Arteriolar Wall Thickening, Capillary Rarefaction and Interstitial Fibrosis in the Heart of Rats with Renal Failure: The Effects of Ramipril, Nifedipine and Moxonidine

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ABSTRACT

In experimental renal failure, increased intramyocardial arteriolar wall thickness, reduced myocardial capillary density, and increased cardiac interstitium are found. The extent to which such alterations can be modified by therapeutic interventions has not been investigated to date. The purpose of this study was to examine the effects of Ramipril, Nifedipine and Moxonidine on these structural changes. Sham-operated and subtotal nephrectomized (SNX) 300-g Sprague-Dawley rats (N = 7 to 11) were left untreated (N = 9) or treated with Ramipril (0.5 mg/kg body wt per day; N = 7), Nifedipine (30 mg/kg body wt per day; N = 9), or Moxonidine (10 mg/kg body wt per day; N = 8) for 8 wk. After perfusion fixation, heart and aorta were examined by stereological techniques. Aortic wall thickness was significantly higher in SNX than in sham-operated control rats and was similarly lowered by all three interventions. In contrast, the wall thickness of intramyocardial arterioles was significantly higher in SNX; this was prevented by Ramipril and Nifedipine, but not by Moxonidine. Intramyocardial capillary length density (Lc) was significantly lower and interstitial volume density (Vint) significantly higher in untreated SNX. Reduction of capillary length density was completely prevented by Moxonidine and in part by Ramipril. The increase in cardiac interstitial volume density was completely prevented by Ramipril and was partially prevented by Moxonidine. The following conclusions can be drawn from the results: (1) all agents normalize aortic wall thickness, but only calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors prevent intramyocardial arteriolar wall thickening; (2) intramyocardial arteriolar wall thickening, capillary rarefaction, and expansion of the cardiac interstitium are seen in SNX even after lowering the blood pressure to subnormal levels; i.e., changes in systemic blood pressure cannot completely explain the altered vascular structure in renal failure; (3) the effects of Ramipril, Nifedipine, and Moxonidine on cardiovascular structures in experimental renal failure are not completely accounted for by their hemodynamic actions.

Key Words: Short-term renal failure, ACE inhibitors, calcium channel blockers, sympatholytic treatment

Cardiac death is the leading cause of death in uremic patients (1). According to the European Dialysis and Transplantation Association and the U.S. Renal Data Registry (2,3), death from cardiac causes is 10 to 20 times more frequent in patients with chronic renal failure compared with the general population. Although coronary atherosclerosis is common in uremic patients as documented by postmortem observations (4) and coronarography (5), the high cardiac mortality in these patients cannot be explained by coronary heart disease alone. Apart from left ventricular hypertrophy (6), additional structural abnormalities of the heart are present in chronic renal failure, e.g., arteriolar thickening (7), reduced capillary density (8), and interstitial fibrosis (9). These findings contribute to myocardial ischemia, left ventricular wall stiffness, diastolic dysfunction, and arrhythmogenicity in patients with renal failure (10). These aspects are clinically important, but not widely appreciated. Angiotensin-converting enzyme (ACE) inhibitors and erythropoietin lead to regression of left ventricular hypertrophy in patients with renal failure (11,12). However, it is currently unknown to what extent arteriolar wall thickening, capillary rarefaction, and interstitial fibrosis of the heart can be modified by therapeutic interventions.

The above-mentioned structural alterations are accompanied by metabolic abnormalities, e.g., deranged control of cytosolic calcium (13) and reduced insulin-mediated glucose uptake (14). In concert with the structural abnormalities, such metabolic disturbances tend to render the heart of the uremic organism more susceptible to ischemic injury (15). Cardiac ischemia is thought to contribute, at least in part, to the high prevalence of noncoronary cardiac death in renal patients (16).

In view of the almost uniform presence of hypertensi-
sion in patients with end-stage renal failure, treatment with ACE inhibitors, calcium channel blockers, and sympatheticolytic agents is required in many patients. Whether treatment with these agents improves survival in these patients is currently unknown.

In this context the questions arise (1) whether myocardial capillary rarefaction, arteriolar thickening and interstitial fibrosis are explained by elevated blood pressure alone, and (2) whether they are prevented to a similar extent by the above-named agents used for lowering blood pressure.

Using stereological techniques, we examined the structure of the heart and the aorta of nonhypertensive uremic rats that had been treated with the ACE-inhibitor Ramipril, the dihydropyridine calcium channel blocker Nifedipine, or the central sympatheticolytic agent Moxonidine.

