Captopril Reduces Aortic and Microvascular Growth in Hypertensive and Normotensive Rats

Duo-Hui Wang and Russell L. Prewitt

This experiment was designed to investigate the effect of converting enzyme inhibition on functional and structural vascular alterations in one-kidney, one clip hypertensive rats and in normotensive rats. Starting 1 day before surgery, 100 mg/kg/day captopril was given chronically to half of the hypertensive and normotensive groups in their drinking water. With use of intravital microscopy in the cremaster muscle, arteriolar dimensions were measured 4 weeks later, both before and after topical application of $10^{-3}$ M adenosine. Mean blood pressure was 124 ± 4 mm Hg in control rats and 103 ± 5 mm Hg in captopril-treated control rats ($p < 0.05$). Mean blood pressure was significantly elevated to 183 ± 5 mm Hg in captopril-treated one-kidney, one clip hypertensive rats and 193 ± 5 mm Hg in one-kidney, one clip hypertensive rats. With use of histological techniques, a marked reduction of medial-intimal area of the abdominal aorta was found in captopril-treated control rats (24%), and hypertrophy of the aortic wall in one-kidney, one clip hypertensive rats was decreased 26% by captopril. Structural diameter reductions occurred in large arterioles of the captopril-treated control and hypertensive groups and the nontreated hypertensive group. In spite of a significant increase in wall-to-lumen ratio of first-order arterioles in all captopril-treated rats, captopril decreased cross-sectional wall area of these vessels 37% in hypertensive and 20% in control rats, respectively. Measured by stereological techniques, small arteriolar density decreased 30% in captopril-treated hypertensive rats and 17% in captopril-treated control rats. Therefore, smaller arteriolar lumens, decreased aortic and arteriolar cross-sectional wall area, and arteriolar rarefaction after converting enzyme inhibition, in spite of rising or falling blood pressure, are evidence that vascular growth was inhibited in vivo. (Hypertension 1990;15:68-77)

The influence of angiotensin II (Ang II) on vascular structure has been widely studied. Ang II has been shown to stimulate DNA and protein synthesis in cardiovascular tissue and induce hypertrophy without cellular proliferation in cultured rat aortic smooth muscle cells (SMCs) maintained in a defined serum-free medium. Ang II also increased growth rates and cell size in cultured human SMCs grown in the presence of serum. However, all of these were in vitro studies. In vivo, captopril not only lowered blood pressure, but was more effective than hydralazine and propranolol in preventing increases in aortic SMC content, medial SMC weight, and percentage of polyploid SMCs in spontaneously hypertensive rats (SHR). SMC volume was also reduced in captopril-treated SHR and Wistar-Kyoto (WKY) rats. In mesenteric arteries, captopril induced a long-lasting decrease in wall-to-lumen (W/L) ratio in SHR and simultaneously induced long-lasting decreases in myocardial and aortic wall hypertrophy that persisted up to 7 weeks after treatment withdrawal. Recently, converting enzyme inhibition in two-kidney, one clip hypertensive rats reversed hypertrophy of aortic SMCs without regression of the increased absolute amount of collagen content.

Other observations show that after renal ischemia, the renin-angiotensin system, independent of its hypertensive effect, restores blood flow to tissues below an aortic ligature by stimulating the development of a collateral circulation. Furthermore, implantation of Ang II in the avascular rabbit cornea facilitated not only the activation of preexisting collateral vascular pathways but also new vessel formation.

The present experiment was designed to evaluate the effect of the renin-angiotensin system on micro-
vascular function and structure in renal hypertensive and normotensive rats and to determine whether captopril alters the cross-sectional area of the aortic and arteriolar wall. The one-kidney, one clip (1K1C) hypertensive rat is an excellent model in which to study the effect of the renin-angiotensin system on aortic and microvascular alterations because it is not renin dependent and blockade of the renin-angiotensin system with a converting enzyme inhibitor will not prevent the development of hypertension,\textsuperscript{9-12} thus avoiding the confounding effect of lowered blood pressure on vascular wall structure. Arteriolar lumen size does not increase with age during the development of 1K1C hypertension in hypertensive rats as it does in control rats, resulting in a significant reduction when compared with control rats.\textsuperscript{13} The wall cross-sectional area, however, increases at the same rate in 1K1C hypertension and control arterioles, indicating that the 1K1C vessels continue to grow, and this growth may be influenced by Ang II. These are the first whole animal data to show effects on aortic and microvascular wall growth when the production of Ang II is blocked and the animals remain hypertensive.

