Adverse Effect of the Calcium Channel Blocker Nitrendipine on Nephrosclerosis in Rats With Renovascular Hypertension

Ulrich Otto Wenzel, Götz Troschau, Wilhelm Schoeppe, Udo Helmchen, and Gerd Schwietzer

The effect of a 6-week treatment with the calcium channel blocker nitrendipine or the angiotensin converting enzyme inhibitor enalapril on blood pressure, albuminuria, renal hemodynamics, and morphology of the nonclipped kidney was studied in rats with two-kidney, one clip renovascular hypertension. Six weeks after clipping of one renal artery, hypertensive rats (178±4 mm Hg) were randomly assigned to three groups: untreated hypertensive controls (n=8), enalapril-treated (n=8), or nitrendipine-treated (n=10). Sham-operated rats served as normotensive controls (128±3 mm Hg, n=8). After 6 weeks of treatment, renal hemodynamics (glomerular filtration rate and renal plasma flow) were measured in the anesthetized rats. Renal tissue was obtained for determination of glomerular size and sclerosis. Enalapril but not nitrendipine reduced blood pressure significantly. After 6 weeks of therapy, glomerular filtration rate was not different among the studied groups. Renal plasma flow increased, but albumin excretion and glomerulosclerosis did not change after enalapril treatment. In contrast, in the nitrendipine-treated group albuminuria increased from 12.8±2 progressively to 163±55 compared with 19.2±9 mg/24 hr in the hypertensive controls. Furthermore, glomerulosclerosis index was significantly increased in the nitrendipine-treated group compared with the hypertensive controls (0.38±0.1 versus 0.13±0.04). In addition, glomerular size was higher in the nitrendipine-treated group (14.9±0.17 10^-3 mm^2) but lower in the enalapril-treated group (11.5±0.15 10^-3 mm^2) compared with the hypertensive controls (12.1±0.17 10^-3 mm^2). These data demonstrate that treatment with the calcium channel blocker nitrendipine is associated with progressive rise of albuminuria, glomerular size, and sclerosis in rats with two-kidney, one clip hypertension. Angiotensin converting enzyme inhibitors may retard the progression of glomerulosclerosis in the long term by its effects on blood pressure and glomerular size. (Hypertension 1992;20:233-241)

KEY WORDS • nitrendipine • calcium channel blockers • enalapril • hypertension • renovascular • albuminuria • glomerulosclerosis • nephrosclerosis • rat studies • angiotensin converting enzyme inhibitors

Hemodynamic factors like systemic and glomerular hypertension as well as nonhemodynamic factors like glomerular hypertrophy obviously play key roles in the progression of chronic renal disease. However, systemic hypertension is not always accompanied by an increase of glomerular capillary pressure. On similar levels of systemic hypertension, glomerular injury occurs primarily in kidneys with preglomerular dilatation causing glomerular hypertension. In spontaneously hypertensive rats (SHR) glomerular pressure is normal because of its high preglomerular resistance, and the development of glomerular damage is slow. Therefore, preglomerular resistance seems to play an important protective role in the progression of hypertensive glomerular damage. In contrast to hypertensive models with preglomerular dilatation (the renal ablation or deoxycorticosterone acetate [DOCA]-salt model), the nonclipped kidney of rats with two-kidney, one clip (2K1C) hypertension has a high preglomerular resistance comparable to that in SHR. Therefore, the effect of a vasodilatory agent on preglomerular resistance is probably one important determinant for the further progression of renal disease.

Calcium antagonists are used as first-step drugs in various forms of hypertension and have been shown to decrease preferentially preglomerular resistance without effects on efferent resistance in most studies. Some investigators have reported that glomerular capillary pressure is reduced, others have found that it is not reduced when calcium antagonists are given either acutely or chronically, despite decrease of systemic blood pressure. In spite of normalization of systemic blood pressure, glomerular capillary pressure increased after acute administration of verapamil in the renal ablation model.
In addition to their numerous nonhemodynamic effects like inhibition of mesangial uptake of macromolecules or inhibition of mesangial contraction and proliferation, converting enzyme inhibitors (CEI) lower glomerular capillary pressure in most studies by a preferential decrease of postglomerular resistance. In studies in the renal ablation model or other hypertensive models, calcium antagonists have beneficial or negative effects on the progression of renal disease. However, chronic studies are still lacking on the effect of calcium channel blockers in comparison with CEI on the nonclipped kidney in renovascular hypertensive model with already established glomerulosclerosis.