**MATERIAL AND METHODS**

**Animals**

Male Sprague-Dawley rats (SD, 300 g; Invanovas Co., Kisslegg/Aigäu, Germany) were housed in single cages at a constant temperature (20°C) and humidity (25%). The animals were fed a diet containing 40% protein and 0.6% NaCl (Altromin C 1002/C 1036; Altromin Co., Lage, Lippe, Germany). After 3 days of adaptation, the animals were randomly allocated to subtotal nephrectomy or sham operation. First, the right kidney was removed under ketamin/diazepam anesthesia (100 mg/kg or 2.5 μg/kg, respectively). Seven days later, the left kidney was subtotally resected by removing two-thirds of the weight of the contra-lateral part from its cortex. Sham-operation on the control animals was performed by decapsulating the kidney, taking special care not to affect the adrenal glands.

Forty-eight h after the second operation, the animals were randomly allotted to the different treatment groups. Treatment comprised the ACE-inhibitor Ramipril (2.8 mg/L in the drinking fluid; new solutions were prepared every 48 h), the calcium channel blocker Nifedipine (400 mg/kg in food pellets), taking care to prevent exposure to light, and the sympatheticolytic agent Moxonidine (130 mg/kg in food pellets). The concentrations were calculated to deliver a daily dose of 0.5 mg/kg (body weight) of Ramipril, 30 mg/kg of Nifedipine, and 10 mg/kg of Moxonidine.

Systolic blood pressure was measured under light ether anesthesia by tail plethysmography every 2 wk. Eight wk after the operation, the experiment was terminated.

**Tissue Preparation**

At the end of the experiment, the abdominal aorta was catheterized under 10% chloralhydrate anesthesia (7 mL/kg body wt ip), blood samples were taken, and the viscera were fixed by retrograde vascular perfusion at a controlled pressure of 110 mm Hg. Before fixation, the vascular system was rinsed with 10% dextran solution containing 0.5 g/L Procain-HCl for 2 min. Ten s after initiating the aortic perfusion, the vena cava was incised so that the blood could be drained. After dextran infusion, the vascular system was perfused for 12 min with 0.2 M phosphate buffer containing 3% glutaraldehyde. After the perfusion, the heart, aorta and kidneys of each animal were taken out for determination of weight and volume. Eight pieces of the left ventricular muscle, including the septum, were sampled according to the orientator method as described elsewhere (17), and embedded afterwards in Epon-Araldite. Semithin sections (1 μm) were stained with methylene-blue and basic fuchsin and examined by light microscopy with oil immersion and phase contrast at a magnification of 1000:1 and 400:1, respectively, for stereological measurement of the small intramyocardial arteries.

The aorta was cut into several 1-mm thick pieces perpendicular to the longitudinal axis, which were also embedded in Epon-Araldite and stained with methylene-blue and basic fuchsin after being sectioned in semithin portions (1 μm).

**Quantitative Stereology**

Stereological analysis was performed on random samples of differently orientated sections of the left ventricular myocardium according to the orientator method (17).

In brief, the length density (L,) of capillaries, i.e., the length of capillaries per unit tissue volume, and the volume density (V,) of cardiac nonvascular interstitium, i.e., the volume of nonvascular interstitial cells and fibers per unit myocardial tissue volume (excluding endothelial cells), were measured in eight systematically subsampled areas per section (57,600 μm²) using a Zeiss eyepiece (Zeiss, Oberkochen, Germany) with 100 points for point counting.

Volume density (Vv) was obtained according to the equation P = Vv (with P as point density) and length density (Lv) was determined using the equation Lv = 2 Q (with Q as area density, e.g., the number of capillary transsects per area of myocardial reference tissue) (17,18). Reference volume was the total myocardial tissue (exclusive of noncapillary vessels, i.e., arterioles and veins).

Intercapillary distance, i.e., the distance between the centers of two adjacent intramyocardial capillaries, was calculated according to a modification of the formula of Henquell and Honig (19), i.e.,

\[
\text{mean intercapillary distance ICD} = \sqrt{\frac{4 \times \frac{1}{\lambda}}{\sqrt{3}}},
\]

and mean capillary diameter was not subtracted. Intramyocardial small arteries/arterioles were identified according to Wiest et al. (20) as vessels having a complete layer of smooth muscle cells separated from the endothelium by a continuous basement membrane.

