

Renoprotection with Anti-Hypertensives: Reduction of Proteinuria and Improvement of Oxygenation via Inhibition of the Renin-Angiotensin System

Masaomi Nangaku*, Takamoto Ohse, Tetsuhiro Tanaka, Ichiro Kojima and Toshiro Fujita

Division of Nephrology and Endocrinology, University of Tokyo School of Medicine, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Abstract: Hypertension is a common cause of chronic kidney disease (CKD) and even more common sequelae of CKD. While strict control of blood pressure is essential to preserve residual renal function, numerous clinical trials have demonstrated that inhibitors of the renin-angiotensin system (RAS), i.e. angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), reduce the progression of CKD. These studies have examined type I and type II diabetic as well as non-diabetic nephropathies, utilizing end points such as serum creatinine, glomerular filtration rate, time to end-stage renal disease (ESRD), and death. These observations suggest that drugs blocking the RAS offer advantages beyond lowering blood pressure in diabetic and non-diabetic CKD. Therefore, guidelines recommend anti-hypertensives that block RAS in patients with CKD.

Previous studies emphasized amelioration of glomerulosclerosis induced by glomerular hypertension as a renoprotective mechanism of inhibition of RAS. It should also be noted that progression to ESRD is mediated by two final common pathways; tubulointerstitial injury induced by proteinuria, and chronic hypoxia in the tubulointerstitium. Recent research indicates that reduction of proteinuria and improvement of oxygenation of the kidney are crucial mechanisms by which inhibition of RAS mediates renoprotection providing additional rationale for the use of ACEi and ARB to protect the kidney.

Keywords: Hypertension, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, kidney failure, hypoxia, tubulointerstitial injury.

INTRODUCTION

There has been a rapid and continuous rise in the number of end stage renal disease (ESRD) patients receiving dialysis and/or transplantation. The incidence and prevalence of CKD are less well-characterized than for ESRD. However, the Third National Health and Nutrition Examination Survey (NHANES III) data indicated that about 3% (5.6 million people) of adults in the United States had elevated serum creatinine values and 70% of these had hypertension [1-3].

Hypertension is a common coexisting condition among patients with CKD as either the primary etiology or as a secondary event. Epidemiological data have convincingly shown that blood pressure (BP) is linked to CKD [4, 5] and kidney disease-related mortality [6]. Persons with proteinuria superimposed on CKD have higher BP than persons with non-proteinuric CKD [7]. The mechanisms of BP increase in renal disease are multifactorial: salt retention, inappropriate activity of the renin-angiotensin system (RAS) and of the sympathetic nerve system as well as impaired endothelial cell-mediated vasodilatation [8].

While renal disease causes an increase in BP, high BP accelerates loss of function of the diseased kidney. Data from the Multiple Risk Factor Intervention Trial (MRFIT)

study identified elevated BP as a strong, independent risk factor for ESRD in 332,544 prospectively evaluated men [9]. In the Modification of Diet and Renal Disease (MDRD) study, individuals with proteinuria had slower rates of progression to ESRD if their systolic BP values were <130 mm Hg [10].

A genetic predisposition to hypertension increases the risk to develop CKD. Parents of type 1 diabetic patients had higher BP values than parents of patients without diabetic nephropathy [11]. Higher BP values were found in parents of type 1 diabetic patients with as compared to parents of patients without diabetic nephropathy [12]. Ambulatory BP measurement revealed higher BP values in offspring of type 2 diabetic patients with as compared to offspring of type 2 diabetic parents without diabetic nephropathy [13].

Thus, the treatment of hypertension has become an important component in the treatment of most CKD patients not only to prevent cardiovascular complications but also to protect the kidney [14, 15]. Meta-regression analyses have indicated that BP reduction accounts for 50% of the variance in glomerular filtration rate (GFR) decline and that each 10-mmHg reduction in mean arterial pressure (down to 92 mmHg) confers a benefit in GFR preservation of 3.7-5.0 ml/min per year [16-19]. A variety of societies recommend strict control of BP and suggestion of initial therapy with reagents to block the RAS to provide maximal protection of residual renal function (Table 1).

