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Pharmacological intervention in progressive renal diseases

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Introduction

There has been increasing recognition in recent years that elevation of blood pressure (BP) or frank hypertension are factors of overriding importance in the progression of renal failure. Correspondingly, target blood pressures have continuously been revised downward. It has also been recognized that there is considerable interaction between the injurious effect of BP on one hand and that of proteinuria on the other. In halting progression, ACE inhibitors, and possibly also angiotensin II receptor blockers, are superior to alternative antihypertensive agents, at least when BP has not been reduced to the low normal range. Exciting new information points to an important role of activation of the sympathetic nerve and endothelin systems as well.

Blood pressure and progression—a historical perspective

Almost a century ago Franz Volhard postulated a role of high BP in accelerating progression [1,2]. He stated: 'Hypertension assumes overriding importance to explain the most sinister and so far unexplained characters of these renal diseases, i.e. their chronicity and progression. Here we are confronted with a vicious circle: overdistension and spasm or both induce and aggravate vascular lesions until one element in the kidney after the other has perished so that the stage of renal failure supervenes'. Observational data to support this view only became available in the 1970s. Interestingly, it was not the nephrologists but the diabetologists who provided the evidence based on both observational and interventional [3–6] studies. Subsequently, this was also shown in observational studies on patients with non-diabetic primary renal disease and progressive renal failure [7].

Of course, observational studies do not prove causality, which requires interventional studies. Meanwhile, it has been clearly shown that lowering of BP by antihypertensive medication attenuates or halts progession not only in diabetic [8–10] but also in non-diabetic patients [11–13]. Such documentation of a beneficial effect of BP lowering was necessary because until recently the opinion prevailed that high BP values were 'necessary' for the injured kidney to maintain renal function. This widespread opinion is well reflected by the famous statement in the cardiology textbook of Paul Dudley White: 'For aught we know the hypertension may be an important compensatory mechanism which should not be tampered with, even were it is certain that we could control it' [14].

Blood pressure, proteinuria or both

Concerning the relationship between BP and progression, the issue remained whether all renal diseases are equally susceptible to high BP and conversely benefit to a similar extent from lowering of the BP. Early on it was shown that non-proteinuric renal disease, autosomal dominant kidney disease being a paradigm, did not benefit from intensified BP treatment [11,12]. This observation obviously raises the issue of whether there was a difference in principle between proteinuric and non-proteinuric renal disease. Convincing evidence for this notion was provided by the data of the Modification of Diet in Renal Disease (MDRD) study (Figure 1). Peterson *et al.* [12] showed that if upon treatment BP was lowered to values substantially below a mean arterial pressure (MAP) of 107 mmHg (equivalent to ~140/90 mmHg), progression was more effectively reduced compared with patients with a MAP of 107 mmHg, i.e. lowering of BP in the so-called 'normal range' further reduces the decline

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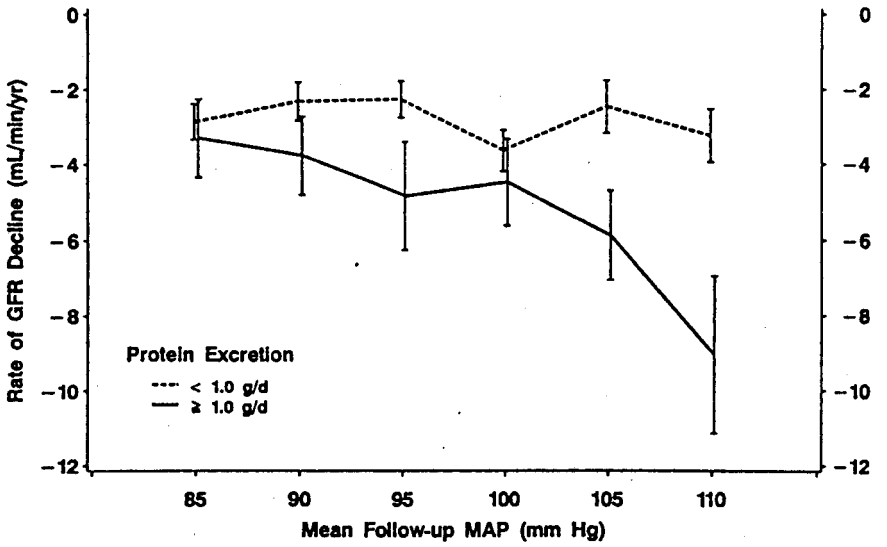

