Angiotensin Converting Enzyme Inhibition Prevents the Increase in Aortic Collagen in Rats

Pierre Albaladejo, Hervé Bouaziz, Micheline Duriez, Peter Gohlke, Bernard I. Levy, Michel E. Safar, Athanase Benetos

Abstract
Four groups of 4-week-old spontaneously hypertensive rats were treated during 4 months with the angiotensin converting enzyme inhibitor quinapril at 1 mg/kg per day (Q1) or 10 mg/kg per day (Q10), hydralazine at 15 mg/kg per day (H), or placebo (P). In the first set of experiments, blood pressure was measured in conscious rats, and plasma and aortic angiotensin converting enzyme activities were evaluated. In the second set of experiments, histomorphometric parameters of the thoracic aorta were evaluated. Mean blood pressure was lower in the Q10 and H groups (136±16 and 149±11 mm Hg) compared with the P group (190±23 mm Hg) (P<.01). The Q1 group showed mean blood pressure values (171±15 mm Hg) lower than the P group (P<.05) but significantly higher than the Q10 and H groups (P<.01 and P<.05, respectively). Aortic medial cross-sectional area was significantly lower in the H and Q10 groups (455±61 and 487±57 x 10³ μm²) than in the P group (636±72 x 10³ μm²) (P<.001). In the Q1 group, medial cross-sectional area was lower (550±65 x 10³ μm²) than the P group (P<.01) but higher than the Q10 and H groups. In the Q10 and Q1 groups, the collagen content of the aortic media was significantly lower than in the two other groups (P<.01) (Q1, 15.3±4.6; Q10, 14.3±4.0; H, 18.6±5.0; P, 21.9±4.7 x 10³ μm²/mm of aorta). Aortic angiotensin converting enzyme activity was inhibited by approximately 60% in both groups treated with quinapril, whereas plasma angiotensin converting enzyme activity was reduced only in the Q10 rats. These results show that, whereas both hydralazine and quinapril prevented the development of aortic hypertrophy in a pressure-dependent manner, the prevention of the increase in aortic collagen was observed only after quinapril treatment. This latter effect of angiotensin converting enzyme inhibition was not related to the blood pressure reduction but was associated with the reduction of aortic and not plasma converting enzyme. (Hypertension. 1994;23:74-82.)

Key Words • collagen • hypertrophy • hydralazine • rats, inbred SHR

Large-artery walls become thicker and stiffer in hypertension. Together with vascular smooth muscle cell hypertrophy, an increase in medial extracellular matrix involving principally collagen is also a major pathological and biochemical finding in hypertension.

A large amount of evidence shows that structural alterations of the arterial wall in hypertension may be partly attributed to elevated pressure and wall stress. Thus, many investigators suggest that hypertrophy is an adaptive mechanism to normalize wall stress during hypertension. Increasing evidence suggests a major role of the renin-angiotensin system and especially angiotensin II (Ang II) in these nonpressure mechanisms: (1) components of the renin-angiotensin system are present in the vascular wall, where Ang II induces hypertrophy and collagen production in vascular smooth muscle cell cultures, and (3) in vivo administration of nonpressor doses of Ang II induces arterial thickening.

Angiotensin converting enzyme (ACE) inhibitors seem to be more effective than other drugs in the regression or prevention of these arterial alterations. These observations are consistent with the possibility that ACE inhibitors have specific effects on vascular structure independent of their antihypertensive action. However, the respective roles of blood pressure reduction and/or ACE inhibition on the prevention of arterial structural alterations remain unclear. In addition, smooth muscle cells, collagen, and elastin may be influenced in different manners by blood pressure reduction, ACE inhibition, or both.

Thus, the aim of this study was to evaluate the respective roles of a decrease in blood pressure and ACE inhibition on the prevention of aortic structural alterations in spontaneously hypertensive rats (SHR). Therefore, hypertensive rats were treated for 4 months with two different doses of the ACE inhibitor quinapril (1 and 10 mg/kg), with only the higher dose having a substantial antihypertensive effect. We have compared the effects of these treatments with those of hydralazine at antihypertensive doses equipotent to the higher dose of quinapril.