Wall thickness and wall and lumen area of small intramyocardial arteries were determined on eight isotropic uniform random (IUR) sections per animal at a magnification of 400:1 and phase contrast. The wall thickness and wall and lumen area were then determined by planimetry by using an automatic image analyzing system (IBAS 2; Kontron Co., Eching, Germany). The contours of the arterial profiles were marked manually with a cursor and the maximal and minimal diameter, as well as the wall and lumen area, were calculated. The wall thickness of the small intramyocardial arteries was then determined as the mean of the measurements of the two opposite walls in direction of the minimal diameter (because this is the direction where measurements are least affected by sectioning angle). The wall:lumen ratio was calculated by dividing the mean minimal diameter by the mean lumen diameter.

The media thickness of the aortic wall was also determined by planimetry by using an automatic image analyzing system (IBAS II) at a magnification of 400:1. Planimetric measurements were performed as described above.
Statistics

Data are given as mean ± SD. The Kruskal-Wallis test and one-way analysis of variance were chosen for analysis of variance, followed by the Duncan's multiple range test to determine whether the differences between the groups were significant or not. The results were considered significant when probability of error (P) was less than 0.05.

RESULTS

Description of the Model

After 8 wk of renal failure, plasma urea concentration was significantly higher in subtotally nephrectomized animals versus sham-operated control animals, and was even more elevated in Ramipril-treated SNX animals compared with untreated SNX animals (Table 1).

The animals were not anemic. Body weight was slightly, but not significantly, lower in ad libitum-fed SNX animals, but in all treatment groups it was significantly lower than in untreated SNX.

The left ventricular weight:body weight ratio was significantly higher in SNX animals and was lower in the treatment groups. With the exception of the Ramipril group, it was not normalized. The left partially resected kidney underwent compensatory hypertrophy.

Intramyocardial Arterioles

Wall:lumen ratio and wall thickness of intramyocardial arterioles were significantly higher in SNX animals compared with sham-operated animals (Table 2). Nifedipine-treated SNX animals had a significantly lower wall:lumen ratio and wall thickness; the wall:lumen ratio tended to be lower in Ramipril-treated animals, but wall thickness was significantly lower in this group.

There were no significant changes of lumen diameter in any group. To exclude sampling artefacts, we plotted the cumulative frequency of sections as a function of vessel diameter. The frequency histogram of lumen diameters is shown in Figure 1. No significant differences between groups were found. This finding excludes systematic sampling artefacts and selective rarefaction of smaller arterioles.

Figure 2 shows the cumulative frequencies of different classes of wall thickness. This figure shows a systematic shift to the right for the SNX group, indicating a higher prevalence of intramyocardial arterioles with greater wall thickness. In the SNX intervention groups, the shift was less marked, but complete normalization did not occur.

Figure 3 shows the lumen diameters of intramyocardial arterioles for different classes of wall thickness. With increasing wall thickness, lumen diameters were higher in all groups. For any given wall thickness, the lumen diameter was greater in Nifedipine-treated SNX than in untreated SNX, or in the other intervention groups, respectively.
### TABLE 2. Intramyocardial arterioles in the left ventricle by stereological analysis—comparison of different treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Wall-To-Lumen Ratio (µm/µm)</th>
<th>Lumen Diameter (µm)</th>
<th>Wall Thickness (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-Op (N = 11)</td>
<td>0.089 ± 0.014&lt;sup&gt;b&lt;/sup&gt;</td>
<td>57.1 ± 14.2</td>
<td>4.42 ± 0.99&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SNX (N = 9)</td>
<td>0.117 ± 0.025&lt;sup&gt;c&lt;/sup&gt;</td>
<td>58.7 ± 22.4</td>
<td>5.69 ± 1.11&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>SNX + Ramipril (N = 7)</td>
<td>0.103 ± 0.023</td>
<td>52.0 ± 10.5</td>
<td>4.61 ± 0.51&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SNX + Moxonidine (N = 8)</td>
<td>0.116 ± 0.028&lt;sup&gt;c&lt;/sup&gt;</td>
<td>50.5 ± 6.4</td>
<td>5.03 ± 0.99</td>
</tr>
<tr>
<td>SNX + Nifedipine (N = 9)</td>
<td>0.091 ± 0.028&lt;sup&gt;b&lt;/sup&gt;</td>
<td>62.0 ± 13.0</td>
<td>4.64 ± 0.49&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Analysis of Variance</td>
<td>P &lt; 0.025</td>
<td>NS</td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values are presented as means ± SD. Abbreviations as in the legend to Table 1.

