries with noradrenaline at approximately 1000 times below the threshold for altering arterial pressure clearly caused hypertrophy that was enhanced after balloon injury (106). The role of sympathetic hyperactivity on cardiac injury in CRF is discussed in more detail further in this review.

Practically all of the experimental models demonstrating beneficial effects of renal denervation or pharmacologic agents are accompanied by some degree of hypertension ranging from very mild, such as in subtotal nephrectomy by surgical excision (52, 107), to very severe, such as in stroke-prone SHR on a high-sodium diet (92, 93). However, at both ends of this range in BP, it has been shown that the deleterious effect of increased sympathetic activity on the kidney is not due only to hypertension. Amann and colleagues (107) showed that renal denervation reduced albuminuria and renal injury without any effect on systolic BP. Similarly, nonhypotensive dosages of moxonidine, a central sympathetic inhibitor (52), or of an α or β blocker (51), reduced glomerulosclerosis and albuminuria in the subtotal nephrectomy model. Specifically, it was found that these agents reduce loss of podocytes, glomerular volume, and proliferation of glomerular and tubular epithelium. In stroke-prone SHR on a high-fat, high-sodium diet, propanolol and carvedilol, both β blockers, increased survival and reduced glomerular, tubulointerstitial, and intrarenal vascular injury (92) without any effect on BP. Carvedilol also reduced proteinuria and renal TGF-β and fibronectin expression and preserved renal function in stroke-prone SHR (93).

In humans, evidence for a beneficial effect of adrenergic blockade independent of BP comes from a recent study by Vonend et al. (108). They found that moxonidine given as add-on therapy in CRF patients already using some form of RAS blockade was able to halt progression of renal insufficiency when compared with the calcium entry blocker nitrendipine, although moxonidine hardly affected BP. However, in the absence of a control group with ACE monotherapy, it remains difficult to demonstrate that central sympatholytic substances per se have a beneficial effect.

The exact mechanism involved in direct damage of the kidney by sympathetic activity has not been resolved. In many renal diseases, podocyte injury is the first step in the development of glomerulosclerosis (109). Adrenergic receptors seem to be present on podocytes, because adrenergic agonists can induce both calcium influx (110) and ATP release, which in turn can induce proliferation (111), at least in vitro. Podocytes also seem to have angiotensin II receptors, and angiotensin II can also induce calcium influx in podocytes ex vivo (112) and apoptosis in cultured glomerular epithelial cells (113). Thus, direct effects of both systems may lead to podocyte injury, independent of their hemodynamic effects. It is interesting that in a short experiment with dietary hypercholesterolemia before the development of proteinuria, we observed protective effects of losartan on podocyte activation (114).

The β agonist isoproterenol induces DNA replication in cultured proximal tubular cells (115). However, it is also well known that angiotensin II can induce DNA replication in proximal tubules (65). Seeing that isoproterenol also stimulates angiotensinogen production by these cells (116), it is uncertain whether this mitotic effect of adrenergic stimulation is angiotensin II independent. In the kidney, ATP is released as a co-transmitter of noradrenaline smooth muscle cells (117, 118). Moreover, ATP has been shown to induce proliferation of smooth muscle cells (119), mesangial cells (120), and visceral epithelial cells (111).

Psychologic stress can induce the release of neuropeptides that stimulate adrenergic activity, as well as glucocorticoid and renin release (121). Catecholamines in turn can either suppress or stimulate the production of proinflammatory cytokines (122). Thus, both positive and negative feedback mechanisms may link sympathetic activity to inflammation.

Regarding these actions of sympathetic activity on the kidney, we have to realize that CRF is, in general terms, a condition of reduced NO availability in the kidney. Many factors reduce renal NO availability, including decreased renal NOS, NOS glycation, decreased availability of L-arginine, elevated levels of natural inhibitors such as asymmetrical dimethyl L-arginine, NOS inhibition by dyslipidemia, hyperho-
mocysteinemia, shortage of folic acid, and excessive NO inactivation by oxidative stress as a result of inflammation and low antioxidant capacity (reviewed elsewhere (123, 124)). In humans, acute inhibition of NOS causes hypertension and lowers MSNA (56), yet simultaneous administration of the α blocker phentolamine was shown to prevent 40% of the rise in BP (125). One week of NOS blockade in rats had no effect on sympathetic activity, yet the hypotensive response to ganglion blockade was markedly increased (58). Hypertension induced by NOS inhibition sustained for weeks has been shown to depend on intact sympathetic activity in several rat models (126–129). These data indicate that under conditions of reduced NO availability, the hypertensive effect of sympathetic activity is enhanced.