Methods

Treatment Groups

Male Wistar rats (Charles River Labs., Wilmington, Massachusetts) weighing 143–254 g were randomly divided into four groups: group 1, uninephrectomized control (n=11); group 2, uninephrectomized control with captopril (CON-CAP) (n=11); group 3, 1K1C hypertension with captopril (1K1C-CAP) (n=11); and group 4, 1K1C hypertension without captopril (1K1C) (n=10). As discussed below, five of the 1K1C rats were eliminated from the study because their blood pressure was not in the proper range. Groups 2 and 3 were given captopril in their drinking water, made fresh daily at a concentration of 380 mg/l, from 1 day before surgery until they were killed. Preliminary studies showed that this concentration would result in a captopril dose of approximately 100 mg/kg/day.

All the rats were anesthetized with a single intraperitoneal injection of ketamine hydrochloride (80 mg/kg) and xylazine (12 mg/kg). Hypertensive rats were produced by removal of the right kidney and by placement of a silver clip with a 230 \( \mu m \) gap width on the left renal artery.\textsuperscript{14} Control rats were uninephrectomized and the left renal artery was isolated in the same manner as in the hypertensive rats without applying a clip. Penicillin G (25,000 units) was injected intramuscularly after the surgery. The rats were individually caged, fed Purina rat chow and tap water (group 1 and group 4) or captopril water (group 2 and group 3) ad libitum, and maintained on a 12-hour light/dark cycle until their use in experiments 4 weeks later.

Systolic Blood Pressures

To assess the development of hypertension, systolic blood pressures were routinely obtained with a Narco Bio-Systems Electro-Sphygmomanometer (Houston, Texas). The pressures were measured in 10 rats in each group except for the 1K1C group, which had five rats, every 3 days for the first 2 weeks and on a weekly basis thereafter.

Adenosine Challenge in Cremaster Arterioles

The rats were anesthetized with an intraperitoneal injection of 100 mg/kg of Inactin (BYK, East Lansing, Michigan). The trachea was intubated, and the left carotid artery was cannulated for the measurements of mean blood pressure and heart rate. The right cremaster muscle was prepared for microvascular observation with a technique previously described by Baez.\textsuperscript{15} During the preparation, warmed Tis-U-Sol solution (Travenol, Deerfield, Illinois) supplemented with \( \text{CaCl}_2 \) (2.5 mM) was continuously dripped on the muscle, and the core temperature of the rats was maintained at 37° C with a heating mat. The muscle was spread over a Plexiglas stage and superfused with a modified Krebs-Henseleit solution equilibrated with 5% CO\textsubscript{2} and 95% N\textsubscript{2}, pumped over the preparation at 2 ml/min with a Cole-Parmer pump (Chicago, Illinois). Water circulating through the base of the stage maintained the temperature at 34.5–35° C. The entire preparation was placed on the stage of a Zeiss microscope (Thornwood, New York) and transilluminated by a 50 W halogen lamp with a heat absorption filter in the light path. Cremaster arterioles were examined by closed-circuit television microscopy with a Model 308 Vista image splitter (Ramona, California) and a Javelin camera (Torrance, California). Arterioles were magnified to ×640 and ×1,298 on the face of a Panasonic Model WV-5470 video monitor (Secaucus, New Jersey) with UDP20\times and UDP40\times objectives, respectively. The lower power objective was used to measure the first-(1A) and second (2A) -order arterioles, and the higher power was used for the smaller arterioles. Based on its numerical aperture of 0.65, the resolution with the UDP40\times objective was 0.2–0.3 \( \mu m \). Five measurements of a 50 \( \mu m \) length scale with the UDP40\times objective gave a value of 50±0.04 \( \mu m \).