*Address correspondence to this author at the University of Tokyo School of Medicine, Division of Nephrology and Endocrinology, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan; Tel: 81-3-5800-8648; Fax: 81-3-5800-8806; E-mail: mnangaku-ky@umin.ac.jp

Table 1. Recommendation for Goal Blood Pressure and Initial Anti-Hypertensive Therapy in Patients with CKD**A Variety of Societies Recommend Strict Control of BP and Use of ACEi and/or ARB in Patients with CKD**

Organization	Goal Blood Pressure (mmHg)	Initial Therapy
NKF [114]	<130/80 mmHg	ACEi/ARB
JNC VII [115]	<130/80 mmHg	ACEi/ARB
ESH [116]	<130/80 mmHg (even lower if proteinuria is >1 g/day)	ACEi/ARB
WHO/ISH [117]	<130/80 mmHg	ACEi/ARB
CHEP [118]	<130/80 mmHg (<125/75 mmHg if proteinuria is >1 g/day in non-diabetic CKD)	ACEi/ARB

PATHOPHYSIOLOGICAL BASIS FOR HYPERTENSION AS A MEDIATOR OF KIDNEY INJURY

A normal kidney can maintain a relatively constant glomerular filtration ratio (GFR) across a broad range of BP. This is termed renal autoregulation of the GFR. The glomerular afferent arteriole normally constricts when BP is high to prevent the transmission of systemic BP to the glomerulus. Conversely, when BP falls, the afferent arteriole dilates to stabilize GFR. However, disordered autoregulation of GFR is known to occur in multiple clinical conditions such as diabetes mellitus and proteinuric kidney disease, leading to the hemodynamic stress on glomeruli and subsequent rise of intraglomerular pressure.

Activation of the RAS, which is often observed in patients with CKD, leads to increased synthesis of angiotensin II. Angiotensin II induces progressive kidney injury via multiple mechanisms [20]. Angiotensin II constricts precapillary arterioles, leading to increased BP, and stimulates aldosterone release from the adrenal cortex, which in turn causes renal sodium retention and expansion of circulating blood volume. Activation of the local RAS also constricts the efferent more than the afferent arteriole. This glomerular hemodynamic change increases single nephron GFR in an attempt to maintain global GFR despite progressive loss of functioning nephrons in CKD. However, if this change is sustained, it will likely result in glomerular injury and an accelerated loss of kidney function over time [21].

In addition, angiotensin II has numerous effects within the kidney, including stimulation of fibrogenic mediators, enhanced free radical formation, and contraction of mesangial cells. Recent studies also demonstrated that angiotensin II is potent promoter of epithelial-mesenchymal-transdifferentiation, which leads to renal fibrosis [22]. Overall, the net result of these effects is fibrogenesis and oxidative stress in the kidney.

INHIBITION OF THE RENIN-ANGIOTENSIN SYSTEM

Among a variety of anti-hypertensives, numerous randomized, controlled clinical trials have demonstrated that inhibitors of the RAS, i.e. angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) (Table 2), ameliorate the progression of CKD [23-25]. Although some studies utilizing BP radiotelemetry showed renoprotection by ACEi or ARB was completely BP

dependent in animal models [26, 27], these observations do not exclude a role for the RAS blockade-mediated, BP-independent mechanisms. There is ample evidence both in primary renal disease and in nephropathy of type 1 and type 2 diabetes that pharmacological blockade of the RAS by ACEi or ARB has BP-independent renoprotective effects, as described below (Table 3).

Pharmacological blockade of the RAS is renoprotective even in states where presumably the RAS is suppressed, as indicated by circulating plasma renin activity. This paradox can be explained by local activation of the RAS. Dissociation between intrarenal and plasma angiotensin II has been shown in a variety of animal models [28-30]. Recent studies demonstrated that renal tubular cells are endowed with all the components of RAS [31, 32]. All these experimental data suggest that the local renal tissue RAS contributes to progressive renal injury.

In line with BP-independent renoprotective effects, some studies suggested that a further increase in the dose of ACEi or ARB than that required to reduce BP is sensible. Peters *et al.* demonstrated that treatment with ACEi or ARB reduced TGF-beta overexpression more effectively at doses clearly higher than those required to control BP [33]. The same principle applies to humans according to some preliminary experience [34-36]. In patients with IgA nephropathy, increasing doses of lisinopril (5, 10, 15, 20 mg/day) caused progressive decrease in proteinuria (39, 44, 61, and 67 %, respectively), although BP was lowered maximally (mean 22 %) by the lowest dose of lisinopril [36].