Fig. 1. Mean glomerular filtration rate (GFR) decline and achieved follow-up blood pressure. Regression lines relate mean decline in GFR to mean follow-up mean arterial pressure (MAP) for groups of patients defined according to baseline proteinuria. Decline in GFR is inversely related to follow-up blood pressure for patients with baseline proteinuria of >1 g/day but not for patients with baseline proteinuria of <1 g/day. Data taken from Peterson *et al.* [12], with permission from the American College of Physicians.

in glomerular filtration rate (GFR) in proteinuric (>1 g/24 h) patients. This observation is in line with the finding of the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) trial [11] that the benefit from ACE inhibitor treatment was particularly pronounced in patients with proteinuria >1 g/24 h.

Substantial evidence has been provided that loading of proximal tubular cells with protein induces an inflammatory phenotype and promotes interstitial fibrosis and progression of renal failure [15]. That this is also true in patients with renal disease is suggested by the results of the Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN) trial [13], which documented that patients with the highest rate of protein excretion were those who benefited most from treatment with an ACE inhibitor compared with alternative antihypertensive agents. The independent detrimental effect of proteinuria is shown in a particularly convincing fashion by the latter study because clinic BP had been lowered to exactly the same target value in patients on ACE inhibitors and their controls (Figure 2).

The optimal blood pressure for renal patients

Once the detrimental effect of BP on progression had been established [5,7–9,11–13,16], an important issue arose, i.e. which BP value is optimal for the patient with progressive renal disease. Observational studies in diabetic patients clearly established that progression, as reflected by the increase in urinary albumin excretion rate as a surrogate marker of renal damage, was progressively less when BP values in the outpatient clinic were in the low normal range [17], as shown in Figure 3. That the same relationship is also true for non-diabetic renal disease was shown by many studies. Figure 4 shows that the renal transplant, as a paradigm of an inflammatory injury to the kidney, was highly sensitive to elevated BP values [18]. Figure 4 shows progressively less actuarial graft survival up to 7 years post-operation for progressively higher systolic BP values. This was true even for values within the normotensive range. The relative risk for a systolic BP between 140 and 149 mmHg was higher by 19%, and if the pressure was >179 mmHg the risk was even increased by 117%. Space does not permit an in-depth discussion, but there are good indirect arguments that high BP in this study is not only a reflection of renal injury, but is also causally related to progression. One of the more convincing observations is that this relation was observed even in grafts coming from related kidney donors and in grafts that had never been treated for an acute rejection crisis.

An interesting issue is whether systolic BP or MAP is more relevant for renal injury. *A priori*, one would anticipate that because of the high pre-glomerular resistance, the glomerulus is not exposed to the pulsatile variation of blood pressures, so that it does not, so to speak, 'see' systolic pressure. Contraintuitively, however, we and others noted that systolic BP was a more potent predictor of progression than diastolic BP or MAP [18]. This can be rationalized with the concept that in injured kidneys pre-glomerular vessels are vasodilated, so that aortic BP and its pulsatile variation are more easily transmitted into the glomerular vascular bed, causing glomerular hypertension [19,20].

