Modulation of Hemodynamics, Endogenous Antioxidant Enzymes, and Pathophysiological Changes by Angiotensin-Converting Enzyme Inhibitors in Pressure-Overload Rats

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Introduction: We sought to assess the role of angiotensin-converting enzyme (ACE) inhibitors on systolic blood pressure (BP), endogenous antioxidant enzymes and histopathological changes in pressure-overload rats.

Methods: Pressure overload was produced in male rats by abdominal aortic banding (AAB) using a blunt 22-gauge needle, as a model of cardiac hypertrophy. After surgery, AAB-induced hypertensive (AABIH) groups were treated with captopril 4 mg and ramipril 10 mg/kg per day p.o. for 16 weeks. At 16 weeks, rats were observed for general characteristics and mortality, non-invasive blood pressure (NIBP) and endogenous antioxidant enzyme catalase and superoxide dismutase (SOD) activity and histological evaluation of target organs.

Results: In the AABIH group a significant increase in systolic BP was observed in week 3 (149.3 ± 0.821) and persisted until week 16, along with lower levels of serum catalase (144.7 ± 2.204) and SOD (12.92 ± 0.4601) activity compared to the control group. Captopril and ramipril treated groups showed a significantly smaller increase in systolic BP (25.47 ± 3.685, 20.21 ± 3.306) and greater serum SOD (27.33 ± 2.338, 28.95 ± 1.143) and catalase (181.7 ± 8.407, 187.9 ± 8.497) activity, respectively, than the hypertensive rats. The histological changes induced in target organs (heart, liver, kidneys and thoracic aorta) in AABIH rats were attenuated in treated rats.

Conclusion: ACE-inhibition causes an improvement in myocardial antioxidant reserve, reduces oxidative stress, and prevents pathophysiological alterations, while showing a trend for potential target organ protection in hypertensive rats.

The renin-angiotensin system (RAS) consists of a cascade of enzymatic reactions leading to the formation of angiotensin-II (Ang-II) from angiotensinogen. Ang-II is the key effector molecule of the RAS and can act either as a systemic hormone (endocrine) or as a locally generated factor (paracrine/autocrine). Most of Ang-II is generated in 2 steps: renin catalyzes the conversion of angiotensinogen to angiotensin I, which is subsequently hydrolyzed to form Ang-II by angiotensin-converting enzyme (ACE).

Alternative ACE-independent pathways for Ang-II production exist. Angiotensinogen can be converted directly to Ang-II by enzymes such as tissue plasminogen activator, cathepsin G, and tonin, whereas chymostatin-sensitive Ang-II-generating enzyme, chymase, and cathepsin G will also
catalyze the hydrolysis of angiotensin I to angiotensin II.\(^1\) Regardless of the pathway of formation, Ang-II mediates its physiological actions by binding to specific receptors located on the cell membrane. In humans, two types of angiotensin II receptors are characterized: angiotensin II type 1 (AT\(_1\)) and angiotensin II type 2 (AT\(_2\)).\(^4\,5\) which display a heterogeneous distribution in peripheral tissues and brain. Despite belonging to the same receptor family, the AT\(_1\) and AT\(_2\) receptor subtypes differ markedly in their signaling cascades and biologic activities. AT\(_1\) and AT\(_2\) receptors are classified by their differential affinities for various non-peptide antagonists.\(^5\) Both of these receptors belong to the family of G protein-coupled receptors, although the pathways are completely different and signal in apparent opposition. For example, AT\(_1\) receptors mediate vasoconstrictor responses, whereas AT\(_2\) receptors are thought to mediate vasodilator responses.

Many clinical and experimental studies have established the therapeutic benefits of ACE inhibitors (ACEIs), not only in treating hypertension and congestive heart failure, but also in reducing re-infarction, limiting infarct size, and reducing reperfusion arrhythmias.\(^6\) For example, it has been reported that ACEIs reduce infarct size,\(^7\) and the incidence of reperfusion-induced arrhythmias in rats\(^7,8\) and in dogs\(^9\) \textit{in vivo}, as well as in isolated rat hearts,\(^10\) and reduce arrhythmias in post-infarction heart failure patients.\(^11\) These effects of ACEIs have been attributed to both blockage of Ang-II synthesis and a decrease in breakdown of bradykinin, which may stimulate the production of prostaglandin and nitric oxide (NO).\(^7,10\)

Constriction of the thoracic or abdominal aorta provides an experimental model of what has been previously described as pressure-overload cardiac hypertrophy. The increased blood pressure proximal to the constriction has been postulated to provide a stimulus for the development of cardiac hypertrophy.\(^12\) This study was designed to evaluate the effects of ACEIs on systolic blood pressure by noninvasive (indirect) tail-cuff method, using an automated cuff inflator-pulse detection system. Endogenous antioxidant enzyme (serum catalase and superoxide dismutase) activity, and histopathological changes in target organs (viz. heart, liver, kidneys and thoracic aorta) were evaluated in order to compare the histopathological changes induced in untreated abdominal aortic-banding-induced hypertension (AABIH) and cardiac hypertrophy in rats.