Methods

Animals
Four-week-old male SHR (Iffa-Credo, L'Abresle, France) were randomly allocated into four groups. They were housed five to seven per cage in our animal room (temperature, 20° to 22°C; humidity, 55% to 65%; 12-hour light/dark cycle), fed a standard diet (0.13 mEq/g Na⁺ and 0.205 mEq/g K⁺), and had free access to tap water.
Treatments

The different treatments were administered daily by gavage during 16 weeks. Groups Q10 and Q1 received, respectively, 10 and 1 mg/kg per day of quinapril (Parke-Davis) diluted in saline solution; group H received 15 mg/kg per day of hydralazine (Sigma Chemical Co, St Louis, Mo) diluted in saline solution; and group P received saline solution (placebo). The volumes administered were similar in the four groups and did not exceed 0.5 mL/100 g body wt per day.

The hydralazine dose was found in a short study to exert a similar hypotensive effect as 10 mg/kg quinapril. For that study, 10 SHR were divided into two groups of 5 rats each. The first group received quinapril at a dose of 10 mg/kg for 3 days, and the second group received only saline solution. We chose to measure blood pressure 20 to 24 hours after each drug administration. After this procedure the dose of 15 mg/kg hydralazine was chosen because it had an antihypertensive effect similar to that of 10 mg/kg quinapril. Because it had an antihypertensive effect similar to that of 10 mg/kg quinapril, after the determination of this dose, rats were treated for 2 weeks. At the end of this period the animals were cannulated with a femoral catheter. Mean blood pressure (MBP) was then evaluated invasively in conscious rats 3 and 24 hours after the last drug administration. The differences observed between the two groups did not exceed 10 mm Hg for both peak and trough antihypertensive effect.

The two doses of quinapril (10 and 1 mg/kg) decrease by more than 90% plasma and aortic ACE activities. In the second set of experiments, the animals were then allowed to recover for 24 hours. Then 3 mL of blood was drawn from the femoral catheter. After centrifugation, plasma samples were stored at −20°C. The rats were killed by a blow on the head, and the thoracic aorta was removed and rapidly cleaned of blood with saline. After freezing in liquid nitrogen, the samples of aorta were stored at −20°C until the assay was performed. Plasma ACE activity was measured in all rats included in the first set of experiments. For technical reasons, aortic ACE activity was measured in 6, 7, 6, and 7 rats of the P, Q1, Q10, and H groups, respectively.

ACE activity in plasma and aortic homogenates was determined by a modified fluorometric assay as described by Depierre and Roth27 using carbobenzoxyphenylalanyl-histidyl-leucine as substrate. The assay conditions have been described previously in detail.28

Morphological Study

In a second set of experiments, histomorphological vascular parameters were measured at 20 weeks of age29 according to the following procedure. The animals were anesthetized with pentobarbital, a catheter was placed in the abdominal aorta through the femoral artery, and MBP was measured. After median thoracotomy, the animals were exsanguinated by means of a catheter placed in the right atrium, and saline was injected into the femoral catheter. When the liquid coming from the atrium was clear, the circulatory tract was rinsed with a 4% formaldehyde solution. The animals died within seconds after the beginning of the formaldehyde infusion. After 1 or 2 minutes, a clamp was positioned on the atrium, and the formaldehyde solution was infused for 3 hours at a pressure equal to the MBP of each animal.30 At the end of the perfusion, the thoracic aorta was dissected and preserved in a 4% formaldehyde solution until the histological study was performed.

The different structures of the aortic media were studied in a segment of thoracic aorta longitudinally embedded in paraffin. Three successive sagittal sections of 5 μm thickness were treated by specific staining to obtain a monochromatic color associated with the various structures studied in the aortic media. Sirius red was used for collagen staining, orcein for elastin, and hematoxylin after periodic acid oxidation for nucleus staining. Morphometric analysis was performed with a specialized automated image processor (NS 15000, Nachet-Vision, Paris, France). This processor is based on morphological mathematic principles and is software controlled. Different algorithms were developed to analyze each of the specific structures shown by the staining in each of the three successive sections. For image processing, the image is sent to the processor via a video camera and can be viewed on the TV monitor. The control of luminosity is automatically adjusted by the software to obtain similar contrasts, taking into account the total luminosity transmitted by the video camera. This
analog image is then digitized as follows: Each elementary point (pixel) is automatically compared with a threshold; if the gray level of a pixel exceeds this threshold, the pixel is given the numeric value 1, otherwise it is given the numeric value 0. Threshold determination is a complex operation mainly involving pixel ensembles. Threshold parameters are the size of such pixel groups and their local contrast (top-hat transformation). The threshold is determined using the top-hat algorithm to minimize variations in nuclear staining and background. For data processing, this binary image is then processed to (1) eliminate background and artifacts, (2) delineate the zones of interest and reference zone, and (3) extract and measure the parameters from the various zones of interest.