Blood pressure variability and progression

With the availability of ambulatory BP measurement (ABPM), the issue has arisen whether the circadian

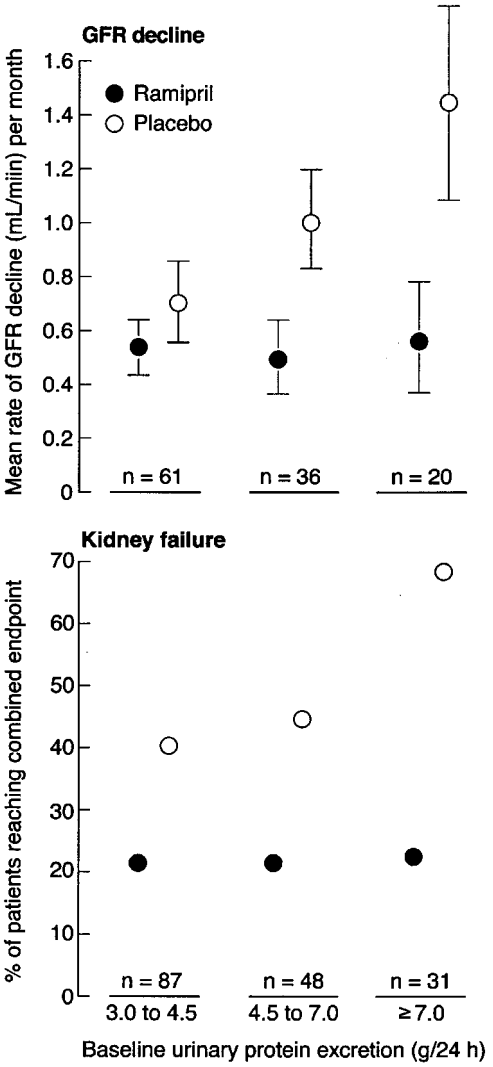

Fig. 2. Rate of decline in GFR and percentage risk of progression of non-diabetic nephropathy (combined end-point = doubling of baseline serum creatinine or end-stage renal failure) in two treatment groups according to baseline urinary protein excretion. Data taken from GISEN [13], with permission from *Lancet* Publishing Group.

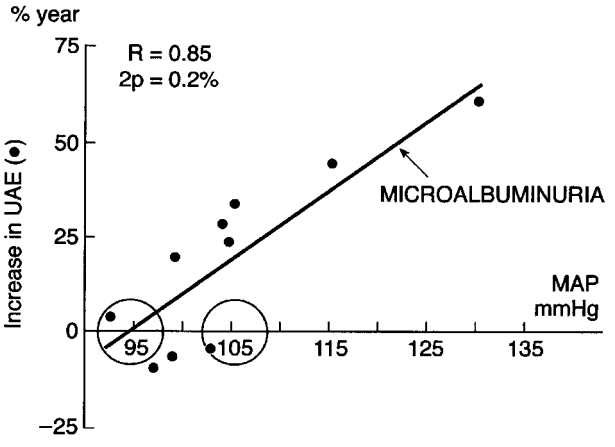

Fig. 3. Relation between mean arterial pressure (MAP) and annual percentage increase of urinary albumin excretion in patients with type 1 diabetes. Data taken from Mogensen [17], with permission from Springer-Verlag.

BP profile is of importance. A number of studies have shown that insufficient nocturnal decline of BP ('non-dipping') is a hallmark of renal disease [21]. Consequently, the issue arose of whether an insufficient nocturnal decline of BP impacts on progression of renal failure. The limited information available is consistent with this possibility. Csiky *et al.* [22] studied normotensive and hypertensive patients with IgA-nephropathy. Normotensive patients who were non-dippers had significantly higher serum creatinine concentrations at the end of follow-up compared with normotensive patients with dipping [16]. Similarly, Timio *et al.* [23] found a more rapid decline in renal function in hypertensive patients with renal failure who were non-dippers than in dippers, although 24-h BP was comparable. This was confirmed by Farmer *et al.* [24] in a retrospective analysis of diabetic patients, where a more rapid decrease in creatinine clearance was noted in non-dippers as compared with dippers.