### Methods

#### Animals

Healthy adult male Wistar rats weighing between 150 g and 210 g were selected. Animals were maintained under standard laboratory conditions at 28 ± 2 °C, a relative humidity of 50 ± 15%, and normal photoperiod (12 h dark and 12 h light). Commercial pellet diet (Amruth Limited, India) and water were provided \textit{ad libitum}. The experimental protocol was approved by the Institutional Animal Ethics Committee and by the animal regulatory body of the government (Al-Ameen College of Pharmacy, India. Reg. No. 83/1999/CPCSEA).

#### Drugs

The test drugs (drug substances) captopril, and ramipril were procured from Micro Labs Private Limited, India.

#### Experimental protocol

Animals were randomly assigned to different groups, each having 8 male Wistar rats and treated accordingly.

- **Group-I:** Control (normotensive) sham-operated.
- **Group-II:** Untreated abdominal aortic banding induced hypertensive (AABIH) rats.
- **Group-III:** AABIH rats treated with captopril (4 mg/kg per day \textit{p.o.})
- **Group-IV:** AABIH rats treated with ramipril (10 mg/kg per day \textit{p.o.}).

Pressure-overload was produced by abdominal aortic banding (AAB), which has been used primarily as a model of cardiac hypertrophy.\(^13\) Briefly, animals were anesthetized using a combination of ketamine (70 mg/kg, \textit{i.p}) and xylazine (10 mg/kg, \textit{i.p}) and the aorta was exposed through a midline abdominal incision. For the banding model, a blunt 22-gauge needle was placed adjacent to the abdominal aorta between the renal arteries just below the renal bifurcations, and a ligature was tightened around the aorta. The muscular layer was sutured, followed by the abdominal skin, and animals were placed isolated in a cage for recovery. Dead animals were removed from the cage. The drug treatment was started upon ani-
mals recovering from the surgery, with captopril and ramipril daily orally for 16 weeks.

**Drug administration**

The drugs captopril and ramipril were formulated freshly using 1% carboxy methyl cellulose (CMC) in distilled water and administered orally in a dose volume of 2 ml/kg body weight. 1% CMC solution was used as vehicle.

**General characteristics and mortality**

After the surgery the animals were placed in the cages under observation for general characteristics and mortality.

**Hemodynamic parameters**

**Blood Pressure**

The noninvasive (indirect) blood pressure (NIBP) was determined by the tail-cuff method, using an automated cuff inflator-pulse detection system (AD Instruments NIBP measurement apparatus). Unanesthetized rats were placed in a restraining holder from which the tail protruded. Vasodilatation was achieved by local warming of the tail with an infrared bulb. Cuff and transducer were placed around the tail and the cuff was inflated until the pulse disappeared. When the cuff was deflated, the point of reappearance of the pulse indicated the value of systolic blood pressure. The reported values are of a minimum of 3 recordings performed on each animal by the same investigator. The NIBP was measured during weeks 1, 3 and 16. The patency of the hypertension induced by AAB was ascertained during week 3.

**Endogenous antioxidant enzyme activity**

**Collection of blood sample**

After the NIBP measurement, the rats were anesthetized with ether and the blood was collected in 2 ml Eppendorff’s tubes from the retro-orbital plexus with the help of heparinized capillary tubes for the estimation of antioxidant enzyme activity. The collected blood was centrifuged for 15 min at 7000 rpm and the supernatant (serum) was used for the estimation of biochemical parameters, viz. catalase and superoxide dismutase activity.

**Superoxide dismutase (SOD)**

SOD activity was determined based on the ability of SOD to inhibit the auto-oxidation of epinephrine to adrenochrome at alkaline pH, as per the method of Misra and Fridovich. A Shimadzu-ultra-violet (UV) 180 double-beam spectrophotometer was used. Protein was estimated according to the Lowry method. The level of protein was expressed as mg protein/g tissue. Briefly, 25 μL of the supernatant obtained from the centrifuged blood was added to the mixture of 0.1 mM adrenaline in carbonate buffer (pH=10.2) in a total volume of 1 mL and the formation of adrenochrome was measured at 295 nm. The SOD activity (U/mg of protein) was calculated using the standard plot.