The first algorithm permitted the analysis of the mean media thickness by measurement of the distance between the internal and external elastic laminae. The medial elastin network was analyzed in terms of relative area and mean thickness of elastin lamella and lamina; the measurements and calculations were made in 10 fields in each section. The second algorithm analyzed the collagen matrix by measurement of relative area density and mean thickness of collagen fibers in 20 contiguous fields in each Sirius red-stained section. Elastin and collagen densities were defined as the ratio of the surface stained by orcein or Sirius red, respectively, to the surface of the studied field. The third algorithm counted the number of nuclei within 20 fields of a 7442-μm² area of measurement in each section and measured the mean area of each nucleus. A two-step procedure (conditional opening then conditional closing) leads to the elimination of all particles under a predetermined size. The final result is retention of the images of the nuclei without any "holes" or deformations because of the structuring element (hexagon). The image processor automatically eliminates "borderline" nuclei before making the measurement of the number of nuclei per unit of surface. Repetitive measurements were performed, pooled, and averaged for the three algorithms in the corresponding stained sections of the aortic wall media of each animal. Results were stored on a floppy disk.

The measurement of media and lumen cross-sectional area (CSA) was performed in samples of the same thoracic aorta included in a gel used for the low-temperature sections (medium of inclusion, ISOSYSTEM) and cooled at -20°C. When the gel was solidified, some transverse sections of the arterial rings were realized in each sample. The sections were examined with a microscope and photographed at a known magnification (×48). When the films were developed, the pictures obtained were projected on a digitizer so that the surface of the vascular lumen and the external surface of the vessel could be measured. The final magnification used (magnification of the microscope×enlargement of the projector) was 160. For each sample, the collected results were the CSA of the vascular media and lumen. This last parameter reflects the degree of arterial hypertrophy better than medial thickness. Different studies have shown that the CSA of the arterial media is the most reliable constant of the vessel wall because it is not influenced by the variations of perfusion pressure.11,12 Morphological analyses were performed twice in a blind fashion by two independent workers.

Statistical Analysis
Results are expressed as mean±1 SD. Data were analyzed with a one-way analysis of variance. When F was less than 0.05, a Fisher test was performed for intergroup comparison.

The aortic ACE activity was analyzed by a nonparametric test of variance (Kruskal-Wallis) followed by a Wilcoxon test. This test was chosen because of the number of studied samples in two of four groups (less than seven per group).

Results
Fig 1 shows the evolution of body weight in the four groups. Q10-treated animals showed a trend toward lower body weight, but this difference did not reach a significant level.

Fig 2 shows the longitudinal changes in SBP evaluated with a tail-cuff method in the four groups at 8, 12, and 16 weeks of age. SBP increase was significantly prevented in the Q10 and H groups from the 12th week of age. The lack of difference at the eighth week may be related to the important variability of the values in younger rats.
Table 1 shows MBP and heart rate measured in conscious animals. In the P group, hypertension was fully developed (190±23 mm Hg), whereas in the H and Q10 groups, hypertension was substantially prevented in a similar way (149±11 and 136±16 mm Hg, respectively). In the Q1 group, MBP was slightly but significantly lower (171±15 mm Hg) than in the P group (P<.05) but higher than in the H and Q10 groups (P<.01 and P<.05, respectively). There were no significant differences among groups concerning heart rate measured 24 hours after the last drug administration.

As shown in Table 1, the pressor response to Ang I injection was significantly (P<.01) decreased in the Q10 rats compared with the three other groups. In Q1 rats, the response was slightly decreased compared with the P group, but this difference did not reach a significant level. The response to Ang II injection was similar in all groups (Table 1).

Aortic media CSA was lower in the H and Q10 groups (455±61 and 487±57 × 10^3 μm^2) compared with the P and Q1 groups (636±72 and 550±65 × 10^3 μm^2) (P<.001). There was a significant difference between the P and Q1 groups (P<.01) (Fig 3). There were no significant differences in internal lumen CSA among the four rat groups (P, 2544±278; Q1, 2474±335; Q10, 2274±326; H, 2499±417 × 10^3 μm^2).