Therefore, this study investigated the chronic effect of a calcium antagonist, in comparison with CEI, on kidney function, albuminuria, and glomerular structure in a hypertensive model with high preglomerular resistance.

**Methods**

**Animals and Protocol**

Studies were performed in male Sprague-Dawley rats (SAVO, Kissleg, FRG) weighing 120–140 g. The animals had free access to tap water and standard rat chow (Altromin, Lage, FRG). Goldblatt 2K1C hypertension was induced: a rigid U-shaped silver clip (0.23–0.25 mm i.d.) was placed around the right renal artery through a loin incision, while the rat was under ketamine/xylazin anesthesia (Parke-Davis/Bayer, Berlin/Leverkusen, FRG) (100/10 mg/kg i.m.). The nonclipped kidney remained untouched. In sham-operated controls, the same procedure was performed without applying a clip.

After 6 weeks without treatment, only hypertensive animals with systolic blood pressure (SBP) exceeding 160 mm Hg were randomly divided into three groups: untreated hypertensive (HC) rats (n=8), enalapril-treated (ENP) (75 mg/1 drinking water) (n=8) (Merck Sharp & Dohme, Munchen, FRG), or nitrendipine-treated (NIT) (1,000 mg/kg food) (n=10) (Bayer, Leverkusen, FRG) for 6 weeks. Sham-operated rats served as untreated normotensive controls (n=8).

Food intake in week 1 of therapy averaged 18.8±2.2 g/24 hr and water intake averaged 31.5±11.2 ml/24 hr. Food intake did not differ among the groups during therapy. Thus, enalapril intake averaged 4–7 mg/kg per day, and nitrendipine intake averaged 40–60 mg/kg per day.

During the treatment period SBP was measured weekly by tail-cuff plethysmography in awake rats. The animals were placed in individual metabolic cages (Ebeco, Castropranzel, FRG), and 24-hour urine collections were made weekly for determination of albuminuria. Albumin concentrations were determined by nephelometry (Beckmann, München, FRG) with a rabbit anti-rat albumin antibody (Cappel Laboratories, Westchester, NY).

**Renal Function**

Six weeks after therapy, rats were anesthetized with Inactin (Byk Gulden, Konslaz, FRG) (100 mg/kg i.p.) and placed on a heated operating table (Palmer Bio-Science, Sheerness UK). A tracheostomy was performed, and polyethylene catheters were inserted in the right jugular vein and in the ureter of the nonclipped kidney for solute infusion and sample collection. A cannula in the left carotid artery, connected to a pressure transducer (model 23Db, Statham Laboratories, Hato Rey, Puerto Rico), allowed continuous measurements of arterial blood pressure and collection of blood.

To replace fluid losses associated with anesthesia and surgery, animals received an ison-octonic albumin infusion with 1.2 ml/100 g body wt over a 30-minute period followed by an infusion rate of 0.15 ml/100 g per hour. A bolus of 0.5 ml/kg of a solution containing 10% inulin and 2% p-aminohippurate (PAH) in 5% glucose was given, followed by an infusion rate of 1.5 ml/kg per hour for a 60-minute control period to reach constant urine flow. Thereafter, two 30-minute clearance periods followed. Blood for determination of inulin and PAH concentration was collected in the middle of each clearance period. At the end of the experiment, arterial and renal venous blood was collected for evaluation of serum albumin, total cholesterol, and PAH extraction. Inulin concentrations were determined by the anthrone reaction according to Führ et al. PAH concentrations were measured by a colorimetric method. Protein concentrations were determined according to Lowry et al. Plasma cholesterol was measured using an enzymatic assay (Boehringer Mannheim, FRG). Glomerular filtration rate (GFR), renal plasma flow (RPF), filtration fraction, and PAH extraction were calculated using standard equations.

