Causes and Consequences of Increased Sympathetic Activity in Renal Disease

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Abstract—Much evidence indicates increased sympathetic nervous activity (SNA) in renal disease. Renal ischemia is probably a primary event leading to increased SNA. Increased SNA often occurs in association with hypertension. However, the deleterious effect of increased SNA on the diseased kidney is not only caused by hypertension. Another characteristic of renal disease is unbalanced nitric oxide (NO) and angiotensin (Ang) activity. Increased SNA in renal disease may be sustained because a state of NO–Ang II imbalance is also present in the hypothalamus. Very few studies have directly compared the efficacy of adrenergic blockade with other renoprotective measures. Third-generation β-blockers seem to have more protective effects than traditional β-blockers, possibly via stimulation of NO release. Although it has been extensively documented that muscle SNA is increased in chronic renal failure, data on renal SNA and cardiac SNA are not available for these patients before end-stage renal disease. It is also unknown whether additional treatment with third-generation β-blockers can delay the progression of renal injury and prevent cardiac injury in chronic renal failure more efficiently than conventional treatment with angiotensin-converting enzyme inhibitors only. (Hypertension. 2004;43:1-8.)

Key Words: renal disease • antihypertensive agents • hypertension • diabetic nephropathy • sympathetic nervous system

It is well known that irrespective of the primary cause of renal injury, chronic renal disease often leads to renal fibrosis and end-stage renal disease (ESRD). Delaying the onset of renal replacement therapy is of utmost importance, both medically and economically.1 Many quite different interventions (dietary protein or phosphate restriction, inhibition of the renin-angiotensin system [RAS], endothelin receptor antagonists, aldosterone antagonists, antioxidants, renal denervation, HMG-CoA reductase inhibitors, etc) have been shown to considerably slow this process in experimental models. In fact, if these were all discrete pathways, then combining such interventions would provide additive protective effects that would exceed the loss of function. Clearly, this is not the case, suggesting that parallel extracellular pathways converge on common intracellular signaling molecules, which in turn activate a limited number of transcription factors that turn on excessive matrix synthesis. Recent studies using modulation of intracellular signaling pathways, eg, by gene transfer of Smad 7,2 or inhibition of transcription factors with antisense technology3 show marked reduction of fibrosis in robust models such as unilateral ureteral obstruction. Another pathway that is gaining increasing attention is the independent role of proteinuria in causing interstitial inflammation and ultimately fibrosis.4 Such inflammation causes cytokine release and consequent monocyte influx. Preventing this monocyte influx by anti-monocyte chemoattractant protein (MCP)-1 gene therapy5 also reduces injury.

In the clinical setting, however, the intracellular domain is not yet accessible and gene therapy lies beyond the horizon. Hence, the focus of much research, both clinical and experimental renal disease, is directed toward manipulation of extracellular pathways. In this review, we focus on the role of the sympathetic nervous system (SNS), which is activated in subjects with renal disease.6 First, we briefly review potential mechanisms that could be responsible for SNS stimulation in renal disease. Then, we summarize the evidence that SNS stimulation contributes to progression of renal disease. Mortality caused by cardiovascular disease is more than 3-times higher in subjects with ESRD than in subjects with normal renal function.7 Hence, we also review recent studies that support a role for the SNS in the myocardial changes that are inherent to uremia.

What Stimulates the SNS in Renal Disease?

In the later stages of chronic renal disease, when renal clearance is substantially decreased, renal catabolism of peptides and low-molecular-weight proteins will decrease. One such peptide is leptin, a peptide produced mainly in adipose tissue, that decreases food intake and increases energy expenditure. The latter is mediated by an increase in SNS activity.8 Hyperleptinemia is common in ESRD.9 It has been postulated that increased SNS activity associated with hyperleptinemia may contribute to hypertension in ESRD10 as
it does in obesity. Accumulation of endogenous nitric oxide synthase (NOS) inhibitors in chronic renal failure (CRF) such as asymmetric dimethyl arginine could potentially directly increase SNS activity by inhibiting cerebral NO production. However, this is not likely because the levels are very low. Moreover, direct effects of uremia cannot be the whole story, because SNS activity is already increased at earlier stages when renal function is not or only slightly impaired and sympathetic hyperactivity remains after correction of uremia by renal transplantation. Increased SNS activity in the presence of normal renal function is also sometimes found in the nephrotic syndrome, in which central cardiovascular stimulation is thought to play an important role in stimulating efferent renal sympathetic nervous activity (RSNA). However, judging by noradrenaline levels, this association only appears to be present in conjunction with hypovolemic symptoms.