Table 2 summarizes the histomorphometric data. Collagen content was similar in both groups treated with quinapril and significantly lower (P<.01) than in the two other groups (Table 2 and Fig 4). A difference of approximately 185% was observed for the elastin media content between the Q10 and P groups (Table 2). This difference was not significant (F=0.10). The nuclei density (number per field) was increased in all treated groups compared with the placebo-treated animals. The increase was more pronounced in the hydralazine-treated animals (H>Q10=Q1>P) (Table 2). Nuclei content was not modified by the different treatments.

Plasma ACE activity was inhibited by 47% in the Q10 group (P<.01), whereas in the Q1 group, no significant difference was observed compared with the P and H groups (Fig 5).

Table 1. Blood Pressure, Heart Rate, and Pressure Response to Angiotensin I and II in Conscious Rats After 4 Months of Treatment

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>Q1</th>
<th>Q10</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>11</td>
<td>9</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>190±23</td>
<td>171±15*</td>
<td>136±16†</td>
<td>149±11§</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>373±47</td>
<td>387±38</td>
<td>374±28</td>
<td>363±35</td>
</tr>
<tr>
<td>Ang I: ΔMBP, mm Hg</td>
<td>26±7</td>
<td>19±10</td>
<td>10±7†§</td>
<td>25±7</td>
</tr>
<tr>
<td>Ang II: ΔMBP, mm Hg</td>
<td>43±7</td>
<td>44±17</td>
<td>39±12</td>
<td>44±8</td>
</tr>
</tbody>
</table>

P indicates placebo; Q1, 1 mg/kg quinapril; Q10, 10 mg/kg quinapril; H, 15 mg/kg hydralazine; MBP, mean blood pressure; HR, heart rate; bpm, beats per minute; Ang I, angiotensin I; Ang II, angiotensin II; and ΔMBP, maximum change in mean blood pressure. Values are mean±SD; n is number of animals.

*P<.05, †P<.01 vs P.
‡P<.01, §P<.05 vs Q1.
||P<.01 vs H.
Aortic ACE activity was significantly ($P<.01$) reduced in both groups treated with quinapril: 59% in Q1 and 61% in Q10 rats (Fig 6). Hydralazine treatment did not affect this parameter.

Discussion

In this study, both hydralazine and 10 mg/kg per day quinapril administered daily for 4 months prevented the development of high blood pressure in SHR. In these two groups, MBP was approximately 40 mm Hg lower than in the P group. The MBP values observed with 10 mg/kg quinapril were comparable to those reported in other experimental studies using quinapril or other ACE inhibitors. Aortic ACE activity was significantly ($P<.01$) reduced in both groups treated with quinapril: 59% in Q1 and 61% in Q10 rats (Fig 6). Hydralazine treatment did not affect this parameter.

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Based on CSA measurements, aortic hypertrophy was prevented to a similar degree in the groups treated with quinapril at 1 and 10 mg/kg doses compared to the placebo group. Hydralazine treatment also showed a similar effect in reducing aortic media thickness and collagen content compared to the placebo group.

**Table 2.** Histomorphometric Parameters of Thoracic Aorta After 4 Months of Treatment

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>Q1</th>
<th>Q10</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Media thickness, $\mu$m</td>
<td>125±19</td>
<td>115±9</td>
<td>101±12*+</td>
<td>99±13+*</td>
</tr>
<tr>
<td>Elastin content, $10^3$/mm</td>
<td>29.1±6.5</td>
<td>26.2±4.9</td>
<td>23.8±3.4</td>
<td>27.2±4.1</td>
</tr>
<tr>
<td>Collagen density, %</td>
<td>17.6±3.9</td>
<td>12.7±3.6§</td>
<td>14.3±4.1</td>
<td></td>
</tr>
<tr>
<td>Thickness of collagen fiber, $\mu$m</td>
<td>1.75±0.2</td>
<td>1.6±0.2</td>
<td>1.7±0.2</td>
<td>1.75±0.2</td>
</tr>
<tr>
<td>Collagen content, $10^3$/mm</td>
<td>21.9±4.7</td>
<td>15.3±4.6*</td>
<td>14.3±4.0</td>
<td></td>
</tr>
<tr>
<td>Nuclei density, No. per field</td>
<td>10.3±1.8</td>
<td>14.6±4.8§</td>
<td>15.5±3.6</td>
<td></td>
</tr>
<tr>
<td>Nuclei content, per mm</td>
<td>240±58</td>
<td>292±59</td>
<td>291±67</td>
<td>322±58</td>
</tr>
</tbody>
</table>

*P indicates placebo; Q1, 1 mg/kg quinapril; Q10, 10 mg/kg quinapril; and H, hydralazine. Values are mean±SD; n is number of animals.