**Renal Morphology**

At the end of the clearance periods, hearts and kidneys were removed and weighed. Kidney slices were fixed in 4% buffered formalin, paraffin embedded, sectioned to 3–4-μm thick sections, and stained with periodic acid Schiff.

Histological studies were performed in a blind fashion. Glomerulosclerosis was assessed by a semiquantitative score (sclerosis score, grade 0 to 4), using the methods of Raij et al and Olson et al. Thereby grade 1 represents involvement of up to 25% of the glomerulus, and grade 4 represents sclerosis of 75% to 100% of the glomerulus. A glomerulosclerosis index was calculated in the following fashion: The number of glomeruli with a score of one was multiplied by 1, with a score of two by 2, three by 3, and four by 4. These numbers were summed and divided by the number of glomeruli assessed, including those with a score of zero. A minimum of 100 glomeruli (range, 100–190) was examined in each specimen.

In addition, the amount of tubulointerstitial damage (tubular casts, tubular atrophy and dilatation, or interstitial fibrosis) was estimated by examining eight fields (×100) and semiquantitatively grading the degree of damage in each field using a 0 to 3+ scale. The mean of eight determinations was calculated as an index for each of the three parameters in each tissue specimen. By contrast, no tubulointerstitial abnormalities were found in normotensive controls. Therefore, statistical analysis was not performed in this group.

Planimetric examinations of cross-sectional area values (PA) were performed by means of a Zeiss drawing tube in combination with a semiautomatic interactive image analysis system (Morphomat 30, Zeiss, Oberkochen, FRG). Using a serpentine movement from kidney to kidney, the cross-sectional area was determined for solute infusion and sample collection. A cannula in the left carotid artery, connected to a pressure transducer (model 23Db, Statham Laboratories, Hato Rey, Puerto Rico), allowed continuous measurements of arterial blood pressure and collection of blood.

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Nitrendipine and Renovascular Hypertension

**Results**

**Blood Pressure**

The development of SBP before and during therapy is shown in Figure 1. At the time of randomization, SBP of animals with unilateral renal artery stenosis was increased to 178±4 versus 128±3 mm Hg in sham-operated controls. In HC rats, SBP increased further to 192±7 mm Hg during the following 6 weeks. Enalapril lowered SBP to 149 ±8 but not to normotensive values of controls (125±3 mm Hg). By contrast, there was no significant decrease of SBP after nitrendipine treatment (183±5 mm Hg) when NIT rats were compared with HC rats.

**Albumin Excretion**

Albumin excretion (ALB) is depicted in Figure 2. There was a slight, but not significant, decrease of ALB after enalapril in the ENP group compared with the HC group (9±5 versus 19.2±9 mg/24 hr). Only in week 10 did ALB decrease significantly in the ENP versus the HC group (3.3±.0.9 versus 23.4±8 mg/24 hr). In contrast to the HC and ENP group, nitrendipine induced a significant progressive rise of ALB to 163±55 mg/24 hr in the NIT group.

**Proteinuria**

There is a significant correlation between proteinuria obtained from the 24-hour collection and those from short-term collections of the nonclipped kidney during the acute study (Figure 3).

**Statistical Analysis**

The data are presented as mean±SEM. Statistical analysis was performed by Mann-Whitney-Wilcoxon test. In addition, the Kruskall-Wallis test was performed as a screening test, if appropriate. Values of $p<0.05$ were considered significant.
Morphological Changes

As shown in Figure 4, glomerular damage in hypertensive rats was significantly higher compared with normotensive controls. Enalapril did not cause a significant change of the glomerulosclerosis index (0.09±0.05) in hypertensive rats. However, nitrendipine significantly increased glomerular lesions in NIT rats compared with HC rats (0.38±0.1 versus 0.13±0.04). Representative glomeruli from the NIT group are shown in Figures 5 and 6.