INHIBITION OF THE RAS IN NON-DIABETIC NEPHROPATHIES

Several large, randomized trials of participants with non-diabetic CKD determined that regimens including ACEi are more effective in reducing the occurrence of kidney endpoints compared to regimens not including ACEi. Two large, multicenter studies, the ACE Inhibition in Progressive Renal Insufficiency (AIPRI) Study and Ramipril Efficacy in Nephropathy (REIN) Study, showed conclusive results.

The AIPRI Study showed that 31 out of 300 patients in the benazepril group and 57 out of 283 in the placebo group had reached the primary end point of a doubling of the baseline serum creatinine concentration or the need for dialysis

Table 2. Currently Available Pharmaceutical Reagents that Block the RAS

Representative ACEi and ARB with Usual Doses

	Brand name in U.S.A.	Brand name in Europe	Brand name in Japan
ACE inhibitors			
benazepril	Lotensin or Ciabacen 10~40mg/day	Cibacen 10~40mg/day	Cibacen 5~10mg/day
captopril	Capoten 25~100mg/day	Capoten 12.5~50mg/day	Captoril 37.5~150mg/day
cilizapril	Not available	Vasace, Dynorm, or Inhibace 1~5mg/day	Inhibace 0.5~2mg/day
delapril	Not available	Delaket 30~120mg/day	Adecut 30~120mg/day
enalapril	Vasotec 2.5~40mg/day	Renitec, Innovace, Xanef, or Reniten 5~40mg/day	Renivace 5~10mg/day
fosinopril	Monopril 10~40mg/day	Staril 10~40mg/day	Not available
imidapril	Not available	Tanatril 2.5~20mg/day	Tanatril 5~10mg/day
lisinopril	Zestril, or Prinivil 10~40mg/day	Zestril, or Carace 2.5~40mg/day	Zestril, or Longes 10~20mg/day
moexepiril	Univasc 7.5~30mg/day	Perdix 7.5~30mg/day	Not available
perindopril	Aceon 4~8mg/day	Coversyl, or Coversum 2~8mg/day	Coversyl 2~8mg/day
quinapril	Accupril 10~40mg/day	Accupro 10~40mg/day	Conan 5~20mg/day
ramipril	Altace 2.5~20mg/day	Tritace 1.25~10mg/day	Not available
temocapril	Not available	Not available	Acecol 2~4mg/day
trandolapril	Mavik 1~4mg/day	Odric, or Gopten 1~4mg/day	Odric, or Preran 1~2mg/day
ARBs			
irbesartan	Avapro, or Aprovel 150~300mg/day	Aprovel 75~300mg/day	Not available
candesartan	Atacand 8~32mg/day	Amias, Blopess, Atacand, or Kenzen 4~16mg/day	Blopess 4~12mg/day
eprosartan	Tevetan 400~800mg/day	Teveten 300~800mg/day	Not available
losartan	Cozaar 25~100mg/day	Cozaar, Cosaar, Lortaan, or Lorzaar 50~100mg/day	Nu-Lotan 25~100mg/day
olmesartan	Benicar 20~40mg/day	Olmetec, or Benetor 10~40mg/day	Olmetec 5~40mg/day
telmisartan	Micardis 20~80mg/day	Micardis 20~80mg/day	Micardis 20~80mg/day
valsartan	Diovan 80~320mg/day	Diovan, or Tareg 80~160mg/day	Diovan 40~160mg/day

Table 3. Large-Scale Clinical Trials Evaluating ACEi or ARB in Patients with CKD**These High-Quality, Randomized Studies Established Renoprotective Effects of ACEi or ARB**

	Subjects	Drug	Dose	Primary end-point	Result
AIPRI [37]	Non-diabetic CKD	Benazepril	10 mg/day	Doubling of serum creatinine level or ESRD	ACEi superior to placebo
REIN [38]	Non-diabetic CKD	Ramipril	2.5-5 mg/day	Decline in GFR	ACEi superior to placebo
Lewis [45]	type 1 diabetic patients with nephropathy	Captopril	75 mg/day	Doubling of serum creatinine level	ACEi superior to placebo
RENAAL [56]	type 2 diabetic patients with nephropathy	Losartan	50-100 mg/day	Doubling of serum creatinine level, ESRD, or death	ARB superior to placebo
IDNT [57]	type 2 diabetic patients with nephropathy	Irbesartan	300 mg/day	Doubling of serum creatinine level, ESRD, or death	ARB superior to placebo

[37]. In the benazepril group, the reduction in the risk of reaching the end point was 53 % overall (95% CI, 27 to 70). However, a significant difference in BP between patients receiving ACEi and placebo made it difficult to separate the beneficial effects to lowering BP from unique effects of ACEi treatment.