Renal ischemia is probably an important primary event leading to increased SNS activity. This was observed experimentally with acute renal artery stenosis. Restoration of renal perfusion in humans with renovascular hypertension reduces muscle sympathetic nerve activity (MSNA) to control levels along with normalization of blood pressure. Increased SNS activity has also been observed in hypertensive subjects with polycystic kidney disease and normal renal function. It is conceivable that renal cysts cause localized intrarenal ischemia, which in turn stimulates α2 adrenoceptors. Campese’s group has shown in rats that unilateral intrarenal injection of a small quantity of phenol induces hypertension that is associated with increased RSNA. Increased norepinephrine content of the posterior hypothalamic nuclei is present in the 5/6-nephrectomy model. Importantly, in the 5/6-nephrectomy model, it was also shown that central sympathetic activation could be dampened by central production of NO from neuronal NOS. Intraventricular administration of angiotensin (Ang) II also directly increases central sympathetic output.

Unbalanced NO Versus Angiotensin and Sympathetic Activity in Renal Disease

Within the kidney, NO synthesis progressively decreases in CRF induced by ablation, as does urinary nitrate plus nitrite excretion. Similar findings have been discovered in immune-mediated glomerulonephritis. Moreover, proteinuria and renal injury induced by hypercholesterolemia are also accompanied by a reduction in renal NO activity. In both ablation and hypercholesterolemia, proteinuria and injury are partially or wholly prevented by molsidomine, a NO donor. Angiotensin-converting enzyme (ACE) inhibition or AT-1 antagonism effectively reduces renal injury in the ablation and NOS inhibition models, and this is also the case for renal injury associated with hypercholesterolemia. Thus, a characteristic of renal disease is unbalanced NO and Ang activity. However, this does not necessarily imply that tissue Ang II is actually increased, but rather that it is high in relation to the protection offered by NO activity. Indeed, Ang II levels were neither increased in the intact portion of the remnant kidney (away from the infarct scar) nor in the whole kidney during NOS inhibition with a high dose of N\(^2\)-nitro-L-arginine (L-NNA), at least not before the development of extensive injury and scarring. Increased SNS activity in renal disease may be sustained because a state of NO-Ang II imbalance is also present in the hypothalamus. Enhanced SNS activity appears to be a direct effect of primary NO deficiency, even before renal insufficiency. Circulating catecholamines, particularly epinephrine, levels were increased several-fold after chronic N\(^2\)-nitro-L-arginine methyl ester (L-NAME) treatment. Intracerebroventricular N\(^2\)-monomethyl-L-arginine (L-NMMA) administration resulted in a mild pressor response but in marked stimulation of RSNA. Recently, it was shown that the acute central antihypertensive action of clonidine, an α2-adrenergic agonist, is caused by the release of NO in the nucleus tractus solitarii (NTS). Thus, the marked antihypertensive effect of chronic clonidine administration observed in the intrarenal phenol model by Ye et al was possibly not only caused by maintenance of intrarenal nNOS mRNA but also caused by direct stimulation of NO release in the brain.