The preparation was allowed to equilibrate 30 minutes to allow vascular tone to stabilize before microvascular observations were begun. During the equilibration period, cremaster arterioles were classified as 1A, 2A, third-(3A), and fourth (4A)-order arterioles on the basis of their branching pattern. Vessels were selected in the upper left quadrant (thin side) of the muscle because the vessels in the periphery lose tone because of operative insults. Resting inside diameters (ID\textsubscript{rest}) were measured for all branching orders of arterioles. After topical application of 10\textsuperscript{-5} M adenosine, relaxed inside (ID\textsubscript{relax}) and outside diameters (OD\textsubscript{relax}) were measured. The number of flowing 4As on a single 3A were also counted before and after adenosine. Wall thickness (WT), W/L ratio, and cross-sectional wall area (CSWA) were calculated from the equations:
Arteriolar density of the muscle. The density as length/area was calculated by using a zoom lens dissecting microscope. The observer did not know the origin of the cremaster muscle. Low power (x7), under which the grid were counted at two different magnifications was performed, and the abdominal aorta was cannulated below the renal arteries. The two hindpaws and the tail were ligated to eliminate low resistance pathways. The cremaster muscle was perfused with saline containing 10^-4 M adenosine, verapamil, and sodium nitroprusside, and 58.7 g/l polyvinylpyrrolidone (PVP) for several minutes, followed by 10% buffered formalin for 5–7 minutes at the individual mean blood pressure of the rat. After perfusion fixation, cremaster arterioles were filled with Microfil MV-122 (Canton Biomedical, Boulder, Colorado). After an equilibration period of 30 minutes, mean blood pressure and heart rate were read every 15 minutes, and the mean value of the readings represented the mean blood pressure and heart rate for each rat. Only hypertensive rats with mean blood pressure greater than 150 mm Hg were included in this study. Five rats were eliminated from the study because hypertension either failed to develop (mean blood pressure<150 mm Hg) or malignant hypertension developed (mean blood pressure>250 mm Hg) along with a major loss in body weight.

Arteriolar Density

After the microvascular observations, the rats were heparinized (1 unit/g body wt). A midline incision was performed, and the abdominal aorta was cannulated below the renal arteries. The two hindpaws and the tail were ligated to eliminate low resistance pathways. The cremaster muscle was perfused with saline containing 10^-4 M adenosine, verapamil, and sodium nitroprusside, and 58.7 g/l polyvinylpyrrolidone (PVP) for several minutes, followed by 10% buffered formalin for 5–7 minutes at the individual mean blood pressure of the rat. After perfusion fixation, cremaster arterioles were filled with Microfil MV-122 (Canton Biomedical, Boulder, Colorado). The Microfil was allowed to polymerize. The muscle was then cleared with increasing concentrations of crenation or compression, the vessel was not used. In addition, vessels that were not sectioned transversely (i.e., WT was asymmetrical) were not analyzed. At least two sections were analyzed from each vessel. Pilot studies were made to determine if the storage of aortas in 10% formalin altered medial-intimal area. Aortas from rats were sectioned, and one end was placed in formalin and the other end was immediately placed in the cryostat without fixation. No significant difference was found in luminal diameter or medial-intimal area.

Statistical Analysis

Results were expressed as mean±SEM. Multiple data were analyzed by analysis of variance. Multiple comparisons were then made using Duncan’s new multiple range test. Differences were considered statistically significant at p<0.05.

Results

Systolic blood pressure was elevated significantly in hypertensive rats, beginning 6 days after renal artery stenosis in 1K1C-CAP rats and 3 days in 1K1C rats (Figure 1). Blood pressure elevation was delayed 3–6 days in 1K1C-CAP rats and was the same as in 1K1C rats after that. However, systolic blood pressure was significantly lower in CON-CAP rats than in control rats at about 28 days. These data were coincident with mean blood pressure measured during the microcirculatory experiments, although tail-cuff pressures in the hypertensive rats appeared to be higher than systolic pressures measured under anesthesia. CON-CAP rats were heavier than the other rats. Heart rates were similar in all groups (Table 1). The response in mean blood pressure to injection of Ang I was significantly decreased in captopril-treated groups compared with the control group. The response to Ang II was the same in all groups (Table 2).