The PA of all glomeruli and of glomeruli with the same glomerulosclerosis index are shown in Table 1. In the first column, PA of all measured glomeruli are shown. The hypertensive groups had a significant increase of PA. However, enalapril significantly inhibited the increase of PA in the ENP group compared with HC rats. In the NIT rats, PA was significantly higher compared with untreated hypertensive controls and the ENP group.

When only glomeruli were analyzed, which did not reveal glomerulosclerosis (second column, score 0), similar differences were found for PA within hypertensive groups. In the ENP group, PA was smaller (11.1±0.16 10^{-3} \text{ mm}^{2}) compared to untreated hypertensive controls and the ENP group. In the NIT group, PA was significantly higher compared with untreated hypertensive controls and enalapril.

The comparisons regarding the areas of NIT-score 1 versus HC-score 1, ENP-score 1 versus ENP-score 0, and ENP-score 1 versus HC-score 1 are not significantly different. The remaining comparisons are still significant. Therefore, the important findings, i.e., nitrendipine increases and enalapril decreases glomerular size, remain valid.

As depicted in Table 2, the mean score for proteinaceous tubular casts or tubular atrophy and dilatation was significantly higher in the NIT group versus the ENP and HC group. The HC and the ENP groups were not significantly different. No significant differences were found in interstitial changes among the three hypertensive groups.

None of the kidneys evaluated showed characteristic changes of malignant hypertension like fibrinoid necrosis, narrowing and obliteration of the lumen, and onion-skinning of arteries and arterioles.

General Characteristics

As shown in Table 3, no significant differences existed between body weights. The heart weight of the

![Figure 4. Glomerulosclerosis in the four examined groups. **p<0.01 versus normotensive controls; ++p<0.01 versus hypertensive controls and enalapril.](image-url)
hypertensive groups was significantly increased compared with normotensive controls, indicating left ventricular hypertrophy. Heart weights of the ENP group tended to decrease more than the NIT and HC groups, but the differences were not significant. In the NIT group, the weight of the stenosed kidney was increased compared with the ENP and HC groups and was similar to that in the normotensive controls. Furthermore, weights of the nonclipped kidneys from rats in the NIT and ENP groups were higher than those of rats in the HC group.

Renal Hemodynamics

The renal hemodynamics of the nonclipped kidney are shown in Table 4. GFR was not significantly different between studied groups. RPF was increased signif-
icantly in the ENP, NIT, and HC groups versus nor-
motensive controls. Filtration fraction and PAH
extraction were lower in all hypertensive groups com-
pared with normotensive controls. After nitrendipine
therapy, plasma albumin values tended to decrease
compared with other groups but did not reach statistical
significance. Plasma cholesterol levels were significantly
higher after nitrendipine administration (155±43 mg/dl)
than after enalapril (53±4 mg/dl).

**Second Study**

After 6 weeks of therapy, SBP was significantly de-
creased in the TRX group versus the HC group (165±7
versus 184±5 mm Hg, p<0.05). Proteinuria did not
differ significantly between both groups and the end of
therapy (TRX, 99±21 mg/day; HC, 87±15 mg/day).
Furthermore, glomerulosclerosis was not different be-
tween groups (TRX, 0.30±0.11; HC, 0.25±0.08). No
significant differences occurred in food and water in-
take, body weight, and relative heart weight (data not
shown).

**Discussion**

In the present study we evaluated the influence of two
different antihypertensive drugs on arterial blood pres-
sure, renal function, morphology, and albuminuria in a
rat model of 2K1C hypertension. The results obtained
were different with respect to the effects of the two
drugs on blood pressure as well as functional and
structural renal parameters.