SNS activity plays an important role in the genesis of hypertension in NO deficiency. Renal denervation can prevent L-NNAME hypertension. Similarly, adrenergic blockade can prevent hypertension when NO deficiency is induced in pregnant rats and in diabetic rats. Catecholamines are potent stimulators of platelet aggregation. Conversely, chronic NO deficiency induced intraglomerular platelet aggregation and glomerular injury, which was ameliorated by renal denervation. Moreover, increased SNS activity may in fact aggravate the NO deficiency induced by L-NNAME, because the α1-adrenoceptor blocker, doxazosin, increased the nitrite production of kidney tissue of L-NNAME-treated rats. However, this may be caused by the partial correction of hypertension, because a calcium channel antagonist and an ACE-inhibitor shared this effect on nitrite production. Interestingly, renal nitrite production was increased above control levels when L-NNAME–induced hypertension was treated with either the α1-adrenoceptor blocker or the ACE inhibitor, suggesting that even under control conditions both RSNA and intrarenal Ang II suppress renal NO production. Thus, once renal insufficiency starts to develop, the resulting depression of renal NO synthesis and enhancement of RSNA and the intrarenal RAS start to reinforce each other in an ominous dance. Neutralization of any one of these factors reduces progression of renal injury. For example, in renal ablation renal function and structure can be preserved by a NO donor, ACE inhibition, or AT-1 antagonism, or by α and β blockade. Moreover, even though this model is classically regarded as being hemodynamically driven, protection by the lymphocyte inhibitor, mycophenolate mofetil, indicates that inflammatory factors play a key role in scarring. Combining hemodynamic and non-hemodynamic interventions may provide somewhat better protection. The challenge is to identify and target different multiple upstream pathways to halt activation of the common downstream pathway.

How Does SNS Stimulation Contribute to Progression of Renal Disease?

Is Hypertension Always Involved?

The deleterious effect of increased SNS activity on the diseased kidney is not only caused by hypertension. In fact,
infusion of noradrenaline for 1 week did not induce proteinuria or decrease glomerular filtration rate (GFR), in contrast to Ang II, despite similar development of severe hypertension.42 Note that longer periods of noradrenaline infusion, even at a lower doses and, hence, blood pressure, do cause vascular43 and renal injury44 vide infra. Moxonidine, an \(\alpha_1\)-imidazoline agonist that inhibits the release of noradrenaline both in the kidney and in the brain,45 reduced glomerulosclerosis and albuminuria without changing blood pressure in the subtotal nephrectomy model.46 Furthermore, in subtotally nephrectomized rats, subantihypertensive doses of \(\alpha\) and \(\beta\) blockade, and particularly their combination, also reduced progression of renal disease.40 Similarly, in extremely hypertensive stroke-prone spontaneously hypertensive rats (SHR) on a high-fat, high-sodium diet, \(\beta\) blockade increased survival and reduced glomerular, tubulointerstitial, and intrarenal vascular injury without any effect on systolic blood pressure.47,48 This contrasts with the renoprotective effects of ACE inhibition and aldosterone blockade in salt-loaded stroke-prone SHR and of ACE-inhibition and AT-1–receptor blockade in renal ablation that were consistently blood-pressure dependent.49,50 Note in the studies by Amann’s group and in those of Bidani’s group that blood pressure was measured continuously in conscious unrestrained animals using telemetry.40,46,49,50 Thus renal protection by blockade of the RAS or by reduction of SNS activity may not follow identical pathways. This supports the notion that complementary combinations may have beneficial effects. Surprisingly, little information is available on the effects of adrenergic blockade in models of renal injury not associated with hypertension, although it has been documented that in experimental nephrotic syndrome RSNA is increased.13

**Sympathetic Hyperactivity: Mainly Vascular and Glomerular Effects**

Prolonged SNS hyperactivity can induce changes in intrarenal blood vessels. Catecholamines induce proliferation of smooth muscle cells and adventitial fibroblasts in the vascular wall.43,51 \(\alpha_1\)-Adrenoceptors mediate these effects.51 In vivo, however, such effects are difficult to prove because the simultaneous hemodynamic effects also have trophic effects. However, suffusion of rat carotid arteries for 2 weeks with noradrenaline at \(\approx\)1000-times below the threshold for altering arterial pressure clearly caused hypertrophy.43 Interestingly, a new hypothesis relating peritubular capillary rarefaction to salt-sensitive hypertension52 was initially supported by observations in rats infused with phenylephrine for 8 weeks.44 However, subsequently this has been observed in many other primary models of hypertensive renal injury,52 so this cannot be viewed as a specific adrenergic effect.