Unfortunately, in renal patients there is no specific information available on the relation of circadian BP profile on morbidity, with the exception of one study from Okinawa, Japan [25]. Data on patients with type 2 diabetes are of considerable concern. Nakano *et al.* [26] showed that patients with reversal of the circadian BP rhythm had a 20-fold higher mortality compared with patients with a night-time decrease of BP.

Although numerous non-haemodynamic adverse effects of smoking are known, it is of interest that intense short-term sympathetic activation and BP elevation occur with smoking [27–29]. This may explain, at least in part, the considerably more adverse renal prognosis in patients with primary renal disease who smoke compared with non-smokers [30].

Renin angiotensin system and its blockade

Today there is consensus that angiotensin II (ANG II) is important in progression, both by haemodynamic and by non-haemodynamic mechanisms. In this context, obviously, the important question arises: are all antihypertensive agents 'created equal'? Today there is no doubt that ACE inhibitors confer a specific benefit [8,9,11–13], but matters are indeed more complex. It is known that ACE inhibitors reduce proteinuria even in normotensive individuals, both diabetic and non-diabetic. If one accepts proteinuria as a surrogate marker for progression, ACE inhibitors decrease proteinuria in diabetic patients by 20%, even if BP is not lowered, according to the meta-analysis of Weidmann *et al.* [31]. As shown in Figure 5, this is not seen with conventional antihypertensive agents. If BP is lowered by ~20%, however, ACE inhibitors no longer have therapeutic superiority compared with conventional antihypertensive agents. Unpublished analysis of the results of the Lewis trial [8] also confirm that an excess benefit with respect to nephroprotection can no longer be shown for ACE inhibitors, when the MAP is

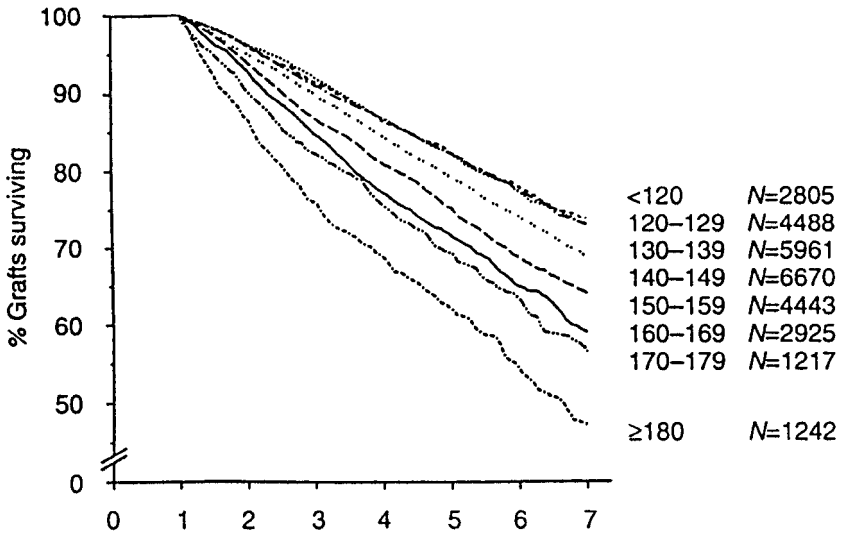

Fig. 4. Association of systolic blood pressure at 1 year with subsequent graft survival in recipients of cadaver kidney transplants. Data taken from Opelz *et al.* [18], reprinted with permission from Blackwell Sciences, Inc.

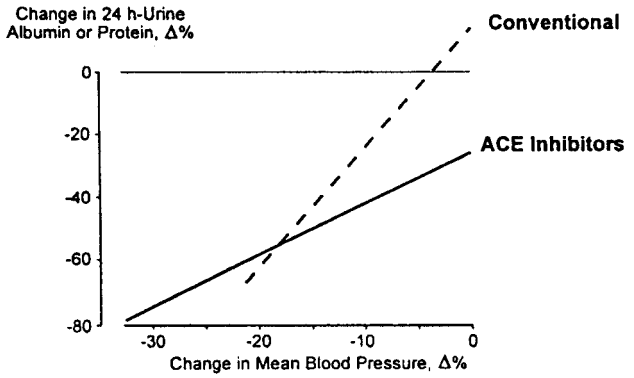

Fig. 5. Meta-analysis of percentage changes in albuminuria/proteinuria as related to BP changes in diabetics on ACE inhibitors or conventional diuretics and/or β-blockers. Data taken from Weidman *et al.* [31], with permission from Oxford University Press.