In rats receiving antihypertensive treatment with ni-
trendipine 6 weeks after clipping of one renal artery,
blood pressure was not controlled, but a progressive rise
of albuminuria, glomerular lesions, and glomerular size
of the nonclipped kidney occurred compared with un-
treated hypertensive controls. During enalapril therapy,
blood pressure decreased significantly, but not to nor-
motensive values, without effects on albuminuria and
glomerular lesions, when analyzed by light microscopy.
However, glomerular planar area was reduced after 6
weeks of enalapril therapy.

In this renovascular hypertensive model, nitrendipine
therapy was not successful in controlling blood pressure.
In other forms of hypertensive injury or immunologi-
cally mediated, chronic renal disease, the dose of ni-
trendipine has been shown to control hypertension and
to retard the progression of the disease.23,25 Kobayashi
et al,26 treating 2K1C rats with nitrendipine (20 mg/kg
s.c. every other day) and Kazda et al24 using nitren-
dipine (45 mg/kg p.o.) were able to decrease blood
pressure, although not to normotensive values. How-
ever, their therapy started earlier during the course of
hypertension than the present study. Obviously, the
duration of hypertension and the resulting intensity of
nephrosclerosis is important for the effect of antihyper-
tensive therapy. It was not primarily the aim of the
present study to lower blood pressure, but rather to
investigate to what extent dilatation of a preconstricted
afferent resistance by a calcium antagonist may lead to
glomerular damage if its effect on systemic blood pres-
sure is small. TRX is one of the most commonly used
drug combinations in experimental antihypertensive
studies.12 However, in contrast to other hypertensive
models, TRX failed to normalize blood pressure to the
same extent as enalapril in the current study. Therefore,
it is difficult to determine the role of the blood pressure
per se in the progression of renal disease in this
hypertensive model.

Two important factors seeming to influence the pro-
gression of chronic renal disease might be glomerular
capillary pressure and glomerular size.12,27

In several models of experimental kidney disease a
decrease of PA during CEI was shown.16,28,29 Appar-
etly, in addition to its direct vasopressory effect, an-
giotensin II (Ang II) also promotes growth of mesangial
cells.30 With respect to growth factors, less data exist
about the behavior of glomerular size or hypertrophy
during therapy with calcium antagonists. Dworkin
his group\textsuperscript{9,10} found only a tendency of decline in the DOCA-salt model but a significant decrease of PA in the renal ablation model after therapy with nifedipine. Tolins and Rai\textsuperscript{18} also were able to show a decrease of PA in the ablation model of Dahl salt-sensitive rats. These results are in agreement with in vitro data in which an antiproliferative effect of calcium antagonists on mesangial cells was demonstrated.\textsuperscript{31}

In contrast to these results, the present study has shown for the first time, at least to our knowledge, a significant increase of PA concomitant to the progressive rise in albuminuria and glomerulosclerosis after nitrendipine compared with HC rats.

In addition to the comparison of all measured glomeruli, we compared the size of glomeruli with different degrees of sclerosis separately in our various experimental groups. At the beginning of segmental glomerular lesions, there is a clear rise of PA.\textsuperscript{32} Therefore, changes in PA could also be a bias due to changes in the incidence of segmental sclerosis. However, separate analysis of the size within light microscopically intact glomeruli (score 0) also revealed significant differences between the hypertensive groups. These data suggest, similar to the results of Yoshida et al,\textsuperscript{32} that glomerular hypertrophy may precede the development of sclerotic changes.

The increase of PA in the NIT group and the decrease in the ENP group may indicate changes in glomerular pressure. However, Yoshida et al\textsuperscript{27} have shown that the PA and glomerular capillary pressure of individual glomeruli were not significantly correlated.

Furthermore, total weight of the nonclipped kidneys was increased after nitrendipine. One could speculate that this may be caused not only by hypertrophy of renal structures, but also by larger amounts of precipitated proteinaceous material in dilatated tubules,\textsuperscript{16} which were found more often in the NIT group.

The pattern of the tubulointerstitial changes among the groups is very similar to the glomerular changes. Therefore, it seems that the tubulointerstitial changes developed secondary to the glomerular abnormalities. However, we cannot exclude from the data of this study that both developed independently.