Perivascular nerves in the adventitia release ATP with noradrenaline and neuropeptide Y from sympathetic nerves to act at smooth muscle P2X purinoceptors resulting in vasoconstriction.53 In preglomerular vessels, ATP and ADP stimulate P2 receptors and cause vasoconstriction by opening calcium channels, whereas AMP and adenosine stimulate P1 receptors (adenosine A1 receptors) and cause relaxation by increasing cAMP formation.54 Although adrenergic fibers do not penetrate the glomerulus,55 podocytes56 have adrenoceptors, and all glomerular cell types have purinoceptors.57 In contrast to the preglomerular vessels in which ATP causes constriction,54 ATP efflux from endothelial cells in isolated glomeruli stimulates P2Y purinoceptor-mediated NO release and causes dilation of glomerular capillaries.56 This microvascular endothelial ATP release is potently reinforced by third-generation \(\beta\)-blockers.58 These apparently conflicting actions of extracellular ATP are possible because extracellular ATPase limits the half-life of extracellular ATP to 0.2 seconds.57

Dissecting the exact mechanism by which sympathetic activity damages the glomerulus independently of Ang II is not trivial. Podocyte injury is a pivotal step in the development of glomerulosclerosis, and an early event is probably calcium influx, constriction, and hence decreased glomerular permeability.55 Adrenergic and purinergic receptors appear to be present on podocytes, because adrenergic and purinergic agonists induced calcium influx.56 Podocytes also have Ang II receptors, and Ang II can also induce calcium influx in podocytes ex vivo.56 Thus direct effects of both the RAS and the SNS may lead to podocyte constriction and proteinuria, independently of their hemodynamic effects. Interestingly, in a 2-week experiment with dietary hypercholesterolemia, ie, before the development of proteinuria, we observed a decrease in renal NOS activity and protective effects of losartan on podocyte activation without a significant decrease in blood pressure.59 Similarly, Amann et al observed podocyte protection with adrenergic blockade without a change in blood pressure in the subtotal nephrectomy model.40

**Secondary Tubulointerstitial Changes**

It is well known that the tubular epithelium is densely innervated and well endowed with both adrenergic55 and purinergic57 receptors. However, in contrast to Ang II that directly stimulates proliferation, apoptosis and collagen synthesis via its receptors on the tubular epithelium,56 adrenergic and purinergic receptors do not appear to be directly involved in the characteristic tubulointerstitial changes of chronic renal disease. Catecholamine infusion, in contrast to Ang II, did not stimulate tubular epithelial or interstitial apoptosis or proliferation.59 The overriding tubulotoxic effects of proteinuria preclude dissection of a sympathetic contribution to interstitial fibrosis in most models.

**Adrenergic Blockade in Different Models of Renal Disease**

**\(\beta\)-Adrenergic Receptor Blockade**

There are several studies showing renal protection by \(\beta\)-adrenergic receptor blockade in 5/6 nephrectomy.40,62–65 Renal protection by \(\beta\)-blockade has also been observed in NOS inhibition66–68 and in stroke-prone SHR on high-salt intake.47 Experimental studies of renal injury that evaluated adrenergic blockade are listed in Table 1. Very few studies have directly compared the efficacy of adrenergic blockade with other renoprotective measures. In the study by Brooks et al,65 very similar protection was found for carvedilol and captopril. There may also be substantial differences between different \(\beta\)-blocking drugs. Third-generation \(\beta\)-blockers,
such as carvedilol and nebivolol, seem to have more protective effects than traditional β-blockers, possibly via stimulation of NO release. In fact, carvedilol is even protective in acute renal failure after gentamicin. Third-generation β-blockers are now rapidly becoming the drug of choice in heart failure in the general population. However, their use in patients with advanced renal failure who experience myocardial infarction is grossly neglected. Hopefully, the marked improvement of heart function and survival of dialysis patients with heart failure achieved by carvedilol will improve this treatment deficit. The important question is whether additional treatment with these drugs can delay the

### TABLE 1. Effects of Renal Denervation or Pharmacological Blockade of the Sympathetic Nervous System on Blood Pressure and Renal Injury in Different Models of Renal Disease