In the REIN Study with 352 patients, the decline in GFR per month was significantly lower in the ramipril group than the placebo group, and the risk of progression was still significantly reduced after adjustment for changes in BP (relative risks, 1.78 [95% CI, 1.10 to 3.13] and 1.81 [95% CI, 1.01 to 3.26], after adjustment for changes in systolic and diastolic BP, respectively) [38]. This study also showed that percentage reduction in proteinuria was inversely correlated with decline in GFR. In the next phase of this study, patients who had previously received placebo were offered the opportunity to start ACEi treatment, and those already on ACEi continued treatment. As expected, there was a significant reduction in the rate of decline in GFR of patients switched to ACEi. In addition, patients continuing on ACEi treatment showed a further reduction in the rate of GFR decline, and from 36 to 54 months of follow-up, no further patients in this group reached ESRD [39]. Among patients with <3g/day of proteinuria, ACEi treatment also significantly reduced the incidence of ESRD, particularly among those with a GFR of <45mL/min at baseline [40].

In a prospective, randomized, double-blind, controlled trial conducted by the PROCOPA study group, a total of 119 patients with primary renal disease in 12 Spanish centers were enrolled and were randomized to trandolapril; atenolol; verapamil or verapamil and trandolapril combination [41]. The attainment of a strict BP control did not ensure a simultaneous fall in proteinuria except when ACEi was used (relative reduction 40.2% [95% CI, 24.3 to 56.2] for trandolapril and 48.5% [95% CI, 31.7 to 64.3] for verapamil + trandolapril, respectively).

The beneficial effects of ACEi were also seen in the African-American Study of Kidney Disease and Hypertension (AASK), a randomized trial with a total of 1,094 self-identified African Americans with hypertensive renal disease [42]. Ramipril was more effective in reducing the secondary composite kidney outcome (50% reduction of GFR, ESRD, or death) than amlodipine (relative risk reduction 38% [95% CI, 14 to 56]) and metoprolol (relative risk reduction 22% [95% CI, 1 to 38]).

In contrast to these observations, ACEi was not shown to be more effective in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [43]. However, it should be mentioned that diuretics were not used in concert with ACEi in most patients unlike other outcome trials (and ordinary clinical settings), and relatively poor BP control in the ACEi group may have contributed to failure of demonstration of beneficial effects of ACEi.

Supporting the class-specific renoprotective effects of ACEi, a recent meta-analysis by the ACE Inhibition of Progressive Renal Disease (AIPRD) Study Group of patient-level data on 1,860 non-diabetic patients enrolled in 11 RCTs found that ACEi remained beneficial after adjustment for BP and urine protein excretion (relative risk, 0.67 [95% CI, 0.53 to 0.84]) [44].

INHIBITION OF THE RAS IN DIABETIC NEPHROPATHY

A number of randomized controlled trials demonstrate that ACEi are more effective than other anti-hypertensive classes in reducing albuminuria and in slowing the decline in GFR and onset of kidney failure in subjects with overt proteinuria.

The first clinical study to show the renoprotective effects of ACEi was the Collaborative Study Group trial of Captopril in Diabetic Nephropathy [45]. In this study, type 1 diabetic patients with nephropathy (proteinuria of 500

mg/day) and serum creatinine <2.5mg/dl were treated with captopril or placebo. Serum creatinine concentrations doubled in 25 out of 207 patients in the captopril group, as compared with 43 out of 202 patients in the placebo group. The risk of the combined primary end point of death, dialysis, and transplantation was reduced by 50%, which was independent of the small disparity in BP between the groups. Subsequent studies in patients with insulin-dependent diabetes mellitus and microalbuminuria found that captopril significantly reduces the incidence of progression to overt proteinuria [46].