<sup>b</sup> Significant differences versus untreated SNX.

<sup>c</sup> Significant differences versus sham-operated controls.

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### Descending Thoracic Aorta

Aortic lumen area, wall thickness, and media area were significantly greater in SNX animals compared with sham-operated animals (Table 3). The latter two parameters were consistently lower in all intervention groups whereas no significant differences were noted between the three intervention groups.

### Cardiac Capillary Length Density and Intercapillary Distances

The length density (L<sub>c</sub>) of capillaries in the left ventricular wall was significantly lower in SNX animals compared with sham-operated control rats (Table 4). Capillary length density was significantly higher in Moxonidine treated SNX than in untreated SNX. In contrast, no significant difference of L<sub>c</sub> was found between untreated SNX animals and SNX animals treated with Ramipril or Nifedipine, respectively.

The (calculated) intercapillary distances were higher in untreated SNX animals than in sham-operated control animals. Normal values were found in Moxonidine-treated SNX rats. The values in Ramipril or Nifedipine-treated SNX rats were not significantly different from those of untreated SNX animals.

### Cardiac Interstitium

The volume density (V<sub>V</sub>) of nonvascular cardiac interstitium was significantly higher in SNX animals compared with sham-operated control rats (Table 5).

Interstitial V<sub>V</sub> was significantly lower in Ramipril-treated SNX animals compared with untreated SNX animals; the values in this group were not significantly different from those of sham-operated control animals. Interstitial V<sub>V</sub> in Moxonidine or Nifedipine-treated SNX was significantly different from both untreated SNX animals and sham-operated control animals.

Figure 4A through C gives representative examples of cardiac interstitial morphology in sham-operated, SNX-, and Ramipril-treated SNX animals, respectively.

### DISCUSSION

In the study presented here, (1) increased wall thickness of intramyocardial arterioles, (2) reduced capillary length density (implying increased intercapillary diffusion distances), and (3) expansion of nonvascular cardiac interstitial volume were noted in nonhypertensive subtotally nephrectomized animals with renal failure of short duration.

Treatment with an ACE inhibitor, a calcium channel blocker, and a sympatholytic agent was initiated 48 h after the second operation to examine whether the above lesions can be prevented by early therapeutic intervention.

The effects of the agents used were not uniform: Ramipril and Nifedipine were the only agents that prevented the increase in intramyocardial arteriolar wall thickness. This finding differed from the observation in the aorta, in which lowering of blood pressure was associated with normalization of media volume, irrespective of the agent used.

With respect to intramyocardial capillary length density and intercapillary distance, values in animals treated with Moxonidine were almost completely normal; Ramipril treatment was considerably less effective and Nifedipine did not have any effect at all on capillary rarefaction and increased intercapillary distance after subtotal nephrectomy.

Finally, as far as intramyocardial interstitial volume expansion is concerned, Ramipril, but not the other two agents, was effective in completely preventing the lesion.

In summary, these observations show that in rats with experimental renal failure and modest elevation of blood pressure and serum urea concentrations, respectively, the agents have dissimilar effects on (1) the three types of structural changes observed in the heart and (2) on the changes of the aortic wall. The observation also suggests that in renal failure, specific blood pressure-independent mechanisms play a role in the genesis of these cardiovascular structural lesions.
Figure 1. Cumulative frequency of sections as a function of vessel diameter. Note that there are no significant differences between groups (see also Table 2).

Figure 2. Cumulative frequency of sections as a function of vessel wall thickness. Note the systematic shift to the right for the untreated subtotaly nephrectomized rats (SNX) and the lesser shift in the SNX intervention groups.
Effects of Ramipril, Nifedipine, and Moxonidine

We are aware of several limitations of the study. Sham-operated animals were not treated at all because previous observations in this laboratory had documented that treatment with these agents does not affect wall thickness and the wall:lumen ratio of intramyocardial arterioles and interstitial volume of the heart in control animals (9,21).

We also admit that interpretation of the results must be done cautiously, because for logistical reasons, the number of animals per group was limited (β-error).