<table>
<thead>
<tr>
<th>Model</th>
<th>Treatment</th>
<th>Study Length</th>
<th>Blood Pressure</th>
<th>Glomerular Filtration Rate</th>
<th>Glomerular Injury</th>
<th>Tubulo-int. Injury</th>
<th>Vascular Injury</th>
<th>Reference</th>
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<tr>
<td>5/6 NX excision</td>
<td>Renal denervation</td>
<td>12 wk</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>75</td>
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<tr>
<td>5/6 NX excision</td>
<td>Moxonidine 1.5 mg/kg per day</td>
<td>12 wk</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>5/6 NX excision</td>
<td>Phenoxybenzamine 5 mg/kg per day</td>
<td>12 wk</td>
<td>↓</td>
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</tr>
<tr>
<td>5/6 NX excision</td>
<td>Metoprolol 150 mg/kg per day</td>
<td>12 wk</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<td>40</td>
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<td>5/6 NX excision</td>
<td>Phenoxybenzamine + Metoprolol</td>
<td>12 wk</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>40</td>
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<td>5/6 NX excision</td>
<td>Nipradilol 10 or 15 mg/kg per day</td>
<td>12 wk</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<td>Propanolol 50 mg/kg per day</td>
<td>12 wk</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>N/A N/A 64</td>
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<td>Nipradilol 10 mg/kg per day</td>
<td>12 wk</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>N/A N/A 64</td>
</tr>
<tr>
<td>5/6 NX excision + L-NAME</td>
<td>Propanolol 50 mg/kg per day</td>
<td>12 wk</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>N/A N/A 64</td>
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<tr>
<td>5/6 NX excision</td>
<td>Carvedilol 30 mg/kg per day</td>
<td>11 wk</td>
<td>↓</td>
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<td>↓</td>
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<tr>
<td>5/6 NX excision</td>
<td>Propanolol 50 mg/kg per day</td>
<td>11 wk</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>63</td>
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<tr>
<td>5/6 NX infarction</td>
<td>Renal denervation</td>
<td>6 wk</td>
<td>↑</td>
<td>↑</td>
<td>N/A</td>
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<td>N/A</td>
<td>N/A 98</td>
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<td>Carvedilol 55 mg/kg per day</td>
<td>6 wk</td>
<td>↓</td>
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<td>↓</td>
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<td>N/A 65</td>
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<td>Carvedilol 5 or 10 mg/kg per day</td>
<td>11 wk</td>
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<tr>
<td>5/6 NX infarction</td>
<td>Carvedilol 20 mg/kg per day</td>
<td>11 wk</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>N/A 62</td>
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<td>Obese SHR</td>
<td>Moxonidine 8 mg/kg per day</td>
<td>13 wk</td>
<td>↓</td>
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<td>↓</td>
<td>N/A</td>
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<td>Doxazosin 40 mg/kg per day</td>
<td>16 wk</td>
<td>↓</td>
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<td>↓</td>
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<td>Doxazosin 30 mg/kg per day</td>
<td>20 wk</td>
<td>↓</td>
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<td>↓</td>
<td>N/A</td>
<td>↔</td>
<td>N/A 82</td>
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<td>L-NAME 70 mg/kg per day</td>
<td>Renal denervation</td>
<td>4 wk</td>
<td>↓</td>
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<td>↓</td>
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<td>Renal denervation</td>
<td>4 wk</td>
<td>N/A</td>
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<td>L-NAME 60 mg/kg per day</td>
<td>Doxazosin 10 mg/kg per day</td>
<td>10 wk, treated last 4 wk</td>
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<td>Doxazosin 30 mg/kg per day</td>
<td>12 wk, treated last 6 wk</td>
<td>↓</td>
<td>↑</td>
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<td>Metoprolol 350 mg/kg per day</td>
<td>12 wk, treated last 6 wk</td>
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<td>L-NAME 35 mg/kg per day</td>
<td>Prazosin 5 mg/kg per day</td>
<td>6 wk</td>
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<td>L-NAME + DOCA</td>
<td>Prazosin 5 mg/kg per day</td>
<td>6 wk</td>
<td>↓</td>
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<td>Nipradilol 20 mg/kg per day</td>
<td>3 wk</td>
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<td>Aging SHRSP</td>
<td>Moxonidine 8 mg/kg per day</td>
<td>3 month</td>
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<td>N/A</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>SHRSP + high salt</td>
<td>Carvedilol 200 mg/kg per day</td>
<td>18 wk (survival)</td>
<td>↓</td>
<td>N/A</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>SHRSP + high salt</td>
<td>Propanolol 200 mg/kg per day</td>
<td>18 wk (survival)</td>
<td>↓</td>
<td>N/A</td>
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<td>↓</td>
<td>↓</td>
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<tr>
<td>SHRSP + high salt</td>
<td>Carvedilol 200 mg/kg per day</td>
<td>7 wk</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>48</td>
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<tr>
<td>Pregnancy + L-NAME</td>
<td>Methyldopa 400 mg/kg per day</td>
<td>D11 to term</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
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<td>N/A</td>
<td>N/A 35</td>
</tr>
<tr>
<td>Gentamicin acute renal failure</td>
<td>Carvedilol 2 mg/kg per day</td>
<td>8 d</td>
<td>N/A</td>
<td>↑</td>
<td>↓</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A 69</td>
</tr>
</tbody>
</table>

