AT₁ Receptor Blockade Improves Vasorelaxation in Experimental Renal Failure

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Abstract—It is not known whether angiotensin II type 1 receptor antagonists can influence the function and morphology of small arteries in renal failure. We investigated the effect of 8-week losartan therapy (20 mg/kg per day) on isolated mesenteric resistance arteries by wire and pressure myographs in 5/6 nephrectomized rats. Plasma urea nitrogen was elevated 1.6-fold after nephrectomy, and ventricular synthesis of atrial and B-type natriuretic peptides was increased 2.2-fold and 1.7-fold, respectively, whereas blood pressure was not affected. Losartan did not influence these variables. The endothelium-mediated relaxation to acetylcholine was impaired in nephrectomized rats in the absence and presence of nitric oxide synthase and cyclooxygenase inhibition. Blockade of calcium-activated potassium channels by charybdotoxin and apamin reduced the remaining acetylcholine response, and this effect was less marked in nephrectomized than in sham-operated rats. Relaxation to levomakalim, a vasodilator acting through adenosine triphosphate-sensitive potassium channels, was also impaired after nephrectomy. The arteries of nephrectomized rats showed eutrophic inward remodeling: Wall-to-lumen ratio was increased without change in wall cross-sectional area. All changes in arterial relaxation and morphology were normalized by losartan therapy. Aortic ACE content, measured by autoradiography, directly correlated to the plasma level of urea nitrogen, suggesting that renal failure has an enhancing influence on the vascular renin-angiotensin system. Losartan normalized relaxation and morphology of resistance arteries in experimental renal failure, independent of its influence on blood pressure, impaired kidney function, or volume overload. The mechanism of improved vasodilation by losartan may include enhanced relaxation through potassium channels. (Hypertension. 2003;41:

Key Words: arteries ■ receptors, angiotensin II ■ endothelium-derived factors ■ angiotensin II ■ potassium channels ■ kidney failure

C hronic renal failure is associated with a high prevalence of cardiovascular disease.1 Large arteries in renal failure are characterized by reduced compliance,2 the possible explanations of which are increased extracellular matrix content, hyperplasia of smooth muscle, and calcification in media.3,4 However, increased vascular stiffness has also been observed in the absence of vascular hypertrophy,4 and decreased endothelial vasodilator function may contribute to vascular pathophysiology in renal failure.6 Indeed, endothelium-dependent vasodilation is impaired in the forearm circulation of hemodialysis patients.7 We found that in experimental renal failure, endothelium-dependent vasorelaxation is impaired by a mechanism involving K⁺ channels in arterial smooth muscle.8 In hypertension, the impaired endothelium-mediated relaxation is ameliorated by treatment with angiotensin II type 1 (AT₁) receptor blockers.9,10 Angiotensin II receptor antagonists have the potential to modulate K⁺ channel–mediated vasorelaxation, since stimulation of AT₁ receptors was recently reported to inhibit ATP-sensitive K⁺ channels (KATP) in arterial smooth muscle by reducing steady-state protein kinase A activity and activating protein kinase C,11 whereas stimulation of unopposed angiotensin II type 2 (AT₂) receptors during AT₁ blockade may directly relax arteries through Ca²⁺-activated K⁺ (KCa) channels.12 Furthermore, the activation of AT₂ receptors can enhance the endothelial production of epoxyeicosatrienoic acids, vasodilators acting through KCa,13 

In this study, we examined the influence of AT₁ receptor blockade on arterial tone in experimental renal failure and tested the hypothesis that losartan treatment will correct the deficient K⁺ channel–mediated vasorelaxation in rats subjected to 5/6 nephrectomy (NTX). Since K⁺ channel activa-
tion is a major mechanism of vasodilation in small arteries, the vascular experiments were carried out with mesenteric resistance vessels. The synthesis of cardiac natriuretic peptides was measured to validate the volume overload induced by NTX. The aortic content of ACE was measured by autoradiography to examine the possible changes in the vascular components of the renin-angiotensin system.