Among patients with non-insulin dependent diabetes mellitus and microalbuminuria, several studies have shown that ACEi treatment reduces or prevents an increase in albuminuria [47-51], and others have found beneficial effects of ACEi on both albuminuria and rate of decline in renal function [52, 53]. A substudy of the Heart Outcomes Prevention Evaluation (HOPE) study, the Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO-HOPE) study, evaluated whether the addition of ramipril to the current regimen in patients with diabetes can lower the risk of overt nephropathy in 1,140 patients with microalbuminuria [54, 55]. Ramipril decreased the risk of overt nephropathy (relative risk reduction, 24% [95% CI, 3 to 40]) and led to a lower albumin-to-creatinine ratio.

Two high-quality, randomized studies compared reduction of ESRD in type 2 diabetic patients treated with ARB vs placebo. Brenner and colleagues performed double-blind randomized controlled studies enrolling 1513 type 2 diabetic patients with nephropathy in the Reduction of End-points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study [56]. The primary end point was the composite of the double of serum creatinine, ESRD, and death. Losartan showed a 16% reduction in the composite primary end point (95% CI, 2 to 28). While 25.5% of the placebo group reached a primary end point of ESRD, only 19.6% of the patients treated with losartan developed ESRD (relative risk reduction, 28% [95% CI, 11 to 42]). These effects were independent of BP, which was similar in the two groups throughout the study.

In Irbesartan type II Diabetic Nephropathy Trial (IDNT), Lewis and colleagues investigated 1715 type 2 diabetic patients with overt nephropathy and compared the subjects with regard to the time to the primary composite end point of a doubling of the base-line serum creatinine concentration, the development of ESRD, or death. Treatment with irbesartan reduced a risk of the primary composite end point by 20 % compared with the placebo group (95% CI, 3 to 33) and by 23 % compared with the amlodipine group (95% CI, 7 to 37). Only 14.2 % of the irbesartan-treated group developed ESRD in contrast to 18.3 % of the amlodipine-treated group and 17.8% of the placebo group [57].

The observations in these studies were supported by two other pertinent trials, IRbesartan MicroAlbuminuria Type 2 Diabetes Mellitus in Hypertensive Patients (IRMA-2) and Microalbuminuria Reduction with Valsartan (MARVAL). In the IRMA-2 study, a total of 590 hypertensive patients with type 2 diabetes and microalbuminuria were randomly assigned to irbesartan or placebo [58]. Irbesartan significantly reduced progression to nephropathy (proteinu-

ria) as compared with placebo (relative risk, 0.30 [95% CI, 0.14 to 0.61] and 0.61 [95% CI, 0.34 to 1.08] for a high dose irbesartan group and a low dose irbesartan group, respectively). This renoprotective effect was independent of its BP-lowering effect. In the MARVAL trial, 382 patients with type 2 diabetes and microalbuminuria were enrolled to treatment with valsartan or amlodipine for 24 weeks [59]. While BP reductions were similar between the two groups over the study period, valsartan lowered urinary albumin excretion more effectively than amlodipine (relative ratio, 0.63 [95% CI, 0.54 to 0.73]).

HOW DOES INHIBITION OF THE RAS PROTECT THE KIDNEY?

All these experimental and clinical studies show BP-independent renoprotective effects of ACEi and ARB. Recent researches have focused on mechanisms of protection of the kidney by inhibition of RAS. ACEi [60] and ARB [61, 62] have each been shown to reduce glomerular capillary pressure and ameliorate glomerular hyperfiltration effectively. Pharmaceutical reagents that block RAS reduce oxidative stress in the kidney [63-65]. Inhibition of RAS has direct immunomodulatory effects [66]. Potential mechanisms of renoprotective effects of ACEi and ARB are listed in (Table 4).

Table 4. Potential Renoprotective Mechanisms of ACEi and ARB

• Decrease of systemic BP
• Amelioration of glomerular hypertension and hyperfiltration
• Reduction of oxidative stress
• Direct immunomodulatory effects
• Reduction of proteinuria
• Improvement of oxygenation of the tubulointerstitium

Among these plausible mechanisms, recent research has focused on tubulointerstitial injury that serves as an important mediator of and a final common pathway to ESRD [67]. Inhibition of RAS also protects the kidney via two important mechanisms that lead to eventual kidney failure via tubulointerstitial injury, reduction of proteinuria and improvement of oxygenation of the tubulointerstitium. We will discuss more details on these mechanisms below.