N/A indicates not available; tubulo-int., tubulointerstitial; NX, nephrectomy; ↑, increased; ↓, decreased; ↔, unchanged (all in comparison to the levels found in the non-treated model).

Abbreviations are defined in the text.

*Calculated from intake and body weight.
progression of renal injury and prevent cardiac injury in chronic renal failure more efficiently than conventional treatment with ACE inhibitors only. To our knowledge, not a single experimental study is available that addresses this question.

**α-Adrenergic Receptor Blockade**

Renal protection by α-adrenergic receptor blockade has also been observed in the 5/6-nephrectomy model, in NOS inhibition, and in type 2 diabetes in corpulent SHR. Combining α-adrenergic blockade (doxazosin) with ACE inhibition only provided slightly better protection (ie, less mesangial expansion) than single-drug treatment in spontaneous type 2 diabetes. However, the use of α-adrenergic blockade has been superseded by the findings of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study in which the most recent analysis conclusively shows a higher risk of stroke and combined cardiovascular disease in patients treated with doxazosin than in those using the diuretic chlorthalidone. Inclusion criteria for the ALLHAT study were age (older than 55 years), hypertension, and at least one additional risk factor. Note that renal disease was not a recognized risk factor, and approximately 36% of the patients had type 2 diabetes; thus, the results of this study cannot be directly extrapolated to chronic renal disease.

**α Plus β-Adrenergic Receptor Blockade**

A combination of α-blockade and β-blockade (phenoxymethylmazine plus metoprolol) aimed at preventing both α-adrenergic–mediated ATP release and β-adrenergic–mediated renin release was more effective in reducing renal damage (glomerular, tubulointerstitial, and vascular) in the subtotal nephrectomy model than α-blockade only. Similar beneficial effects were observed in this model with the central sympatholytic agent moxonidine and renal denervation. A recent comparative study in patients with advanced CRF showed that moxonidine superimposed on some form of RAS inhibition delayed loss of renal function over a 24-week period, whereas superimposing nitrindipine did not. However, as pointed out by Laverman and Remuzzi, this observation needs a follow-up because at the start of the trial, the albumin excretion was substantially lower (1.3 versus 1.9 g/dl) in the group subsequently treated with moxonidine.