**Estimation of protein content by the Lowry method**

Standard: Pipette 100, 200, 300, 400, 500, 600, 700, 800, 900 μL of bovine serum albumin (BSA) solution in test tubes, diluted with distilled water to make volume up to 1 mL. Then 5 mL of alkaline copper reagent was added and incubated for 10 minutes at room temperature. To the above mixtures, 0.5 mL working Folin-Phenol reagent solution (1:1) was added and kept in the dark for 30 minutes. The absorbance was read at 750 nm against the reagent blank.

Sample: To 0.5 mL of distilled water, 0.5 mL of 10% tissue homogenate and 5 mL of alkaline copper reagent were added and incubated for 10 minutes at room temperature. To the above mixture 0.5 mL working Folin-Phenol reagent solution (1:1) was added and kept in the dark for 30 minutes. The absorbance was read at 750 nm against the reagent blank. The standard curve was plotted between absorbance and concentration of BSA and was used for the calculation of total protein in HTH. Total protein was expressed as mg/g of tissue.

**Catalase**

The catalase activity was determined spectrophotometrically according to the standard protocol, as per the Clariborne method. Briefly, to 1.95 mL of 10 mM H₂O₂ in 60 mM phosphate buffer (pH=7.0), 0.05 mL of the plasma/serum was added; degradation of H₂O₂ was followed at 240 nm per min and the rate of decomposition of H₂O₂ was calculated using the formula \( k = \frac{2.303}{\Delta t} \times \log \left( \frac{A_1}{A_2} \right) \) S⁻¹ followed by calculation of catalase in terms of units/mg of protein. A unit of catalase is defined as the quantity that decomposes 1.0 μmole of H₂O₂ per min at pH=7.0 at 25°C, while this H₂O₂ concentration falls from 10.3 to 9.2 mM.
Histopathological evaluation of the target organs

At the end of 16 weeks after the NIBP measurement, the rats from each group were anesthetized with ether and the target organs (heart, liver, kidneys and thoracic aorta) were collected and placed in separate containers containing 10% neutral buffered formalin, pH 6.8-7.0 (40% formaldehyde 10 mL, sodium-di-hydrogen phosphate anhydrous 0.35 g, disodium hydrogen phosphate anhydrous 0.65 g, distilled water 90 mL). The samples were sectioned, stained and processed for histopathological evaluation. The organs were processed, sectioned at 5 micron thickness and stained with standard hematoxylin and eosin. The slides were mounted and evaluated under microscope by a qualified pathologist. The histological evaluation was performed to compare the changes induced in untreated and treated AABIH rats with ACEIs in comparison with the control sham-operated rat organs (heart, liver, kidneys and thoracic aorta).

Statistical analysis

The values are expressed as mean ± standard error of the mean (SEM). Data were analyzed by analysis of variance (ANOVA) followed by Tukey’s multiple comparison test to compare the treatment groups with the control group using a GraphPad Prism.

Results

General characteristics, body weight and mortality.

Sham operated control (normotensive) group, AABIH rats, and the groups treated with ACEIs (captopril and ramipril) were monitored periodically. In terms of general appearance and behavior, nothing unusual was noted in any of the treatment groups. The body weight gain in both the treated and untreated groups was slightly lower than in their respective sham control group, but the differences were not significant (p>0.05). Mortality in the AAB animals during or immediately after the surgery was about 20%. Another 15% of the animals died within 24 h following the surgery.

Endogenous antioxidant enzyme activity / biochemical parameters

Catalase activity

In the AABIH group the level of catalase activity was significantly lower than in the control-sham operated group. In the groups treated with captopril and ramipril the level of catalase activity was significantly higher compared to the AABIH group (p<0.01 and p<0.001, respectively; Table 2).

SOD activity

In the AABIH group the level of SOD activity was significantly lower than in the control-sham operated group. Serum SOD activity level was significantly higher (p<0.001) in the captopril and ramipril treated groups compared to the AABIH group (Table 2).