Methods

Animals and Experimental Design

Systolic blood pressure of male Sprague-Dawley rats was measured indirectly by tail-cuff, and the animals were housed as previously described. Surgery was performed under ketamine/diazepam anesthesia (75 mg/kg and 2.5 mg/kg, respectively) at 8 weeks of age: NTX (n = 26) was carried out by removal of upper and lower poles of the left kidney and the whole right kidney, whereas sham operation (n = 25) was performed by kidney decapsulation. Antibiotics (metronidazole 60 mg/kg, ceftazidime 225 mg/kg) were given after surgery, and pain was relieved with buprenorphine (0.2 mg/kg, 3 times daily, 3 days). Four weeks later, the rats were divided to untreated (Sham, n = 17; NTX, n = 18) and losartan-treated (20 mg/kg per day) groups (Sham-Losartan, n = 8; NTX-Losartan, n = 8), whereafter the treatment continued for 8 weeks. This dose of losartan had a marked antihypertensive action in experimental hypertension. Surgery was performed under ketamine/diazepam anesthesia (75 mg/kg and 2.5 mg/kg, respectively) at 8 weeks of age: NTX (n = 26) was carried out by removal of upper and lower poles of the left kidney and the whole right kidney, whereas sham operation (n = 25) was performed by kidney decapsulation. Antibiotics (metronidazole 60 mg/kg, ceftazidime 225 mg/kg) were given after surgery, and pain was relieved with buprenorphine (0.2 mg/kg, 3 times daily, 3 days). Four weeks later, the rats were divided to untreated (Sham, n = 17; NTX, n = 18) and losartan-treated (20 mg/kg per day) groups (Sham-Losartan, n = 8; NTX-Losartan, n = 8), whereafter the treatment continued for 8 weeks. This dose of losartan had a marked antihypertensive action in experimental hypertension. Losartan had a marked antihypertensive action in experimental hypertension. The aortic content of ACE was measured by autoradiography to examine the possible changes in the vascular components of the renin-angiotensin system.

Autoradiography of Aortic ACE

Quantitative in vitro autoradiography was performed on 20-μm-thick aortic tissue sections with the radioligand [125I]-MK351A, as described earlier. The optical densities were quantified by a computer image analyzing system (AIDA 2D densitometry) coupled to the FUJIFILM BAS-5000 PhosphorImager.

Drugs, Data Presentation, and Analysis of Results

Drugs and buffer solutions were prepared as previously reported. Data were presented as mean ± SEM. Statistical analysis was carried out by 1-way ANOVA, supported by a 2-tailed t test. ANOVA for repeated measurements was applied for data consisting of repeated observations at successive points. Differences were considered significant at a value of P < 0.05. Arterial wall tension was expressed in milli-Newtons per millimeter. The EC50 for contractile agents was presented as negative logarithm (pD2); relaxation was presented as percentage of preexisting contraction. The Spearman correlation coefficient (r; 2-tailed) was used in the correlation analysis, which was considered significant at a value of P < 0.01.

Results

Blood Pressure and Animal Data

At the age of 20 weeks, systolic blood pressures in all groups were comparable and not significantly different from those measured in the beginning of the study (Table 1). Animals in all groups gained weight similarly, and heart weight-to-body weight ratios in the NTX, NTX-Losartan, and sham groups were comparable. However, heart weight-to-body weight ratio was lower in the Sham-Losartan than in the sham group. The total renal mass in NTX rats, representing the weight of the remnant kidney, was 28% lower than the weight of both kidneys in Sham rats, whereas losartan therapy was without effect on renal mass. Drunking fluid intake and urine output were higher in NTX than in Sham rats and not affected by losartan (Table 1).

In the NTX rats that were followed until the age of 32 weeks, blood pressure at study weeks 24 and 32 was higher than in Sham rats. In these NTX rats, the heart weight-to-body weight ratio was also increased (Table 2).

Laboratory Findings

The plasma concentrations of creatinine, urea nitrogen, and phosphate were increased, whereas hemoglobin, hematocrit, plasma-ionized calcium, and creatinine clearance were decreased in NTX rats when compared with Sham rats (Table 2, Table 3). No changes in plasma potassium and sodium concentrations and in pH were detected between the groups. Losartan treatment had no effects on the laboratory findings (Table 3).