<95 mmHg. Apparently ACE inhibitors lose their therapeutic superiority at such low BP levels.

It follows from these considerations that by far the most important point is to lower BP in renal patients. Selective blockade of the renin–angiotensin system using ACE inhibitors is of proven benefit, but the selection of the drug is less important than lowering of BP *per se*.

Whether ANG II receptor blockers will duplicate the beneficial effect of ACE inhibitors is currently the subject of two large international trials using Irbesartan and Losartan.

The issue arises of whether the beneficial effect of ACE inhibitors is related to blockade of the circulating renin–angiotensin system. Whilst ACE inhibitors are uniquely effective in diabetic patients, diabetic patients are, paradoxically, characterized by suppressed plasma renin activity, at least in the absence of major renal involvement [32]. Yet, despite low plasma renin activity, ACE inhibition caused a more striking increase of renal plasma flow in type 2 diabetics compared with non-diabetic individuals [33], suggesting that the kidney is exposed to increased action of ANG II. This is also in line with the study of Wagner *et al.* [34], which showed that renal expression of the AT_1-subtype receptor for ANG II is reduced in the kidneys of type 2 diabetic patients. The study of Wang *et al.* [35] showed that high glucose concentrations increased the transcription of the angiotensinogen gene in the kidney and this may explain the observation of Miller [36] that the ANG II-dependency of renal plasma flow in diabetic patients is demonstrable under hyperglycaemic, but not under normoglycaemic conditions. The important role of the local renin–angiotensin system is also illustrated in non-diabetic models of renal damage, where intense expression of ANG II in tubular cells was noted [37]. In contrast to the juxtaglomerular apparatus, where the AT_1 receptor blocker Losartan raised expression of ANG II because of interruption of the short loop feedback, ANG II expression was reduced by Losartan in tubular epithelial cells, indicating that the two renin–angiotensin systems are differentially regulated.

If the intrarenal concentration of ANG II is important, and if proteinuria is a strong nephrotoxin, the question arises of whether dosing ACE inhibitors (or AT_1 receptor blockers) according to reduction of BP is sufficient. In an experimental study, Peters *et al.* [38] were able to show that further attenuation of glomerulosclerosis and reduction of TGF-β mRNA were achieved when the dose of ACE inhibitor or AT_1-receptor blocker was further increased even though BP was not additionally lowered any longer, and this is in agreement with the observation of Palla *et al.* [39] in patients with IgA glomerulonephritis.

Sympathetic nervous system

In the past there have been many studies investigating the effect of the renin–angiotensin system on progres-

sion, but a potential effect of excess sympathetic nerve activity on progression has not been investigated or even considered. In experimental animals [40,41], as well as in humans with renal disease [42,43], increased efferent sympathetic nerve traffic has been shown, in the latter case using microneurography as the methodological gold standard.

There is good evidence for the hypothesis that stimulation of chemoreceptors and mechanoreceptors within the kidney generates afferent signals that travel to the hypothalamus and stimulate efferent nerve traffic [44]. This is illustrated in Figure 6. In subtotally nephrectomized rats, interruption of afferent nerve traffic to the central nervous system by rhizotomy largely, but not completely, prevented the increase of BP with time [40]. As shown in Table 1, non-hypotensive doses of the central sympathicoplegic agent moxonidine reduced the development of glomerulosclerosis and of albuminuria in subtotally nephrectomized rats, although BP was not decreased as documented by telemetry [45]. The *in vivo* relevance of this observation in humans is documented by the observation of Strojek *et al*. [46] who showed that moxonidine at doses that did not affect BP by ambulatory BP-measurement caused significant lowering of albumin excretion in the morning urine in normotensive non-smoking microalbuminuric type 1 diabetic patients. That this effect is not unique to moxonidine is shown by further experiments: non-hypotensive doses of metoprolol [47] (Table 2) or surgical denervation of the kidney [48] had a similarly protective effect.