Internal diameters of the abdominal aorta were 1,282±40 μm in control (n=8), 1,381±66 μm in
CON-CAP (n=3), 1,273±57 μm in 1K1C-CAP (n=4), and 1,356±47 μm in 1K1C (n=5) rats. There were no statistical differences among the four groups. Medial-intimal area of the abdominal aorta was significantly decreased in CON-CAP rats but increased in 1K1C rats (Figure 2) compared with control. Captopril reduced the aortic wall hypertrophy significantly in 1K1C-CAP rats (Figure 2). Representative micrographs of vessels are shown in Figure 3.

There was a significant decrease in the resting and relaxed diameters of 1As and 2As in 1K1C-CAP and 1K1C rats versus both control groups (Figure 4). Captopril treatment significantly reduced resting and relaxed diameters of 1As in CON-CAP versus control rats (Figure 4). There were no significant changes in resting or relaxed diameters of 3As, but resting diameters of 4As were reduced in captopril-treated and hypertensive rats (Figure 4).

There was less tone in large arterioles than in small arterioles (Figure 4), but captopril appeared to increase the tone of 1As and 2As, especially in the hypertensive rats. Tone in 3As and 4As does not appear to be elevated in the hypertensive groups (Figure 4), but calculated tone in this study does not take closed vessels into account. Under resting conditions, more 4As were closed to flow in the 1K1C group, and these vessels opened to flow with the addition of adenosine. If newly opened 4As are included in the calculation, the amount of tone for 4As in the 1K1C group is much higher than in the other groups.

Figure 5 shows the number of flowing 4As on a 3A before and after the application of 10⁻² M adenosine. There were no significant differences in the number of 4As opened to flow under resting conditions. The number of open 4As in the 1K1C group under resting conditions tended to be lower but was not quite statistically significant. The number of open 4As significantly increased after the application of adenosine in all groups, but this number was significantly lower in the captopril-treated groups.

There were significant decreases in CSWA in 1As, 2As, and 4As in 1K1C-CAP rats (Figure 6). CSWA in CON-CAP 1As was also significantly decreased. The reduction in CSWA was greater in the 1K1C-CAP group, but as shown in previous experiments¹³ and in Figure 6, CSWA was not reduced by hypertension alone.

Table 3 shows the WT after maximal vascular relaxation with 10⁻² M adenosine, which was used to calculate W/L ratio. W/L ratio was significantly increased in all orders of arterioles of 1K1C rats versus all three other groups except for control 3As. These increases, however, were not accompanied by increases in CSWA (Figure 6), but were due solely to

---

**Table 1. Mean Arterial Blood Pressure, Heart Rate, and Body Weight at 4 Weeks After Renal Artery Stenosis**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>MBP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>BW (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>11</td>
<td>124±4</td>
<td>378±3</td>
<td>330±7</td>
</tr>
<tr>
<td>CON-CAP</td>
<td>11</td>
<td>103±5*</td>
<td>349±16</td>
<td>363±11*</td>
</tr>
<tr>
<td>1K1C-CAP</td>
<td>11</td>
<td>183±5†</td>
<td>348±13</td>
<td>316±8†</td>
</tr>
<tr>
<td>1K1C</td>
<td>5</td>
<td>193±5†</td>
<td>389±5</td>
<td>310±16†</td>
</tr>
</tbody>
</table>

Values are mean±SEM. n, number of rats; MBP, mean blood pressure; HR, heart rate; BW, body weight; CON-CAP, control-captopril rats; 1K1C-CAP, hypertensive-captopril rats; 1K1C, hypertensive rats.

*p<0.05 vs. control group. †p<0.05 vs. CON-CAP group.