Ventricular ANP and BNP mRNA and Ventricular BNP and Plasma NT-proANP Levels

The synthesis of natriuretic peptides was measured as a marker of volume overload to validate the model of renal failure. Plasma NT-proANP concentration, ventricular ANP

Analysis of Cytoplasmic RNA and Radioimmunooassay of BNP and NT-proANP

Total RNA was isolated, and for Northern blot analysis, 20 μg of ventricular RNA was transferred to a MAGNA nylon membrane (Osmonics Inc.). PCR-amplified probes to bases 76 to 509 of rat B-type natriuretic peptide (BNP; GeneEMBL access number M25297), 922 to 1403 of rat ribosomal 18S RNA (M11188), and full-length rat atrial natriuretic peptide (ANP) cDNA probe Car-55 (provided by Dr P.L. Davies, Queen’s University, Kingston, Canada) were labeled and handled as previously, with the modification that after hybridization the membranes were washed at +60°C and exposed to Phosphor screens (Eastman Kodak). Radioactivity was measured by PhosphorImager SI and ImageQuant software (Molecular Dynamics). ANP and BNP mRNA were normalized to 18S in each sample. Radioimmunoassays for BNP and N-terminal pro-atriuretic peptide (NT-proANP) were done as previously described.
TABLE 1. Data From Rats Followed for 20 Weeks

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham (n=9)</th>
<th>Sham-Losartan (n=8)</th>
<th>NTX (n=10)</th>
<th>NTX-Losartan (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 8 wk</td>
<td>284±5</td>
<td>283±9</td>
<td>281±4</td>
<td>273±5</td>
</tr>
<tr>
<td>Age 20 wk</td>
<td>469±7</td>
<td>465±10</td>
<td>467±8</td>
<td>460±6</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 8 wk</td>
<td>134±6</td>
<td>133±5</td>
<td>131±6</td>
<td>132±5</td>
</tr>
<tr>
<td>Age 14 wk</td>
<td>137±5</td>
<td>135±5</td>
<td>147±4</td>
<td>144±3</td>
</tr>
<tr>
<td>Age 20 wk</td>
<td>151±5</td>
<td>138±7</td>
<td>148±5</td>
<td>152±6</td>
</tr>
<tr>
<td>Heart weight, g</td>
<td>1.59±0.03</td>
<td>1.46±0.02</td>
<td>1.68±0.07</td>
<td>1.67±0.08</td>
</tr>
<tr>
<td>Heart weight/body weight, g/kg</td>
<td>3.40±0.07</td>
<td>3.14±0.06*</td>
<td>3.60±0.13</td>
<td>3.64±0.18</td>
</tr>
<tr>
<td>Total renal mass, g</td>
<td>3.10±0.08</td>
<td>3.03±0.15</td>
<td>2.23±0.12*</td>
<td>2.47±0.18*</td>
</tr>
<tr>
<td>Total renal mass/body weight, g/kg</td>
<td>6.61±0.13</td>
<td>6.50±0.24</td>
<td>4.77±0.23*</td>
<td>5.35±0.41*</td>
</tr>
<tr>
<td>Fluid intake, mL/24 h</td>
<td>26±3</td>
<td>28±4</td>
<td>51±7*</td>
<td>51±6*</td>
</tr>
<tr>
<td>Urine volume, mL/24 h</td>
<td>19±2</td>
<td>21±3</td>
<td>42±4*</td>
<td>39±7*</td>
</tr>
</tbody>
</table>

Sham-Losartan, NTX, and NTX-Losartan indicate losartan-treated, 5/6 nephrectomized, and losartan-treated 5/6 nephrectomized rats, respectively. *P<0.05 compared with Sham (ANOVA).

and BNP mRNA content, and ventricular BNP levels were higher in NTX rats than in Sham rats (Figure 1). Losartan treatment was without effect on any of the measurements of the natriuretic peptides.

Aortic ACE

At study week 20, the content of aortic ACE in NTX rats did not differ from the Sham group. Losartan treatment reduced aortic ACE in Sham rats but not in NTX rats (Table 3). The content of aortic ACE directly correlated to the level of plasma urea nitrogen and inversely correlated to creatinine clearance at study week 20 (Figure 2). In the NTX rats that were followed for 32 weeks, a 1.5-fold increase in aortic ACE was observed (Table 2).