*P<.01, §P<.05 vs P. 
**P<.01, †P<.05 vs Q1. 
§P<.01, †P<.05 vs H.

Aortic ACE activity was significantly ($P<.01$) reduced in both groups treated with quinapril: 59% in Q1 and 61% in Q10 rats (Fig 6). Hydralazine treatment did not affect this parameter.

The principal goal of our study was to evaluate the effects of preventive treatment on the histomorphological parameters of the aorta. The pressure perfusion fixation technique was used as a physiological method enabling the evaluation of the physiological medial and luminal dimensions. A 3-hour fixation with formaldehyde was performed to avoid tissue deformation when transmural pressure is released. For reasons explained in “Methods,” the CSA rather than the thickness of the aortic media was chosen for evaluation of arterial hypertrophy. In the present study, the placebo-treated animals developed, as expected, significant medial aortic hypertrophy, with CSA values comparable to those observed in SHR of the same age.

Based on CSA measurements, aortic hypertrophy was prevented to a similar degree in the groups treated with quinapril at 1 and 10 mg/kg doses compared to the placebo group. Hydralazine treatment also showed a similar effect in reducing aortic media thickness and collagen content compared to the placebo group.
hydralazine or a high dose of quinapril, whereas in the Q1 group the effect on these parameters was less significant. Thus, the differences among the four groups were parallel to those observed for MBP. These findings strongly suggest that in this experimental model of hypertension, elevated blood pressure is the main factor involved in the development of aortic medial hypertrophy. Similar findings have been shown previously by other authors.20,34

Hydralazine has been reported to be less effective than ACE inhibitors in preventing arterial hypertrophy.36,37 In SHR, hydralazine was not able to prevent the development of mesenteric or renal artery hypertrophy despite a significant decrease in blood pressure.37,38 However, Owens34 showed that in the aorta the efficacy of hydralazine and captopril in preventing the development of medial hypertrophy was the same as their efficacy in lowering blood pressure. These discrepancies are consistent with the observation that the aorta, a rather elastic artery, is mainly sensitive to blood pressure changes, whereas in peripheral arteries, which are rather muscular, hypertrophy may be modulated mainly by nonhemodynamic factors such as autonomic nervous system activity. Therefore, stimulation of this system after hydralazine administration could be responsible for the lack of an antihypertrophic effect at the side of the peripheral arteries. One may further add that medial thickening in the aorta is mainly due to cellular hypertrophy, whereas in mesenteric arteries hyperplasia rather than hypertrophy occurs. These observations can explain the differences reported between hydralazine and other antihypertensive drugs20,34,37,38 and suggest that caution is required when results are extrapolated from one artery to another.
Aortic ACE activity

\[ \text{nMol His-Leu/min/ml} \]

\[
\begin{array}{c}
\text{PLACEBO} \\
\text{QUINAPRIL 1mg/kg} \\
\text{QUINAPRIL 10 mg/kg} \\
\text{HYDRALAZINE 15 mg/kg}
\end{array}
\]

\[ \uparrow p<0.05 \text{ vs. P; } \uparrow \uparrow p<0.05 \text{ vs. H} \]

In the present study the antihypertrophic effect of the drugs also was shown by the significant increase in aortic wall nuclei density. It is known that chronic experimental hypertension is associated with a significant decrease in the relative number of nuclei, reflecting an increased size of vascular smooth muscle cells.\(^1\) In contrast, the increase in nuclei density is consistent with a decrease in smooth muscle cell size. A similar increase in the number of nuclei after treatment with quinapril has been reported by Richer et al.\(^2\)

Taken together, these findings provide clear evidence that in SHR, when treatment started before the development of genetic hypertension, hydralazine and quinapril prevented aortic hypertrophy in a manner parallel to prevention of high blood pressure development. This effect was principally due to a reduction in arterial smooth muscle cell size.