Furthermore, we acknowledge that blood pressure in subtotaly nephrectomized animals was reduced to levels below that in sham-operated control animals. This was done intentionally because we wanted to exclude beyond doubt that different effects of the three agents were related to different degrees of blood pressure control. Substantial lowering of blood pressure was also a safeguard against the known effects of intermittent elevation of blood pressure in subtotaly nephrectomized animals (22). It is interesting to note, however, that the left ventricular weight:body weight ratio was not completely normalized by the interventions, with the notable exception of Ramipril. We emphasize that the interpretation of the absolute figures has to take into consideration the fact the heart had been perfusion-fixed. This precludes comparison with previous work in which the left ventricular weight:body weight ratio was calculated from the nonperfused organ (23).

**TABLE 3. Wall of descending thoracic aorta by stereological analysis—comparison of different treatments**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Lumen Area (mm²)</th>
<th>Wall Thickness (mm)</th>
<th>Media Area (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-Op (N = 11)</td>
<td>2.98 ± 0.37⁹⁵</td>
<td>0.088 ± 0.009⁵</td>
<td>0.56 ± 0.06⁵</td>
</tr>
<tr>
<td>SNX (N = 8)</td>
<td>3.58 ± 0.36⁶</td>
<td>0.102 ± 0.020⁶</td>
<td>0.72 ± 0.17⁶</td>
</tr>
<tr>
<td>SNX + Ramipril (N = 6)</td>
<td>3.17 ± 0.38</td>
<td>0.084 ± 0.009⁶</td>
<td>0.56 ± 0.07⁶</td>
</tr>
<tr>
<td>SNX + Moxonidine (N = 6)</td>
<td>2.81 ± 0.39⁹⁵</td>
<td>0.089 ± 0.011⁹⁵</td>
<td>0.55 ± 0.07⁹⁵</td>
</tr>
<tr>
<td>SNX + Nifedipine (N = 7)</td>
<td>3.24 ± 0.47</td>
<td>0.084 ± 0.010⁶</td>
<td>0.56 ± 0.10⁶</td>
</tr>
<tr>
<td>Analysis of Variance</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.05</td>
<td>P &lt; 0.01</td>
</tr>
</tbody>
</table>

⁹⁵ Values are presented as means ± SD. Abbreviations as in Table 1.
⁹⁶ Significant differences versus untreated SNX.
⁹⁷ Significant differences versus sham-operated controls.
Presumably because of disturbed renal autoregulation after subtotal nephrectomy, plasma urea concentrations tended to be higher in the subtotally nephrectomized groups with lowering of blood pressure to subnormal values. We emphasize that these subtotally nephrectomized animals were not in advanced terminal uremia. The presence of cardiac abnormalities even at a stage of only modest elevation of urea notable in view of past observations that the frequency of cardiac events is higher even in early renal failure (24).

The use of multiple parallel groups precluded a pairfeeding protocol. Animals were given free access to food and consequently differed with respect to final body weight. Lower final body weight in treated animals went in parallel with more marked rise in plasma urea concentration in the treated subtotally nephrectomized animals.

The study presented here confirms that wall thickening of intramyocardial arterioles occurs in animals with renal failure of short duration despite lowering of blood pressure to subnormal values. This is in agreement with the previous findings of our laboratory (7) and of Kakinuma et al. (25). In these studies in uremic animals, arteriolar wall thickening could be clearly dissociated from elevated blood pressure. The finding of increased wall thickness of intramyocardial arte-
riebes itself does not permit to distinguish whether thickening is the result of hypertrophy, hyperplasia, or remodeling (26,27), even if the finding of increased wall thickness in the presence of unchanged lumen diameters argues against remodelling. It is notable that the finding of vessel wall thickening is not explained by blood pressure elevation alone and this is in agreement with findings in patients with renal disease where abnormalities of the carotid wall and elastic properties were more pronounced in uremic subjects than in patients with primary hypertension (28).

Our results are in accordance with those previously obtained by Kakinuma et al. (25), although these authors studied renal failure in a model of renal vascular ligation, a known high-renin model of renal damage (29). It is known that surgical resection of the kidney causes considerably less activation of the renin-angiotensin system. In the study of Kakinuma et al., reversal of established vascular hypertrophy was more efficacious with ACE inhibitors than with other antihypertensive agents (25).

It is remarkable that the differential response of intramyocardial arteriololes (resistance vessels) to blood pressure lowering with various agents differed strikingly from that of the aorta (elastic vessel): aortic media volume was significantly lower in all of the treated groups, irrespective of which agent was used.