Taken together these studies show that the sympathetic nerve system is a mediator of renal damage independent of BP and does constitute a potential therapeutic target. In retrospect, the highly successful treatment of nephropathic diabetic patients with α-blockers 20 years ago [3,5,6] may have been not only a non-specific effect of BP lowering, but, in addition, also a specific effect of sympathetic blockade.

Endothelin system

Despite the convincing evidence that antihypertensive treatment, particularly with ACE inhibitors, interferes with progression [8,9,11–13], progression still cannot be completely halted and there is a dire need for additional therapeutic interventions. There are a number of mediators involved, the blockade of which may ultimately prove to be beneficial. In the context of this discussion, we wish to close with a brief comment on the endothelin (ET) system. A role of the ET system on progression is suggested by increased ET production in rats with reduced renal mass, increased urinary excretion of endothelin-1 (ET-1) in subjects with renal disease, increased renal ET gene expression in the remnant kidney model and protection against renal disease progression by ET receptor antagonists, specifically ET subtype A receptor (ET_A) antagonists (for review see references [49] and [50]). The issue is somewhat complex because of different pharmacokinetic properties, variable effects on BP, and the confounding effect of salt intake [51]. Nevertheless, we found that a specific ET_A, and less impressive a non-specific $ET_{A/B}$ receptor antagonist, ameliorated renal morphology in the renal ablation model of the rat despite a lack of effect on BP [52]. In the uninephrectomized stroke-prone spontaneously hypertensive rat (SHRsp), which develops malignant hypertension, the highly bioavailable ET_A receptor specific blocker LU 135252 not only protected animals from death, but also strikingly ameliorated glomerular morphology, despite no effect on BP in rats on high

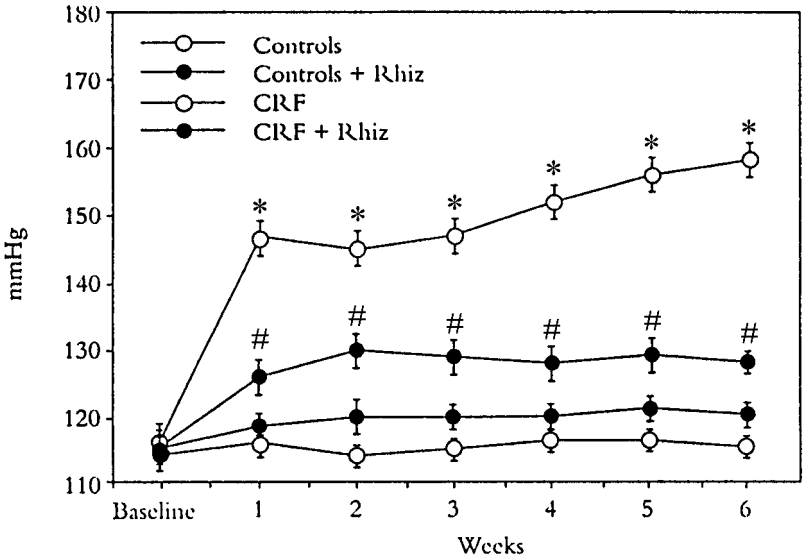

Fig. 6. Blood pressure (mmHg) in subtotally nephrectomized rats with chronic renal failure (CRF) and influence of dorsal rhizotomy (Rhiz), i.e. renal afferent denervation. $*P < 0.01$ *vs* other groups of rats; $\#P < 0.05$ *vs* control rats. Data taken from Campese and Kogosov [40], with permission from the American Heart Association.