Probably, this is also true for its inflammatory action. NO, when released in a controlled manner (130), has anti-inflammatory and antiproliferative properties (131). When the natural protection by NO is reduced, normal or even low activity of the sympathetic system can become detrimental for the kidney. This principle is already known for angiotensin II (132, 133). An example is renal ablation. This model is associated with downregulation of inducible NOS and eNOS in the remnant kidney (134, 135) and increased nitrotyrosine abundance (135). Both intrarenal angiotensin II and noradrenaline content are also low (52), yet both ACE inhibition and adrenergic blockade are able to ameliorate development of proteinuria and glomerulosclerosis (51, 52). A related interesting observation is that low-dose moxonidine attenuated microalbuminuria without lowering BP in incipient diabetic nephropathy (136), even though sympathetic activity in these patients is already low (137). How this works and whether this concerns common mechanisms of increased sensitivity to angiotensin II and sympathetic activity still have to be resolved. Although overexpression of TGF-β increases density and activity of cardiac adrenergic receptors (138), inhibition of adrenergic receptors did not reduce renal TGF-β expression in the chronic remnant kidney model (51) or in acute anti-Thy-1 glomerulonephritis (139). However, moxonidine did reduce renal TGF-β expression in the chronic remnant kidney model (52), as did carvedilol in stroke-prone SHR (93). These differences cannot readily be ascribed to a pressure response, because none of the treatments in these conflicting studies had any effect on BP (51, 52, 93, 139). Overall, the implication of these findings is that the combination of decreased renal availability of NO and increased sympathetic activity to the kidney has a double detrimental impact on the kidney (Figure 5).

**Sympathetic Hyperactivity and the Heart**

Cardiac remodeling and functional alterations, as a result of direct neurohumoral and metabolic actions on the myocardium, coronary insufficiency, and increased pressure afterload, is highly prevalent in patients with CRF (140, 141). These factors lead to premature development of left ventricular hypertrophy, dysfunction, and failure. Even young patients with CRF often have advanced coronary artery lesions (142), and mortality through cardiac events is greatly increased. In adults with CRF, cardiac deaths constitute 40 to 50% of the total mortality. As is the case for kidney damage, the pathogenesis involves hemodynamic, neurohumoral, metabolic, and inflammatory factors.

Catecholamine infusion is known to induce left ventricular hypertrophy and heart failure in rats (143) and rabbits (144). This is at least due to direct actions of catecholamines on the heart, as several studies showed that noradrenaline induces hypertrophy of cultured cardiomyocytes (145, 146). It is interesting that this action involves induction of superoxide (145, 146). Whether sympathetic hyperactivity in CRF specifically contributes to the cardiac damage beyond its effect on BP has received relatively scant attention considering the magnitude of the problem in the clinic. Although most of the experimental studies in which BP is decreased by sympathetic inhibition also found a decrease in left ventricular hypertrophy (88), this can hardly be viewed as a specific effect. In renal ablation studies, both moxonidine (147) and carvedilol (83) reduced myocardial interstitial volume and restored the abnormal myocardial capillary density. Similar findings were documented in aging stroke-prone SHR (148). However, because BP decreased in these studies, it remains difficult to distinguish a specific effect of decreased adrenergic action on the heart.

Whether patients with renal failure have high sympathetic cardiac stimulation is not known. Heart rate in patients with CRF is often high, although published figures are scarce (24). Many data have been published on heart rate variability, but analysis of frequency power spectrum is hardly available. Two small studies showed, in fact, decreased low-frequency power, reflecting sympathetic activity, in heart rate variability (149,
However, the high-frequency signal, reflecting parasympathetic activity, is also low, which may aggravate the detrimental effect of sympathetic activity (34). Cardiac scanning with the radiolabeled noradrenaline precursor metaiodobenzylguanidine showed patchy cardiac uptake and greatly enhanced clearance, in association with increased plasma noradrenaline levels, suggesting increased cardiac sympathetic activity (150, 151).

In patients with essential hypertension, positive correlations were found between (growing) left ventricular mass and cardiac noradrenaline spill-over (152, 153) and MSNA (154). Such data are not available for CRF, but recently a correlation was reported between plasma noradrenaline and left ventricular mass in patients on hemodialysis (155). An exciting observation is that polymorphism in the gene coding for the β1-adrenergic receptor (predominantly located in the heart) is a determinant for left ventricular mass in patients with CRF (156).