Together with vascular smooth muscle cell hypertrophy, an increase in arterial medial extracellular matrix produced by vascular smooth muscle cells is one of the major findings of hypertensive arterial structure. Aging and chronic hypertension induce a significant increase in extracellular matrix, especially in its collagen content.\(^3\) In the normotensive rat, accumulation of elastin and collagen in the aorta occurs mainly during the first 10 to 12 weeks of life.\(^3\) Although the increase in arterial collagen content seems to be partly related to elevated blood pressure, other factors have been found to stimulate collagen synthesis in hypertensive animals. More specifically, Ang II receptor stimulation is able to increase collagen synthesis by acting directly on smooth muscle cells.\(^4\) In hypertensive animals, arterial collagen accumulation is prevented by ACE inhibitors when used at antihypertensive doses.\(^5\) In normotensive animals, early treatment with ACE inhibitors was able to slow the age-related collagen accumulation in the arterial wall.\(^6\)

In our study, there is a clear dissociation between blood pressure levels and collagen content in the different groups. Whereas hydralazine and high-dose quinapril substantially prevented development of high blood pressure, the accumulation of collagen in the arterial wall was hindered only in rats treated with quinapril and not in those treated with hydralazine. In the two groups treated with quinapril, similar values of arterial collagen content were found, despite different blood pressure profiles. In this respect, two hypotheses can be made: (1) hydralazine increased the collagen content by a direct effect or through sympathetic stimulation countering the beneficial effect of lowering blood pressure, and (2) quinapril has a specific action on collagen accumulation. Although the first hypothesis cannot be eliminated, the observed results with a low dose of quinapril suggest an effect of ACE inhibitors on aortic collagen turnover.

In the present study we cannot conclude whether the observed effects on collagen accumulation are related to an inhibition of the normal maturation process or to the hypertension-induced collagen increase because we did not study normotensive controls. However, this point is very difficult to elucidate because hypertension and aging have synergic effects on cardiovascular structure, and one cannot separate the effects of these two factors. Moreover, important genetic differences between SHR and their normotensive controls would impair the interpretation of such a comparison. Taking into consideration these limitations, the present study shows that factors other than pressure are involved in the prevention of hypertension-induced arterial collagen accumulation.

Recently, Himeno et al\(^\text{41}\) showed that a nonhypotensive dose of quinapril was able to reverse the fibronectin mRNA expression induced by Ang I. Also, ACE inhibitors have been shown to be able to decrease arterial collagen content in prevention and regression studies.\(^3\) However, our study is the first to our knowledge to clearly demonstrate that in hypertensive rats this effect may be mediated through blood pressure-independent factors.

An important finding of the present study was that both doses of quinapril decreased aortic ACE activity to the same extent, whereas only the high dose of quinapril
blocked plasma ACE activity 20 to 24 hours after the last drug administration. This result differs from previously reported data in which ACE activity was evaluated after a single dose of ACE inhibitor and not after chronic treatment. Fabris et al. studied the time course of plasma and tissue ACE inhibition after a single dose of 0.3 mg/kg quinapril. The highest ACE inhibition in plasma and aorta occurred 2 hours after the drug administration. After 24 hours, ACE was still inhibited by 25% in plasma and by 30% in the aorta. In our study, the lack of inhibition of plasma ACE in the Q1 group was confirmed by the absence of changes in the Ang I pressure response compared with the P group. In Q10-treated rats, ACE activity and response to Ang I injections were decreased by approximately 50% compared with the P group. Unger et al. showed that after chronic treatment with angiotensin-converting enzyme (ACE) inhibitors, tissue ACE activity was significantly inhibited several days after the discontinuation of the drugs, whereas plasma ACE activity and the pressor response to Ang I returned to pretreatment levels 24 hours after drug withdrawal. Our study shows a significant inhibition of aortic ACE activity even at nonhypotensive doses of quinapril. This effect may be related to the high affinity of this compound for the tissue ACE as shown in binding studies. Taken together, the results of our study strongly suggest that the prevention of aortic collagen accumulation is not related to blood pressure levels but rather to the inhibition of ACE activity. Our study cannot clarify whether tissue Ang II inhibition, bradykinin activation, or other mechanisms are responsible for these effects on arterial structure. Further investigations are needed to define the exact mechanisms of this action.

In conclusion, the present study clearly demonstrates differences in the factors influencing aortic structural parameters during chronic hypertension. Thus, aortic hypertrophy and smooth muscle cell size were mainly dependent on blood pressure levels, whereas collagen accumulation occurred even when hypertension development was prevented, as was the case in the hydralazine group. On the other hand, chronic ACE inhibition prevented collagen accumulation even when hypertension developed, as shown in the low-dose quinapril group.

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