Table 1. Effect of ACE inhibitors on systolic blood pressure (BP) in rats with abdominal aortic banding-induced hypertension and cardiac hypertrophy. There was a statistically significant increase (149.3 ± 0.821) in systolic blood pressure during week 3 in comparison to week 1. (The patency of the hypertension induced by abdominal aortic banding was ascertained during week 3.)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Systolic BP (mmHg)</th>
<th>Systolic BP (mmHg)</th>
<th>% Increase in systolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 1</td>
<td>Week 16</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>94.14 ± 0.589</td>
<td>105.9 ± 0.7004</td>
<td>12.96 ± 1.21</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>114.5 ± 0.816</td>
<td>158.7 ± 2.194</td>
<td>39.37 ± 1.494</td>
</tr>
<tr>
<td>Captopril</td>
<td>100.1 ± 0.4467</td>
<td>125.8 ± 4.603</td>
<td>25.47 ± 3.685*</td>
</tr>
<tr>
<td>Ramipril</td>
<td>98.76 ± 0.775</td>
<td>119.8 ± 4.014</td>
<td>20.21 ± 3.306†</td>
</tr>
</tbody>
</table>

*Significantly lower than hypertensive group, p<0.05. †Significantly lower than hypertensive group, p<0.01.
**Histopathological evaluation**

**Heart**

The section of normal control sham-operated rat hearts showed normal structure and architecture. The heart section of the untreated AABIH rat showed a mild to moderate degree of hemorrhage (accumulation of red blood corpuscles in between the cardiac fibers), mild perivascular fibrosis (fibrous tissue proliferation around the blood vessels), defragmentation of cardiac fibers (loss of striations), congestion (accumulation of red blood cells in the blood vessels in the parenchyma), edema (separation of cardiac fibers), mild vacuolations and focal areas of necrosis in 1-2 areas. The tissue also showed mild lymphocytic infiltration. Compared to the untreated AABIH group, the captopril treated group showed a mild degree of hemorrhage, mild edema and separation of cardiac fibers, defragmentation and congestion. The ramipril treated group showed mild to moderate hemorrhage, mild vacuolations in tubules, a moderate degree of hemorrhage, and congested blood vessels (Figure 1 A-D).

**Liver**

The section of normal control sham-operated rat liver showed normal structure and architecture. The liver section of the untreated AABIH rat showed congestion, multifocal areas of necrosis, and dilation of the central vein. There was also a severe degree of degeneration and vacuolations restricted to border areas below the hepatic capsule, indicating the initial stages of ischemia (lack of blood supply). Compared to the untreated AABIH group, the captopril treated group showed congestion, dilation of the central vein, mild hemorrhage and a mild degree of vacuolations in the sub-borders of the hepatic parenchyma. The ramipril treated group showed congestion, dilation of the central vein, mild hemorrhage and a mild to moderate degree of vacuolations in the borders of the hepatic parenchyma (Figure 1 E-H).

**Kidneys**

The section of normal control sham-operated rat kidneys showed normal structure and architecture. The kidney section of the untreated AABIH rat showed edema, vacuolations in tubules, moderate to severe hemorrhage and congested vessels. Compared to the untreated AABIH group, the kidney sections of the captopril treated group showed moderate edema, a moderate degree of hemorrhage, and congested blood vessels. The kidney sections of the ramipril treated group showed mild to moderate edema, mild vacuolations in tubules, a moderate degree of hemorrhage, and congested blood vessels (Figure 2 A-D).

**Thoracic aorta**

The section of normal control sham-operated rat thoracic aorta showed normal structure and architecture. The thoracic aorta section of the untreated AABIH rats showed mild accumulation of foam cells in between the fibers. Compared to the untreated AABIH group, the thoracic aorta sections of the captopril and ramipril treated groups showed no changes (Figure 2 E-F).

From the results of the histopathological evaluation, it is evident that treatment with ACEIs (captopril and ramipril) significantly reduced the histological changes in the target organs, heart, liver, kidneys and thoracic aorta, compared to the untreated AABIH group. Hence, ACEIs tend to have potential end-organ protection traits and proved to have beneficial effects in the treatment of hypertension, by both decreasing the blood pressure and protecting the target organs.

**Discussion**

The results of this study demonstrate that inhibition of ACE with captopril and ramipril reduces the systolic blood pressure significantly, causes an improvement in the myocardial antioxidant reserve (serum catalase and SOD enzyme activity), decreases oxidative stress, and reduces the histopathological changes induced in a pressure-overload rat model of AABIH and cardiac hypertrophy.