**Table 2. Mean Arterial Pressure Changes After Intravenous Injection of Separate Test Doses of Angiotensin I and Angiotensin II at End of Experiment**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Ang I (mm Hg)</th>
<th>Ang II (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7</td>
<td>45±4</td>
<td>49±6</td>
</tr>
<tr>
<td>CON-CAP</td>
<td>8</td>
<td>16±4*</td>
<td>34±5†</td>
</tr>
<tr>
<td>1K1C-CAP</td>
<td>11</td>
<td>20±3†</td>
<td>43±5†</td>
</tr>
</tbody>
</table>

Values are mean±SEM. n, number of rats; Ang I, angiotensin I; Ang II, angiotensin II; CON-CAP, control-captopril rats; 1K1C-CAP, hypertensive-captopril rats.

*p<0.05 vs. control. †p<0.05 vs. Ang I.
the reduction in lumen size. Likewise, the W/L ratio of 1As in the 1K1C-CAP group increased significantly compared with both control groups.

Figure 7 shows the relation between CSWA and ID$_{relax}$ for all four orders of arterioles in all groups (n=152). The regression line was plotted on a log-log graph ($r=0.98$, $p<0.001$) in which the best fit for the data was a third-order polynomial equation ($y=-2.9x^3+14.5x^2-21.7x+10.3$). When plotted separately, there were no significant differences among the regression curves for the four groups. However, there is a tendency for the data points from the large arterioles of the hypertensive rats to fall above the line. This is not due to hypertrophy of the wall but to a structural reduction in the diameter of the vessels related to hypertension.

Figure 8 shows the arteriolar density of large and small arterioles as total length per unit area of tissue. There were no differences in large arteriolar density. Arteriolar density for 3As, 4As, and 5As was significantly decreased in captopril-treated groups and the 1K1C group. The statistically unchanged number of 4As per 3A in the vasodilated 1K1C group in Figure 5 does not contradict the data in Figure 8. The density of 3As is included in the latter sample and the stereological measurements are based on a much larger sample of the tissue, enabling them to demonstrate a statistical significance not shown by arteriolar counts from the same rats. The important finding is that structural rarefaction of arterioles was not pre-
vented by captopril. Rather, long-term treatment with large doses of captopril appeared to cause rarefaction of small arterioles in normotensive rats.

Discussion

The present study confirms the concept that long-term blockade of converting enzyme with captopril does not prevent the development of chronic hypertension or attenuate its severity in the 1K1C rat. As shown in Figure 1, blood pressure elevation was delayed 3–6 days in 1K1C-CAP rats and was the same as in 1K1C rats after that. Other investigators have also shown that captopril delays the onset of 1K1C hypertension for less than 8 days.12 This is in agreement with reports that the acute high renin phase of 1K1C hypertension in rats lasts for no more than a week.17,18 Captopril lowered blood pressure in normotensive rats after 4 weeks of treatment, a finding in agreement with other studies.11,12,19

The reason that mean blood pressure still rose somewhat after injection of Ang I into captopril-treated rats is unclear (Table 2). It is possible that: 1) After long-term captopril treatment, peripheral vascular reactivity to Ang II is elevated and Ang II receptor binding is greater.20 However, this does not seem to be the case in this experiment because the response to injection of Ang II did not differ between captopril-treated groups and the control group (Table 2). 2) Alternatively, tonin and nonrenin protease, which convert angiotensinogen and Ang I to Ang II

![Graph showing arteriolar dimensions in the resting state and after dilation with topical 10^-3 M adenosine.](image-url)
FIGURE 5. Bar graph showing number of flowing fourth-order arterioles (4As) on each third-order arteriole (3A) before and after topical application of \(10^{-3}\) M adenosine. *p<0.05 versus control rats. CON-CAP, control-captopril rats; 1K1C-CAP, hypertensive-captopril rats; 1K1C, hypertensive rats.