Mesenteric Arterial Responses and Morphology

Endothelium-Dependent Relaxation

Vasorelaxation to acetylcholine (ACh) after precontraction with norepinephrine (NE) was impaired in NTX rats when compared with Sham, Sham-Losartan, and NTX-Losartan rats (Figure 3A). The nitric oxide synthase (NOS) inhibitor L-arginine methyl ester (L-NAME) moderately diminished relaxation to ACh, but the response in the NTX group was still reduced when compared with the other groups (Figure 3B). Cyclooxygenase inhibition with diclofenac (in the presence of L-NAME) was without significant effect on ACh-induced relaxation (Figure 3C). In contrast, addition of apamin and charybdotoxin, inhibitors of small and large conductance KCa, respectively (in the presence of L-NAME and diclofenac), markedly reduced relaxation to ACh so that the remaining response was similar in all groups. The effect of KCa inhibition was less marked in the NTX group (P<0.05) when compared with all other groups (Figure 3D). No differences in relaxation elicited by ACh were observed between the groups when precontraction was induced by 50 mmol/L KCl (data not shown).

Endothelium-Independent Relaxation

To properly interpret the endothelium-dependent relaxation, vasodilatory properties of arterial smooth muscle were examined. The relaxation of endothelium-denuded NE-precontracted rings to nitroprusside and isoproterenol, vasodilators acting through the formation of exogenous nitric oxide (NO) and activation of β-adrenoceptors, respectively, did not differ between the study groups (Figures 4A and 4B).
However, the relaxation to levcromakalim, a K<sub>ATP</sub> opener, was impaired in the NTX group, whereas the NTX-Losartan group did not differ from Sham (Figure 4C).

**Vasoconstrictor Responses**

The contractile experiments with NE and KCl were performed to elucidate possible differences in vasoconstrictor sensitivity that could curtail the results on vasorelaxation. The groups showed comparable sensitivity and maximal wall tension development in response to NE and KCl. Therefore, no contractile changes were observed in the losartan-treated NTX rats that could explain enhanced vasorelaxation in the arteries of these animals (Table 4). The sensitivity and maximal wall tension to angiotensin II were comparable in NTX and Sham rats at the age of 20 weeks (Table 4). However, in NTX rats studied at week 32, maximal wall tension induced by angiotensin II was higher than in Sham rats (Table 2). Effective AT<sub>1</sub> receptor blockade was verified by the fact that angiotensin II caused almost no contraction in the arterial rings of losartan-treated rats (Table 4).

**Vascular Morphology**

Wall-to-lumen ratio of isolated, perfused, third-order mesenteric artery branches was increased in the NTX group.
whereas the NTX-Losartan group did not differ from Sham. Lumen diameter was increased in the NTX-Losartan group when compared with the NTX group, whereas wall thickness was higher in the NTX group than in the Sham-Losartan group. The cross-sectional area of the arterial wall did not significantly differ in the study groups (Table 4).

Discussion
The results from this study showed that impaired vasorelaxation in renal failure was normalized by AT1 receptor antagonism, independent of the effects of losartan therapy on renal failure per se. It is noteworthy that deficient vasorelaxation, volume overload, and changes in resistance vessel morphology preceded the development of hypertension in this model of renal failure. At 20 weeks of age, the elevation in creatinine and urea nitrogen in the NTX groups corresponded to previous results after 5/6 nephrectomy. Moreover, the decreased hemoglobin and plasma-ionized calcium are characteristic findings in renal failure. Fluid intake and urine output were increased and creatinine clearance decreased, with no difference between the NTX and NTX-Losartan rats.

The major determinant of ANP and BNP secretion is myocyte stretch. The synthesis of these peptides is upregulated in pressure and volume overload, and changes in resistance vessel morphology preceded the development of hypertension in this model of renal failure. At 20 weeks of age, the elevation in creatinine and urea nitrogen in the NTX groups corresponded to previous results after 5/6 nephrectomy. Moreover, the decreased hemoglobin and plasma-ionized calcium are characteristic findings in renal failure. Fluid intake and urine output were increased and creatinine clearance decreased, with no difference between the NTX and NTX-Losartan rats.

Collectively, the findings on natriuretic peptides document the permanent volume overload after subtotal nephrectomy and show that it was not alleviated by AT1 receptor blockade. Prevailing volume overload provides an explanation why losartan did not reduce heart weights in NTX rats, although it lowered heart-to-body weight ratio in sham-operated rats.