**Diabetes and Obesity**

Diabetes triggers mechanisms that in parallel enhance and suppress NO bioavailability in the kidney. In the early phases of diabetic nephropathy, the balance between these opposing forces appears to be shifted toward increased NO, whereas in a later phase, factors that suppress NO bioavailability prevail. A similar situation may apply to SNS activity. MSNA is typically reduced in insulin-dependent diabetes mellitus patients without diabetic complications, and RSNA is decreased after 2 weeks in normotensive streptozotocin (STZ)-induced diabetes in rats. Indeed, Matsuoka found that renal denervation before induction of diabetes with STZ enhanced albuminuria. At a later stage, however, sympathetic nerve activity is clearly deleterious, because when α-adrenergic blockade was started 1 week after STZ, albuminuria decreased. Normotensive type 1 diabetic patients who had had diabetes for >15 years showed a reduction in microalbuminuria after treatment with a dose of moxonidine that did not affect blood pressure. However, when diabetic nephropathy is allowed to progress, renal denervation is no longer able to decrease albumin and transforming growth factor (TGF)-β excretion. In meta-analyses of studies exclusively directed at diabetes, ACE-inhibition was approximately twice as effective as diuretics and/or β-blockers in reducing proteinuria and cardiovascular events. The only exception was the United Kingdom Prospective Diabetes Study (UKPDS), which did not show any difference and involved 758 of 2180 patients in the meta-analysis by Pahor et al. Thus, in the race to save diabetic patients from renal and cardiovascular disease, the conventional β-blockers seem to have been beaten by the ACE inhibitors. However, in the next run-off, third-generation β-blockers have good chances.

A common disorder that is closely linked to diabetes is obesity. Obesity is also associated with microalbuminuria. As mentioned, doxazosin reduced albuminuria in corpulent SHR, and proteinuria was also lower in obese SHR treated with moxonidine. Interestingly, in the latter study the antihypertensive and renoprotective actions of moxonidine were accompanied by improvement of glucose tolerance and insulin sensitivity. Although renal SNS activity is clearly increased in normotensive and in hypertensive obesity, an effect of adrenergic blockade on microalbuminuria has yet to be shown in obesity.

**SNS Stimulation and Cardiac Injury in Chronic Renal Disease**

**Experimental Studies**

Experimental studies that evaluated effects of adrenergic blockade on cardiac injury in chronic renal disease are listed in Table 2. Although most of the experimental studies in which blood pressure is decreased by sympathetic inhibition also found a decrease in left ventricular hypertrophy, this cannot be viewed as a specific effect. In renal ablation studies, both moxonidine and carvedilol reduced myocardial interstitial volume and restored the abnormal myocardial capillary density. Similar findings were documented in aging stroke-prone SHR. Because blood pressure decreased in these studies, it remains difficult to distinguish a specific effect of decreased adrenergic action on the heart. However, in stroke-prone SHR on a high-salt diet, good cardiac protection was observed with carvedilol without any change in blood pressure. In this model, we have previously found partial reduction of proteinuria and total remission of cerebral edema for many months after late initiation of ACE inhibition or AT-1 receptor blockade once injury was present, despite persistent severe hypertension. Thus, part of the protective action of carvedilol in this model may be caused by a decrease in tissue Ang II activity in target organs.

**Clinical Studies**

Cardiac sympathetic nervous activity (CSNA), MSNA, and RSNA are coordinately increased in essential hypertension.
associated with left ventricular (LV) hypertrophy. Similarly, CSNA and RSNA are increased in congestive heart failure suggests that at this stage carvedilol markedly improves survival in dialysis patients before ESRD. The recent report available for these patients before ESRD. The recent report increased in CRF, data on RSNA and CSNA are not although it has been extensively documented that MSNA is models of renal disease document renoprotective effects of Whether sympathetic hyperactivity in CRF specifically contributes to the cardiac damage beyond its effect on blood pressure has received relatively scant attention considering the magnitude of the problem in the clinic. However, considering the excellent reduction in LV hypertrophy and hypertension achieved recently in the general population with an ACE inhibitor plus a selective aldosterone blocker, it would appear logical in predialysis patients to add a third-generation β-blocker to such a combination.

Conclusion
Although many experimental and clinical studies in diverse models of renal disease document renoprotective effects of α-blockers and β-blockers, it remains unclear how adrenergic blockade can best be used in chronic renal disease. There are very few comparative trials. For instance, to date no comparison has been made between the third-generation β-blockers and an AT-1 receptor blocker, whereas there is ample reason to believe that both agents will also enhance NO activity. Unbalanced NO versus Ang II and sympathetic activity is characteristic of renal disease. In this setting, both Ang II and sympathetic activity become damaging factors for kidney and heart. Given the overwhelming evidence of renoprotection and cardioprotection provided by interference with the renin-angiotensin-aldosterone system, now is the time to investigate whether complementary combinations are even more effective in the clinical setting.

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