FIGURE 6. Bar graphs showing cross-sectional wall area of first (1A), second (2A), third (3A), and fourth (4A)-order arterioles in cremaster muscle. Wall area includes intima, media, and adventitia. Symbols indicate statistical significance at p<0.05 versus control (*), control-captopril (CON-CAP) (+), and hypertensive-captopril (1K1C-CAP) (#) rats. 1K1C, hypertensive rats.

independently of angiotensin converting enzyme, could produce Ang II locally to cause vasoconstriction.\(^{21,22}\)

3) The other possibility for this pressure rise is that, because of its short elimination half-life (1.7 hours), concentrations of captopril were too low to achieve total blockade when tested at the end of the microcirculation experiments. By then, the rats had not received captopril for over 2 hours.

The pronounced structural reduction of large arteriolar diameters in 1K1C-CAP and 1K1C rats (Figure 4) is the most important microvascular change found with long-term renal hypertension in terms of its effect on vascular resistance. These reductions have been reported by other investigators\(^{13,23,24}\) and appear to start in the 1A and proceed downstream with time. Although they are not related to hypertrophy of the vascular wall, they do result in an increase in W/L ratio and increased vascular resistance. A similar, although smaller, reduction was found in the 1A in the CON-CAP group (Figure 4), which may be indicative of an inhibition of growth by captopril.

One of the most important findings in this experiment is the pronounced decrease in CSWA of aortas and arterioles in captopril-treated rats. Hypertension is associated with growth of the vascular wall, at least in arteries,\(^{25}\) and antihypertensive treatment can prevent or reverse these changes through the reduction in pressure alone.\(^{26}\) In this study, however, prevention of the hypertrophy of the aortic wall in 1K1C-CAP rats cannot be explained by altered mechanical stress because the blood pressure was not lowered by captopril (Figure 2 and Table 1). In addition, as shown in Figure 6, the CSWAs were significantly decreased in large and small arterioles of the 1K1-CAP rats. CSWA was also significantly decreased in the 1As of CON-CAP rats. These data are strong evidence that vascular growth was inhibited, suggesting the involvement of either Ang II or bradykinin in the regulation of vascular wall structure in normotensive as well as hypertensive rats.

Although 1K1C hypertension is not a renin-dependent model, as discussed above, captopril may inhibit local formation of Ang II produced by increased vascular wall renin activity in hypertension\(^{27,28}\) as well as in normotension.\(^{29}\) The exact mechanism whereby Ang II influences vascular wall structure is not known. Ang II may bind to receptors on nuclear chromatin and initiate nuclear events that result in protein synthesis and cell proliferation.\(^{1,30,31}\) Alternatively, the acceleration of hydrolysis of polyphosphoinositide lipids by occupation of receptors by Ang II could increase nuclear activity.\(^{32}\) Increased Ang II levels within the vascular wall could influence vascular growth, either by direct effects on vascular smooth muscle as discussed above or indirectly by potentiation of sympathetic activity.\(^{33,34}\) Norepinephrine and epinephrine have been shown to increase the growth rate of cultured vascular SMCs,\(^{35}\) and the sympathetic nervous system has a role in vascular SMC growth in hypertension.\(^{36}\)

The blockade of Ang II formation by captopril in SHR has an effect on the vascular wall over and above that predicted by its blood pressure–lowering effect. Captopril not only prevented the development of SMC polyploidy and medial hypertrophy in SHR, it also significantly reduced SMC size and medial SMC content in WKY rats.\(^{4}\) The W/L ratio of
TABLE 3. Wall Thickness and Wall-to-Lumen Ratio After Maximal Vascular Relaxation With 10^{-3} M Adenosine