PROTEINURIA, A FINAL COMMON PATHWAY TO ESRD

In humans with CKD, disease progressed more quickly when proteinuria was more severe [68, 69]. Proteinuria was a strong and independent predictor of renal outcome in a series of 840 patients with non-diabetic CKD entering the MDRD study [70] and in 409 patients with type 1 diabetes and nephropathy [71]. The onset of de novo proteinuria after years of stable renal function indicated subsequent decline in renal function in patients with nephrosclerosis [72]. While proteinuria had been considered merely a marker of glomerular damage, accumulating evidence indicates proteinuria as a cause of progression of renal injury [73].

Proteinuria is nephrotoxic and exposure of tubular epithelial cells to protein induces an activated inflammatory

phenotype [74]. Excess delivery of protein may damage tubular cells in a non-specific manner and lead to tubulointerstitial injury. Biochemical events associated with tubular cell activation in response to protein stress include up-regulation of the genes encoding vasoactive and inflammatory substances and synthesis of the corresponding protein products, such as endothelin-1 [75], monocyte chemoattractant protein-1 [76], RANTES [77], and C3 [78].

Various components in the proteinuric urine may damage tubular cells directly. These include growth factors, transferrin, albumin, albumin-bound fatty acids, and complement components. Toxic effects of these specific components are the focus of current investigation. Among a variety of molecules, complement components in the proteinuric urine are believed to play a crucial role [79-83].

In chronic proteinuric nephropathies, limiting protein traffic or the biological effect of excessive tubular protein reabsorption should prevent or slow the progression of renal disease. In experimental diabetes, treatment with ACEi or ARB reduced proteinuria and conferred protection [84, 85]. Studies in aging male Munich Wistar Fromter/Ztm rats showed that the protective effect of enalapril on the development of proteinuria and glomerular sclerosis in this model was due to its property of ameliorating size selectivity and hydraulic permeability of the glomerular capillaries [86]. Perindopril significantly reduced proteinuria and limited glomerular and tubulointerstitial injury in rats with passive Heymann nephritis, a model that mimics membranous nephropathy in humans [87].

Amelioration of glomerular hypertension decreases the amount of proteinuria. Furthermore, in isolated, perfused kidneys, infusion of angiotensin II results in a loss of glomerular size permselectivity and proteinuria, showing a non-hemodynamic effect of angiotensin II on glomerular permselectivity [88]. Recent studies utilizing transgenic rats with overexpression of the angiotensin II type 1 receptor in podocytes revealed that increased AT1 signaling in podocytes leads to structural podocyte damage and protein leakage [89]. To support this finding from a therapeutic point of view, recent studies showed that ACEi and ARB induce redistribution of the molecules in the slit diaphragm, which determine leakage of protein through glomerular filtration barrier [90-92].

As well as in animal models, treatment with ACEi or ARB in humans improves selectivity of proteinuria in patients with glomerular diseases [93, 94]. In controlled trials in CKD, ACEi and ARB reduce protein excretion by approximately 40%, which is greater than other anti-hypertensive agents, even when the effect of BP reduction on urinary protein excretion has been taken into account [17, 95]. When patients with biopsy-proven IgA nephropathy with proteinuria were randomized to receive enalapril or irbesartan, both treatments resulted in significant and equivalent reductions in proteinuria (61 and 55 % for enalapril and irbesartan, respectively) [96]. Recent studies demonstrated that the greater beneficial effect of ACEi in renal disease patients with higher baseline proteinuria could be explained by the greater anti-proteinuric effects in these patients [97].

Results of large-scale, randomized studies support these findings. In the REIN study, ramipril induced median percentage changes in urinary protein excretion compared with baseline by -33%, -50%, and -55% at 12, 24, and 36 months, respectively [38]. Further analysis of the patients enrolled in the REIN study revealed that short-term changes in proteinuria and residual proteinuria reliably predict deterioration of kidney function [98]. The benefit of losartan was associated with a 35% reduction in proteinuria in the RENAAL study [56], and irbesartan reduced proteinuria by 33% in the IDNT trial [57]. Another randomized, double-blind, placebo controlled study conducted by Zandbergen *et al.* showed reduction of urinary albumin excretion by losartan in normotensive patients with type 2 DM and persistent microalbuminuria [99]. Thus, one of the protective mechanisms of ACEi and ARB is the reduction of the amount of proteinuria.