Many studies have shown that β blockers are helpful to prevent or reduce left ventricular hypertrophy in patients with essential hypertension, although two independent meta-analyses made at a 10-yr interval showed that this effect is less than that of ACE inhibitors (157, 158). Uncontrolled studies in small numbers of patients showed such an effect for the α-adrenergic blocker doxazosin (159, 160), but the single-drug therapy study in patients with mild to moderate hypertension found reduction of left ventricular mass after β blockade but not after the α blocker prazosin or the central sympatholytic agent clonidine (161). Again, it is difficult to say whether beneficial effects of adrenergic blockers occurred separate from their antihypertensive action. Little is known regarding patients with renal disease. A recent study in patients with CRF and known left ventricular hypertrophy showed a comparable BP control by an α-β blocker (arotinol) and an ACE inhibitor, when added on top of a calcium entry blocker, but reduction in ventricular wall thickness only with the α-β blocker (96). β Blockers are effective to improve left ventricular hypertrophy and function in patients with diabetes (162), but a subanalysis in patients with nephropathy is not available. A recent uncontrolled study showed improved cardiac function after selective β blockade in hemodialysis patients with dilated cardiomyopathy (163). The third-generation β blocker carvedilol was shown to improve heart function in dialysis patients with heart failure in a controlled trial (164), but whether it can also prevent left ventricular hypertrophy and dysfunction in these patients before heart failure has not been reported.

**Strategies to Combat Sympathetic Hyperactivity**

As often stipulated by Ritz and colleagues (12, 165, 166), treatment with sympatholytic agents is obviously rational in patients with CRF but still a neglected issue. This is all the more remarkable, because, for instance, β blockers are still high on the list for the treatment of essential hypertension (167), in which sympathetic activity may be increased but not nearly as much as in CRF. Reviews of antihypertensive strategies in patients with progressing CRF hardly touch the subject of the (possible) need for targeted adrenergic suppression (168–170). In many drug trials regarding progression of renal disease, use of adrenergic blockers in the control groups is left to clinical judgment (5, 7) or suggested as third choice after RAS inhibitors and calcium antagonists (171). Although exact figures are difficult to give, we estimate that 35 to 40% of patients with some form of progressing CRF are prescribed β blockers (2, 172, 173). In dialysis patients, use of α and β adrenergic blockers or central sympatholytic agents has slowly been rising over the past decennium but does not exceed approximately 15% (174). In the Dialysis Outcomes and Practice Patterns Study population, only a minority of the dialyzed patients received β blockers (175). Adrenergic neglect is grossly prominent in patients who have advanced CRF and experience myocardial infarction (176, 177).

What can we do about the increased sympathetic activity of patients with CRF? Quite something, because we have many direct but also indirect options. α Blockade with both prazosin (161, 178, 179) and doxazosin (180) are effective in patients with CRF, and (if required) the dosage can be titrated on the BP response. However, the use of α adrenergic blockade has been superseded by the finding of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial in patients with essential hypertension and an additional risk factor, in which the most recent analysis conclusively shows a higher risk of stroke and combined cardiovascular disease in patients who are treated with doxazosin than in those who use the diuretic chlorthalidone (181). β Blockers can be titrated on heart rate response, and some need adjustment of the dosage with decreasing kidney function. Physicians have been reluctant to prescribe β blockers to patients on hemodialysis because of the association with intradialytic hypotension. However, recent studies showed that a supervised low dose regimen is safe and successful in this group as well (182, 183). Non-selective β blockers, such as carvedilol, may have the advantage over selective blockers of reducing cardiac noradrenaline release through their action on prejunctional β adrenergic receptors (184). This drug is well tolerated in patients with advanced CRF (185). So-called third-generation β blockers selectively block β1 receptors and α receptors. Of this group, arotinol has proved effectiveness to reduce left ventricular mass in patients with CRF (96), whereas nebivolol is particularly interesting for its ability to prevent inducible NOS uncoupling (186). The latter characteristic may be of great advantage in patients with CRF in view of their inflammatory state (187).