<table>
<thead>
<tr>
<th>Arteriole</th>
<th>Control</th>
<th>CON-CAP</th>
<th>1K1C-CAP</th>
<th>1K1C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wall thickness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1A</td>
<td>27.3±0.3</td>
<td>26.5±0.4</td>
<td>27.8±0.3</td>
<td>37.5±0.5*†#</td>
</tr>
<tr>
<td>2A</td>
<td>18.7±1.2</td>
<td>18.4±1.1</td>
<td>13.0±1.0*†</td>
<td>18.6±1.6#</td>
</tr>
<tr>
<td>3A</td>
<td>4.4±0.3</td>
<td>3.8±0.3</td>
<td>3.3±0.3</td>
<td>4.7±0.3#</td>
</tr>
<tr>
<td>4A</td>
<td>3.3±0.2</td>
<td>2.6±0.2*</td>
<td>2.5±0.1*</td>
<td>3.2±0.1†#</td>
</tr>
<tr>
<td></td>
<td>Wall-to-lumen ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1A</td>
<td>0.169±0.004</td>
<td>0.211±0.008*</td>
<td>0.318±0.012*†</td>
<td>0.388±0.009*†#</td>
</tr>
<tr>
<td>2A</td>
<td>0.202±0.008</td>
<td>0.184±0.013</td>
<td>0.189±0.018</td>
<td>0.257±0.020*†#</td>
</tr>
<tr>
<td>3A</td>
<td>0.147±0.009</td>
<td>0.119±0.010</td>
<td>0.132±0.010</td>
<td>0.177±0.015†#</td>
</tr>
<tr>
<td>4A</td>
<td>0.180±0.006</td>
<td>0.151±0.011</td>
<td>0.175±0.015</td>
<td>0.247±0.015†#</td>
</tr>
</tbody>
</table>

Values are mean±SEM. 1A, 2A, 3A, 4A: first- through fourth-order arterioles, respectively; CON-CAP, control-captopril rats; 1K1C-CAP, hypertensive-captopril rats; 1K1C, hypertensive rats. Symbols indicate statistical significance at p<0.05 vs. control (*), CON-CAP (†), or 1K1C-CAP (#) rats.

mesenteric arteries and hypertrophy of the myocardial and aortic wall were significantly decreased by captopril not only during treatment but also up to 7 weeks after treatment ceased. A recent study shows that treatment with converting enzyme inhibitors in two-kidney, one clip hypertensive rats decreased WT and reversed SMC hypertrophy, as indicated by an increase of relative nuclear density per unit area and a decrease in cross-sectional area of the nuclei. Although blood pressure was normalized in this model by converting enzyme inhibition, a decreased thickness of the media was also produced in normotensive rats without lowering blood pressure.

Another possible effect of captopril is its influence on bradykinin and prostaglandin levels by blocking the catabolism of bradykinin. However, bradykinin is a mitogenic agent, and therefore it might be expected that increased bradykinin concentrations would augment the proliferative response. Furthermore, if plasma levels of prostaglandins were increased during captopril treatment, the result should be an increase in angiogenesis rather than a decrease.

CSWA of 1K1C rats without captopril did not differ from control values, regardless of an increased W/L ratio that was due to the decreased lumen size (Figures 4 and 6, Table 3). This is in agreement with
Ang II in the avascular rabbit cornea not only facilitated the activation of preexisting collateral circulation. Furthermore, implantation of Ang II in the avascular rabbit cornea not only facilitated the activation of preexisting collateral circulation.7 However, it also had angiogenic properties and therefore could play an active role in the development of collateral circulation.8

In conclusion, the results of these experiments indicate that captopril treatment resulted in a reduction in cross-sectional wall area of aortas and arterioles in normotensive and hypertensive rats, as well as a reduction in the number of small arterioles. Although the possibility cannot be ruled out that these findings are related to a build up of bradykinin levels, it is more likely that they are due to the blockage of Ang II production because Ang II is known to have hypertrophic and angiogenic effects.

Acknowledgments

We thank the Squibb Institute for Medical Research for generously supplying the captopril. We thank Clark Efaw for excellent technical help and Shanna Richardson for her expert secretarial skills.

References


Acknowledgments

We thank the Squibb Institute for Medical Research for generously supplying the captopril. We thank Clark Efaw for excellent technical help and Shanna Richardson for her expert secretarial skills.

References

Captopril reduces aortic and microvascular growth in hypertensive and normotensive rats.

D H Wang and R L Prewitt

Hypertension. 1990;15:68-77
doi: 10.1161/01.HYP.15.1.68

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://hyper.ahajournals.org/content/15/1/68

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/