Another cause for the documented negative renal effects of nitrendipine may be the impairment of renal blood flow autoregulation by calcium channel blockers.\textsuperscript{33} As recently demonstrated in the renal ablation model, intact autoregulation is important in protection of the glomerulus from hypertensive injury.\textsuperscript{34} Autoregulation capacity is decreased in the nondipped kidney of 2K1C rats.\textsuperscript{35} A further impairment of autoregulation by calcium channel blockers, especially at high systemic blood pressure, could lead to the transmission of the increased perfusion pressure to the glomerular capillaries. The resultant "barotrauma" could contribute at least in part to the observed albuminuria and glomerulosclerosis in the NIT group.

Acute effects of calcium antagonists on glomerular capillary pressure are variable. In two studies, a decrease of glomerular capillary pressure was shown after acute administration of verapamil or diltiazem in the renal ablation model.\textsuperscript{17,26} By contrast, glomerular capillary pressure increased in the same model after acute verapamil administration, despite a decrease of systemic blood pressure.\textsuperscript{11} Therefore, effects of calcium antagonists on glomerular capillary pressure may depend on the dose and basal renal hemodynamic state.

In spite of increased glomerular damage, total GFR and plasma flow of the nonclipped kidney in the NIT group were not impaired after nitrendipine when compared with normotensive control and HC rats. Probably the intact nephron population maintains total GFR by adaptive hyperfiltration, which may facilitate a further increase of albuminuria and glomerulosclerosis in the long term.\textsuperscript{2}

### Table 3. Body and Organ Weights

<table>
<thead>
<tr>
<th>Group</th>
<th>Body weight (g)</th>
<th>Heart weight (mg/100 g body wt)</th>
<th>Kidney weight (mg/100 g body wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive controls</td>
<td>430±10</td>
<td>268±4</td>
<td>310±9</td>
</tr>
<tr>
<td>Hypertensive controls</td>
<td>446±12</td>
<td>344±17*</td>
<td>284±3*</td>
</tr>
<tr>
<td>ENP</td>
<td>439±5</td>
<td>307±10*</td>
<td>253±13*</td>
</tr>
<tr>
<td>NIT</td>
<td>410±13</td>
<td>349±14*</td>
<td>331±21†</td>
</tr>
</tbody>
</table>

Heart and kidney weight divided by body weight. NIT, nitrendipine-treated group; ENP, enalapril-treated group.

\( \ast p<0.05 \) versus normotensive controls.

\( \ast p<0.01 \) versus normotensive controls.

\( \ast p<0.001 \) versus hypertensive controls.

### Table 4. Renal Hemodynamics and Biochemical Parameters

<table>
<thead>
<tr>
<th>Group</th>
<th>GFR (ml/min/g)</th>
<th>RPF (ml/min/g)</th>
<th>FF (%)</th>
<th>( E_{\text{PAH}} ) (%)</th>
<th>Plasma albumin (mg/dl)</th>
<th>Plasma cholesterol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive controls</td>
<td>1.6±0.2</td>
<td>7.35±1.76</td>
<td>27.4±3.7</td>
<td>91±7</td>
<td>2,478±83</td>
<td>66.7±5</td>
</tr>
<tr>
<td>Hypertensive controls</td>
<td>1.8±0.3</td>
<td>10.70±1.80*</td>
<td>16.4±1.8†</td>
<td>75±5†</td>
<td>2,492±72</td>
<td>66.5±8</td>
</tr>
<tr>
<td>ENP</td>
<td>1.9±0.3</td>
<td>13.76±2.64*</td>
<td>15.5±1.2†</td>
<td>77±5†</td>
<td>2,383±97</td>
<td>53.0±4</td>
</tr>
<tr>
<td>NIT</td>
<td>1.7±0.2</td>
<td>11.22±1.6†</td>
<td>17.5±2.1†</td>
<td>65±4†</td>
<td>2,071±170</td>
<td>155.0±43†</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate; RPF, renal plasma flow; FF, filtration fraction; \( E_{\text{PAH}} \), extraction \( p \)-aminohippurate; ENP, enalapril-treated group; NIT, nitrendipine-treated group.