The study presented here also confirms the previous finding of reduced cardiac capillary density after 1 yr of uremia (8) and extends this observation by documenting that in growing animals this effect is noted as early as 8 wk after subtotal nephrectomy. In spontaneously hypertensive rats (SHR), Nifedipine increased capillary length density (21), possibly as a result of anglogenesis triggered by vasodilation. In contrast, in the study presented here on subtotally nephrectomized rats, capillary length density was not affected by Nifedipine, whereas it was significantly higher after treatment of SNX rats by the central sympatholytic agent Moxonidine. The mechanisms leading to the reduction of capillary density in the heart have not been elucidated. Reasonable working hypotheses would include a role of factors involved in capillarogenesis, e.g., bFGF or VEGF. Abnormalities in tissue oxygen sensing (which is thought to monitor the need of the tissue to generate capillaries), an idea based on the demonstration of the oxygen sensing sequences of the promoter region of the erythropoietin gene in extrarenal and extrahepatic tissue (30)) and others.

The unique efficacy of the sympatholytic agent Moxonidine, but not Nifedipine, on capillary density of the heart, would be compatible with a specific inhibitory role of sympathetic nerve traffic on heart capillarization in renal failure. Capillary growth in the heart of SHR and Wistar-Kyoto control rats was significantly stimulated by sympathectomy in the study of Torrey et al. (31). This agrees with previous observations in SHR (21): low doses of Moxonidine, which failed to lower blood pressure, increased capillary length density in the heart. Furthermore, recent studies (32) showed that renal failure after subtotal nephrectomy is a state of excess sympathetic activity triggered by afferent signals generated in the damaged kidneys (33). Reduced capillarization of the heart may compromise cardiac ischemia tolerance by increasing intercapillary oxygen diffusion distances, i.e., the distance between the centers of two adjacent intramyocardial capillaries. This increase in intercapillary distance is not only the result of capillary rarefaction, i.e., diminution of the number of capillaries per volume myocardial tissue, but is also the result of myocyte hypertrophy and expansion of the myocardial nonvascular interstitium. Increased intramyocardial intercapillary distance impedes myocardial oxygen traffic from the capillaries to the myocytes, thus compromising myocardial ischemia tolerance. If the finding of increased intramyocardial intercapillary distances can be extrapolated to humans, it would provide a strong argument for the correction of anemia of renal failure.

In contrast to a previous study (9), intramyocardial interstitial volume density and left ventricular mass were significantly lower in Ramipril-treated SNX rats. Similar results were recently reported by Suzuki and coworkers (34). The difference in our previous study may be explained by the more marked interstitial fibrosis in the experiment presented here (3.5 versus 1.5% in the previous experiment), and more importantly by the exclusion of endothelial cells when measuring intramyocardial interstitial volume. The inclusion of endothelial cells may have obscured an underlying difference in the previous study. It should also be mentioned that in the previous experiment (9), treated blood pressure was significantly higher than that in the study presented here. Interstitial fibrosis in subtotally nephrectomized rats is associated with an activation of interstitial fibroblasts as assessed by measurements of cytoplasm and nuclear volume and ultrastructural investigations (35). The net increase of intramyocardial interstitial volume points to an imbalance between synthesis and degradation of extracellular matrix but this has not been investigated in detail. In this context, it is interesting to note that ACE inhibition increases protease activity in renal failure (34), and that low doses of Lisinopril, which did not lower blood pressure, reversed intramyocardial interstitial fibrosis in rats with renovascular hypertension (36). Thus, expansion of intramyocardial interstitial tissue volume in renal failure might be the result of permissive effects of the local renin-angiotensin system, parathyroid hormone (35), accumulation of advanced glycosylation end products, or of modified extracellular matrix proteins. A role of myocardial ischemia per se in the genesis of cardiac interstitial volume expansion in renal failure is also a possibility, although we did not observe reparative processes as a result of myocyte degeneration or death in our short-term experiment.

In summary, the above results document (I) that Ramipril, Nifedipine, and Moxonidine have different
effects on abnormal cardiac structure in uremic animals, and (2) that these effects are not explained by the changes in blood pressure.

It is difficult to determine to what extent these experimental data can be extrapolated to humans. Not only might there be species differences, but one must also consider that the experiment presented here was a prevention study, whereas in clinical practice, antihypertensive agents are usually given to patients with established structural abnormalities of the heart. Nevertheless, this study shows that some structural abnormalities of the heart can be prevented, at least in part, by antihypertensive agents.

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