Central sympathetic inhibition with agents such as the α2 adrenoceptor blockers α-methyldopa and clonidine have been shown to lower BP and plasma catecholamines in patients with CRF (18, 188). The newer I1-imidazoline agonist moxonidine also leads to peripheral sympatho-inhibition but with less adverse reactions (189). However, information regarding its effect on MSNA is limited. Sustained moxonidine treatment at a regular dosage (0.4 mg/d) reduces the elevated MSNA in patients with essential hypertension by approximately 25% (190). In patients with heart failure, much higher dosages were
used, causing progressive dose-dependent suppression of plasma noradrenaline, but high dosages (1.8 to 6.0 mg/d) were associated with increased mortality (191). The experience in patients with CRF is limited. Moxonidine is predominantly eliminated by the kidney (192), and its dosage should be adjusted in advanced renal failure (193). Preliminary data from our department show that 6 wk of moxonidine at 0.2 mg/d superimposed on an AT-1 receptor antagonist further lowers BP and MSNA in patients with advanced CRF (194). In fact, the combination was able to normalize the elevated MSNA, something that could not be accomplished by the AT-1 antagonist alone. The recent study by Vonend et al. (108) in a large group of patients with advanced CRF showed that moxonidine (0.3 mg/d) superimposed on some form of RAS inhibition caused additional renoprotection but only a modest further BP-lowering effect.

ACE inhibition interferes with the central sympathetic stimulation by angiotensin II and lowers the sympathetic hyperactivity in patients with CRF (24). In this respect, the ACE inhibitor enalapril and the AT-1 receptor antagonist losartan were equally effective, but neither drug normalized MSNA completely (95). Although these drugs are widely used in patients with CRF and very effective for BP reduction and for halting the progression of CRF and cardiovascular disease, it is unclear whether and how much these beneficial effects depend on this sympatholytic action. We have to remember that studies in the 1980s consistently showed that most of the hypertensive effect of a renal artery clip or infusion of angiotensin II was obliterated by simultaneous sympatholytic treatment or renal denervation (36–38). Because angiotensin II also inhibits presynaptic reuptake of noradrenaline, interference with the RAS can also reduce sympathetic action locally by decreasing noradrenaline availability (44). This effect may be more pronounced when AT-1 receptor blockers are used (195).

Recently, a central sympatholytic effect was reported for the hepatic hydroxymethyl glutaryl CoA reductase inhibitor simvastatin in a rat model of heart failure (196), but this has not been substantiated in humans. Simvastatin is also able to inhibit the hypertrophic action of noradrenaline on cultured cardiomyocytes (145). These drugs are also widely used in patients with CRF.

Preliminary data in patients on hemodialysis have shown that, compared with conventional three-weekly sessions, daily short dialysis or nocturnal long dialysis reduces BP and MSNA (197). These observations suggest that conventional dialysis in fact enhances sympathetic activity, as a result of the unphysiologic, large shifts in fluid and electrolytes. However, the mechanism remains obscure. This subject clearly deserves further study.

As discussed above, detrimental action of sympathetic activity is enhanced when protection by NO is low. In that respect, patients with CRF have a dual problem: High sympathetic activity (and RAS activity) on the one hand and decreased availability of NO on the other. Any measure that is able to support the NO system in patients with CRF, such as folic acid supplementation, lipid lowering, and prevention of endothelial NOS (eNOS) uncoupling, therefore will indirectly halt damage by sympathetic hyperactivity. Obviously, factors that may contribute to sympathetic hyperactivity and reduce NO availability at the same time, such as smoking and overweight, deserve emphasis in these already so heavily charged individuals.

What, then, can we recommend? That is obviously the most difficult question at the moment, because good clinical trials are lacking, but after >6000 words of introduction, we feel so loaded with responsibility that at least we should make an educated guess. RAS inhibitors, statins, and folic acid (of course in addition to some mode of volume control) should be standard therapy in patients with CRF (198, 199). Each component of this medication will directly or indirectly interfere with the damaging actions of sympathetic activity (whether elevated or not). On top of that, we need to prescribe sympatholytic drugs, not in high dosages as if these were single therapies but only low dosages to eliminate any residual imbalanced sympathetic activity in target organs. For obvious reasons, this additional therapy has to be simple, i.e., a conventional or third-generation β adrenergic blocker or a central sympatholytic agent.

Conclusion

Sympathetic hyperactivity is common in CRF and contributes to organ damage both through and beyond its effect on BP. Experimental and clinical studies have shown protective effects of both α and β adrenergic blockade. There is a strong interaction with angiotensin II, which enhances central sympathetic tone and peripheral sympathetic activity, and with NO, which by its suppressed availability enhances the damaging action of sympathetic tone. Although we have many options to cope with this problem, targeted sympathetic suppression in patients with CRF is still a neglected subject, as if the problem is only remote. Well, it is not; we should wake up.

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