\( \ast p<0.01 \) versus normotensive controls.

\( \ast p<0.05 \) versus normotensive controls.

\( \ast p<0.01 \) versus ENP.
In contrast to the other experimental groups, the NIT group had higher plasma cholesterol levels, probably as a consequence of pronounced proteinuria and hyperalbuminemia. Hypercholesterolemia per se may in turn increase glomerular injury.\(^\text{23}\) We cannot exclude that increased cholesterol levels are in part responsible for the progression of glomerular injury. However, in models where cholesterol is believed to play a role in the progression of renal disease, like aminoglycoside-induced nephropathy or diet-induced hypercholesterolemia, plasma cholesterol levels are two to three times higher than in the NIT group.\(^\text{24,27}\) In addition, the enhancement of glomerulosclerosis in rats with renovascular hypertension required a cholesterol-rich diet for 9 months.\(^\text{38}\) In our study nitrendipine treatment lasted only 6 weeks.

Protective effects of calcium antagonist therapy have been shown in various models of renal disease and hypertension such as renal ablation, DOCA-salt, SHR, or Ang II infusion.\(^\text{5,10,13-15,25,29,40}\) Seemingly to play important roles are cellular rather than hemodynamic mechanisms, such as cytoprotection to prevent calcium overload, or antiproliferative and platelet aggregation inhibiting effects.\(^\text{14,31}\)

However, there are some studies in which calcium antagonists caused a deterioration of renal parameters: Two groups found an increase of proteinuria in post-salt Dahl salt-sensitive rats with renal ablation and in the remnant kidney model after therapy with two different calcium antagonists.\(^\text{17,18}\) But in both studies, glomerular injury did not increase. Furthermore, Brunner et al.\(^\text{16}\) described an increase of proteinuria but also an increase of glomerular damage after verapamil in the renal ablation model, despite a decrease of systemic blood pressure. In these studies, CEI were superior in nephroprotection with equal effects on blood pressure. The different effects of CEI and calcium antagonists on progression of chronic renal disease probably are not caused solely by different efficiency to decrease systemic blood pressure. In the present study, the failure of enalapril to decrease ALB and glomerulosclerosis significantly despite its blood pressure-lowering effect could be explained by already irreversible structural glomerular damage before therapy or by the fact that the treatment period was too short.

As in animal studies, calcium channel blockers showed different effects on protein excretion in diabetic patients (for review, see Reference 41). There are data showing that structurally different calcium channel blockers may have contrasting effects on proteinuria in patients with diabetic nephropathy, since diltiazem decreased and the dihydropyridine nifedipine increased proteinuria in a recent crossover trial.\(^\text{12}\) However, in nondiabetic patients with hypertension and renal impairment, there are only a few prospective published studies comparing CEI and calcium channel blockers. Recent reports suggest that calcium antagonists like nitrendipine or other dihydropyridines may lead to an increase\(^\text{43}\) or a smaller decrease\(^\text{44,45}\) of proteinuria compared with CEI, despite similar hypotensive effects.

In summary, chronic administration of the calcium antagonist nitrendipine in rats with 2K1C Goldblatt hypertension did not control hypertension but increased albuminuria, glomerulosclerosis, and glomerular size of the nonclipped kidney, when compared with untreated hypertensive rats. Nitrendipine could have accelerated the progression of glomerulosclerosis by preglomerular dilatation and insufficient arterial blood pressure decrease, facilitating a rise of glomerular pressure. Therapy with the converting enzyme inhibitor enalapril lowered blood pressure and reduced glomerular size but did not influence albuminuria and glomerulosclerosis. Therefore, it is possible that unfavorable hemodynamic effects of calcium antagonists may override its cytoprotective effects in hypertensive models with an increased basal preglomerular resistance if a sufficient blood pressure control is not achieved.

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