Many reports suggest that endothelial function is impaired in uremia, whereby we examined the effect of AT1 receptor blockade on ACh-induced vasorelaxation in vitro. In previous 6-week studies in rats with reduced renal mass, we found that endothelium-mediated relaxation was reduced in the main branch of the mesenteric artery but not in the second-order branches of the same arterial bed. In this investigation, endothelium-dependent relaxation of small arterioles was impaired in the NTX group, whereas the NTX-Losartan group did not differ from Sham. Lumen diameter was increased in the NTX-Losartan group when compared with the NTX group, whereas wall thickness was higher in the NTX group than in the Sham-Losartan group. The cross-sectional area of the arterial wall did not significantly differ in the study groups (Table 4).

Figure 3. Relaxation to acetylcholine in endothelium-intact small mesenteric arterial rings from rats followed for 20 weeks. Responses were induced in the absence (A) and presence of 0.1 mmol/L L-NAME (B), in the presence of L-NAME, diclofenac, and 50 mmol/L apamin plus 0.1 mmol/L charybdotoxin (C), and in the presence of L-NAME, diclofenac, and 50 mmol/L apamin plus 0.1 mmol/L charybdotoxin (D). Sham-Losartan, NTX, and NTX-Losartan indicate losartan-treated, 5/6 nephrectomized, and losartan-treated 5/6 nephrectomized rats, respectively. n=8 to 10 in each group; \*P<0.05 NTX vs other groups, ANOVA for repeated measurements.

Figure 4. Relaxation to nitroprusside (A), isoproterenol (B), and levocromakalim (C) in endothelium-denuded small mesenteric arterial rings from rats followed for 20 weeks. Sham-Losartan, NTX, and NTX-Losartan indicate losartan-treated, 5/6 nephrectomized, and losartan-treated 5/6 nephrectomized rats, respectively. n=8 to 10 in each group; \*P<0.05, ANOVA for repeated measurements.
The sensitivity of arterial smooth muscle to cGMP- or cAMP-mediated pathways was not altered in NTX rats. The blockade of K<sup>+</sup> channels and hyperpolarization of smooth muscle, and this deficit was normalized by losartan. The sensitivity of arterial smooth muscle to hyperpolarizing stimuli was decreased in experimental renal failure and that the sensitivity was improved by chronic AT<sub>1</sub> receptor blockade. Impaired endothelium-derived hyperpolarization could result from reduced sensitivity of smooth muscle to, or decreased endothelial release of, hyperpolarizing factor(s). The effect of AT<sub>1</sub> receptor blockade on resistance artery morphology in renal failure has not been characterized. We found that arteries of NTX rats showed increased wall-to-lumen ratio, whereas losartan treatment increased lumen diameter and normalized wall-to-lumen ratio in NTX rats. Because the cross-sectional area of arterial wall was not increased, the change in morphology in NTX rats is compatible with eutrophic inward remodeling, and this was corrected by AT<sub>1</sub> receptor blockade. Vascular wall-to-lumen ratio gives information about the ability of vessel to contract against intravascular pressure, whereas cross-sectional area indicates the amount of material within the vascular wall and provides information about vascular growth. It is of note that in experimental NO-deficient hypertension, AT<sub>1</sub> receptor blockade reduced blood pressure and cardiac load, but the mesenteric resistance vessels still showed an inward hypertrophic response.

The present results show that the effect of renal failure on resistance vessel structure and the correction of these changes by losartan can be dissociated from the level of blood pressure. AT<sub>2</sub> receptor stimulation may decrease ACE activity tonically. An AT<sub>2</sub>-mediated mechanism is possibly involved in the downregulation of aortic ACE during AT<sub>1</sub> receptor blockade in Sham rats in this study. However, aortic ACE was not reduced after losartan treatment in NTX rats,

### Table 4. Parameters of Contractile Responses, and Morphology at 100 mm Hg Pressure in Standard Sections of Small Mesenteric Arteries From Rats Followed for 20 Weeks