Table 1. Effects of low dose sympathetic inhibition on blood pressure, glomerulosclerosis and albuminuria in subtotally nephrectomized rats [45].

Group	Blood pressure (BP) mmHg	Glomerulosclerosis index (GSI) arbitrary unit	Urinary albumin excretion rate (after 12 weeks) mg/24 h
Control ($n=5$)[a]	111 ± 3.19*	0.07 ± 0.01*	16.6 ± 9.6
Untreated SNX ($n=12$)[a]	134 ± 10.4†	1.55 ± 0.28†	210 ± 119†
SNX + moxonidine ($n=10$)	138 ± 12.4†	0.88 ± 0.09*	136 ± 57.2*†
ANOVA	$P<0.05$	$P<0.05$	$P<0.001$

Control = sham-operation; SNX = subtotal nephrectomy; ANOVA = analysis of variance; BP measured by 24 h telemetry in four randomly selected animals per group; moxonidine was administered in food pellets to deliver a daily dose of 1.5 mg/kg; [a]the number of animals per group for measurement of urinary albumin excretion rate differed as follows: Control $n=10$, untreated SNX = 9, SNX + moxonidine $n=10$. *$P<0.05$ *vs* SNX; †$P<0.05$ *vs* control.

Table 2. Effects of low dose α- and β-receptor blockade with phenoxybenzamine and metoprolol on blood pressure, glomerulosclerosis and albuminuria in subtotally nephrectomized rats [47].

Group	Blood pressure (BP) mmHg	Glomerulosclerosis index (GSI) arbitrary unit	Urinary albumin excretion rate (after 12 weeks) mg/24 h
Control ($n=8$)	91 ± 14.0	0.07 ± 0.02	0.29 ± 0.21
Untreated SNX ($n=10$)	113 ± 14.4*	0.74 ± 0.24*	133 ± 73.6*
SNX + phenoxybenzamine ($n=10$)	113 ± 23.5*	0.64 ± 0.21*†	64.2 ± 50.3*‡
SNX + metoprolol ($n=10$)	109 ± 10.7*	0.56 ± 0.14*‡	53.3 ± 40.3*‡
SNX + phenoxybenzamine + metoprolol ($n=12$)	110 ± 17.4*	0.49 ± 0.11*‡	43.7 ± 35.7*‡
ANOVA	$P<0.05$	$P<0.001$	$P<0.05$

Control = sham-operation; SNX = subtotal nephrectomy; ANOVA = analysis of variance; BP measured by 24 h telemetry in four randomly selected animals per group; phenoxybenzamine and metoprolol were administered in food pellets to deliver a daily dose of 5 mg/kg and 150 mg/kg, respectively. *$P<0.05$ *vs* control; †$P<0.05$ *vs* SNX + phenoxybenzamine + metoprolol; ‡$P<0.05$ *vs* untreated SNX.

salt intake [51]. The same was true in a model of chronic transplant nephropathy, the 'Fisher-to-Lewis' model, suggesting that the ET system plays an important role in the genesis of chronic graft rejection [53]. Since immunoreactive ET-1 levels are increased in the vasculature of human renal allografts undergoing chronic transplant nephropathy [54], it is reasonable to assume that ET receptor blockade may also be beneficial in humans.

The issue arises of whether there is a place for ET receptor blockers in the management of patients with progressive renal disease. Unfortunately, the pharmaceutical industry has not yet addressed the issue of progression for several presumable reasons. First, some of the early compounds have adverse effects, particularly hepatotoxicity [50]. Second, renal patients are thought not to provide a sufficient market to justify heavy investment. Third, some intervention studies on renal damage other than progression, e.g. post-transplant acute renal failure and radiocontrast nephrotoxicity [50], have yielded inconclusive results. Nevertheless, we feel that based on the impressive efficacy of ET_A-specific receptor blockers in renal damage models, the indication of progressive renal failure should be (and hopefully will be) addressed in controlled trials.

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