CHRONIC HYPOXIA, ANOTHER FINAL COMMON PATHWAY TO ESRD

Despite a high overall oxygen supply, the tissue oxygen tension in the kidney is comparatively low due to shunt diffusion of oxygen between arterial and venous vessels that run in parallel in close contact. Thus, the kidney is rather sensitive to changes in oxygen delivery. Chronic ischemic damage in the tubulointerstitium is another crucial common pathway to ESRD [100-103]. The pathogenic importance of this pathway was emphasized even more by recent analysis employing a novel transgenic rat line that enabled us to monitor hypoxia *in vivo* [104]. Quantification of the hypoxia-responsive transgene showed an increase in its expression throughout the observation period in two different kinds of chronic kidney disease models, a puromycin nephrosis model and a remnant kidney model of systemic hypertension and glomerular hyperfiltration. Furthermore, the degree of hypoxia showed a positive correlation with microscopic tubulointerstitial injury and extracellular matrix accumulation in both these models. These results clearly demonstrated a pathogenetic role of chronic hypoxia as a final common pathway to end-stage renal disease.

Mechanisms of tubulointerstitial damage induced by hypoxia are multifactorial. Hypoxia can induce transdifferentiation of cultured tubular cells into myofibroblasts, predisposing the kidney to fibrosis [105]. Hypoxia induces apoptosis of renal tubular and endothelial cells via the mitochondrial pathways [106-108].

Chronic ischemia in the tubulointerstitium can occur via several mechanisms. Extensive tubulointerstitial injury is associated with the loss of peritubular capillaries, which results in a decrease in blood flow to the corresponding region. As peritubular capillaries occur downstream of the glomerular efferent arterioles, impairment of the "parent" glomerular capillary bed decreases peritubular perfusion. Anemia in CKD may also accelerate deterioration of renal function by decreasing tubular oxygen supply. However, one important mechanism to induce chronic hypoxia is imbalance of vasoactive substances such as local activation of the RAS.

Local activation of the RAS can lead to intrarenal vasoconstriction and subsequent hypoperfusion and chronic

hypoxia in the tubulointerstitium. Chronic angiotensin infusion resulted in a decrease in peritubular blood flow, which was accompanied by hypoxia in the tubulointerstitium [109]. Because angiotensin II has the preferential vasoconstrictive action on the efferent arteriole, inhibition of RAS should increase oxygen delivery to the tubulointerstitial compartment by reducing resistance in this vessel with subsequent rise in outflow from the glomerulus.

In order to address the question of whether inhibition of RAS alters the microvascular pO₂ of the renal interstitial compartment in normal rats, Norman and colleagues employed the porphyrin phosphorescence technique, an approach to the measurement of renal interstitial pO₂ which allowed for dynamic measurement of the exposed kidney and which does not require the insertion of potentially damaging microelectrodes into the renal parenchyma [110]. While there was a slow decline in pO₂ in control animals under anesthesia over the 180-min experimental period, administration of the ACEi, enalaprilat, or the ARB, candesartan, completely abrogated this decline and protected pO₂ levels throughout this period.

We also demonstrated a decrease in blood flow in peritubular capillaries and hypoxia in a very early phase in a remnant kidney model [111] and in a model of progressive glomerulonephritis [112]. These changes were associated with narrowing and distortion of peritubular capillaries. Treatment of the animals of a remnant kidney model with ARB, olmesartan, restored blood flow in peritubular capillaries and improved oxygenation of the kidney, which was estimated by deposition of pimonidazole, a marker of hypoxia. The expression of hypoxia-responsive genes was also decreased in ARB-treated animals.

TREATMENT OF CKD PATIENTS WITH ACEI OR ARB

The overwhelming weight of evidence indicates that treatment of CKD patients with ACEi or ARB affords efficient renoprotection. In patients with hypertension and chronic renal insufficiency, it is not uncommon for the serum creatinine concentration to rise as the BP is lowered. Serum creatinine and potassium concentrations should be checked approximately 1 week after starting treatment in patients with already elevated serum creatinine levels. However, the decline in renal function is in most cases hemodynamic in origin and not secondary to structural injury to the kidney. Only in situations in which the initial increase in creatinine is greater than 30 % above baseline during the first 2 months or repeated measurements show a progressive increase, we should discontinue ACEi or ARB and search for other causes of renal function, including renal artery stenosis, decreased effective circulating volume, and use of nonsteroidal anti-inflammatory drugs [16]. A small, non-progressive increase in the serum creatinine concentration occurring in the context of better BP control should be viewed as a promising sign indicating that the intraglomerular pressure has been successfully reduced [113].

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