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham (n=9)</th>
<th>Sham-Losartan (n=8)</th>
<th>NTX (n=10)</th>
<th>NTX-Losartan (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine (+E)</td>
<td>5.57±0.05</td>
<td>5.65±0.04</td>
<td>5.65±0.02</td>
<td>5.53±0.06</td>
</tr>
<tr>
<td>pD&lt;sub&gt;2&lt;/sub&gt;, –log mol/L</td>
<td>4.81±0.43</td>
<td>4.54±0.71</td>
<td>4.68±0.74</td>
<td>5.71±0.79</td>
</tr>
<tr>
<td>Potassium chloride (–E)</td>
<td>1.29±0.02</td>
<td>1.27±0.02</td>
<td>1.26±0.02</td>
<td>1.25±0.02</td>
</tr>
<tr>
<td>pD&lt;sub&gt;2&lt;/sub&gt;, –log mol/L</td>
<td>4.72±0.59</td>
<td>4.71±0.48</td>
<td>5.64±0.96</td>
<td>5.70±0.89</td>
</tr>
<tr>
<td>Angiotensin II (+E)</td>
<td>7.85±0.14</td>
<td>8.15±0.47</td>
<td>7.86±0.12</td>
<td>8.09±0.24</td>
</tr>
<tr>
<td>pD&lt;sub&gt;2&lt;/sub&gt;, –log mol/L</td>
<td>1.52±0.40</td>
<td>0.16±0.09*</td>
<td>1.24±0.30</td>
<td>0.17±0.06†</td>
</tr>
<tr>
<td>Maximal wall tension, mN/mm</td>
<td>8.0±0.3</td>
<td>7.0±0.4</td>
<td>9.6±0.5†</td>
<td>8.2±0.3</td>
</tr>
<tr>
<td>Wall thickness, μm</td>
<td>338.4±10.8</td>
<td>347.1±4.2</td>
<td>325.7±10.2</td>
<td>364.0±9.0†</td>
</tr>
<tr>
<td>Lumen diameter, μm</td>
<td>27.3±1.6</td>
<td>24.3±1.4</td>
<td>31.2±1.8‡</td>
<td>29.8±1.4</td>
</tr>
<tr>
<td>Wall cross-sectional area, μm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>31753±2810</td>
<td>28426±1809</td>
<td>35293±2788</td>
<td>37012±2393</td>
</tr>
</tbody>
</table>

E, endothelium intact and –E, endothelium-denuded arterial rings, respectively. pD<sub>2</sub> is negative logarithm of the concentration of agonist producing 50% of maximal wall tension.

*p<0.05 compared with the Sham group; †P<0.05 compared with the NTX group; ‡P<0.05 compared with the Sham-Losartan group (ANOVA).
whereby renal failure may influence the regulation of vascular ACE. This view is supported by the inverse correlation between renal function and aortic ACE content at study week 20. In more advanced renal failure at study week 32, both aortic ACE and vasoconstrictor response to angiotensin II were higher in NTX than in Sham rats. These findings agree with the notion that renal failure has an enhancing influence on the vascular renin-angiotensin system.

**Perspectives**

We found that experimental renal failure is associated with impaired vasorelaxation through $K^+$ channels in resistance vessels, which also show eutrophic inward remodeling. Since these changes were normalized by AT$_1$ receptor blockade, the local renin-angiotensin system may be involved in the mechanisms that impair hyperpolarization of arterial smooth muscle and participate in vascular remodeling in renal failure. This view is supported by the observed increase in aortic ACE content in advanced renal failure. Vascular changes during impaired kidney function could also result from elevated blood pressure, uremic toxins, volume overload, disturbed calcium-phosphorus balance, acidosis, anemia, or changes in vasoconstrictor properties. It is noteworthy that in this study, normalization of the vasodilation by losartan could not be explained by changes in any these factors that are characteristic of renal failure. In clinical medicine, treatment with AT$_1$ receptor antagonists confers benefits beyond blood pressure control. In patients with type 2 diabetes, losartan and irbesartan slow the progression of nephropathy, whereas in patients with hypertension, losartan prevents more cardiovascular morbidity than atenolol for a similar reduction in blood pressure. The current results suggest that the functional and structural disturbances of uremic arteries can be ameliorated by treatment with AT$_1$ receptor blockers and that these beneficial influences are independent of changes in blood pressure and volume control.

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**References**


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