### Table 2. Effect of ACE inhibitors on serum superoxide dismutase (SOD) and catalase levels in rats with pressure-overload (abdominal aortic banding) induced hypertension and cardiac hypertrophy.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SOD Units/mL</th>
<th>Catalase Units/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>19.61 ± 0.4095</td>
<td>160.0 ± 5.768</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>12.92 ± 0.4601</td>
<td>144.7 ± 2.204</td>
</tr>
<tr>
<td>Captopril</td>
<td>27.33 ± 2.338†</td>
<td>181.7 ± 8.407*</td>
</tr>
<tr>
<td>Ramipril</td>
<td>28.95 ± 1.143†</td>
<td>187.9 ± 8.497†</td>
</tr>
</tbody>
</table>

*Significantly greater than hypertensive group, p<0.01.
†Significantly greater than hypertensive group, p<0.001.
Figure 1. Heart and liver tissue sections of control, hypertensive and angiotensin-converting enzyme inhibitor treated groups. A: section of normal control heart showing normal structure and architecture (40×); B: hypertensive heart showing moderate inflammatory cell infiltration (10×); C: captopril treated heart showing mild edema (40×); D: ramipril treated heart showing minimal vacuolations in cardiac parenchyma (40×); E: section of normal control liver showing normal structure and architecture; F: hypertensive liver showing severe vacuolar degeneration characterized by formation of vacuoles in the hepatocytes, clear cells and perivascular cuffing (10×); G: captopril treated liver showing minimal vacuolar changes (4×); H: ramipril treated liver showing minimal vacuolar changes in the subcapsular region (4×).
Figure 2. Kidney and thoracic aorta sections of control, hypertensive and angiotensin-converting enzyme inhibitor treated groups. A: section of normal control kidney showing normal structure and architecture (4×); B: hypertensive kidney showing severe edema, characterized by dilatation of tubules, hemorrhage in glomeruli and tubules (10×); C: captopril treated kidney showing moderate hemorrhage in the parenchyma (40×); D: ramipril treated kidney showing mild edema and hemorrhage, hypertrophy of tubules (10×); E: section of normal thoracic aorta (4×) F: hypertensive thoracic aorta showing minimal formation of foam cells in between the fibers (4×); G: captopril treated thoracic aorta showing no changes (4×); H: ramipril treated thoracic aorta showing no changes (4×).
In our study, the AAB was found to increase the systolic blood pressure in a consistent manner that was sustainable throughout the period of study. Constriction of the thoracic or abdominal aorta provides an experimental model of what has been previously described as pressure-overload cardiac hypertrophy. The increased blood pressure proximal to the constriction has been postulated to provide a stimulus for the development of cardiac hypertrophy. Bardy and coworkers have reported that the increased transmural pressure in the aorta may cause the local generation of Ang-II, which acts synergistically with the transmural pressure to increase vascular fibronectin expression through the AT1 receptor. In the aortic banding model, the decreased blood pressure distal to the banding stimulates the kidneys to release renin, resulting in increased levels of circulating Ang-II. However, as shown by other investigators, the elevation of plasma renin demonstrated within a few days post aortic banding does not account for the increased levels of the AT2 receptor mRNA over 3 weeks. Since Ang-II binds to both AT1 and AT2 receptors with similar affinity, the contractile response of the aorta to Ang-II depends on the relative expression level and/or responsiveness of both receptors. Hence, it seems that the decreased response to Ang-II in the pressure-overloaded aorta is likely to depend on, at least in part, the up-regulation of the AT2 receptor. In the present study, we observed a reduction in systolic blood pressure in the AABIH rats treated with ACEIs, which is in consonance with previously reported studies.

In addition to the systemic hypotensive activity, ACEIs may provide cardiac preservation through afterload reduction, a local action that interrupts the regional cardiac tissue’s RAS and may participate in the cardioprotective effects of these drugs.

Hirsch and coworkers demonstrated that an increase in myocardial ACE activity occurs after permanent coronary artery ligation in rats. Paracrine and autocrine control of regional myocardial function and perfusion has been suggested for hormones such as endothelium-dependent relaxing factor (EDRF), bradykinin and the prostanoids, all factors that may interact with a local RAS to facilitate integrated cardiac regulation. Bradykinin is tightly linked to the RAS because the bradykinin degradative enzyme, kinase II, has been determined to be identical to ACE. Data suggest that blockade of the RAS will decrease proteinuria. It has been suggested that these drugs be used preferentially (usually with a small dose of a diuretic drug), not only in type I diabetic hypertensive patients with nephropathy, but also in patients with type II diabetes in an effort to slow down the progression of renal disease. Because of the selective effect of ACE inhibition on the afferent arteriole of the glomerulus and a reduction in arteriolar resistance, the use of these agents has proved beneficial in the treatment of patients with proteinuria and diabetic nephropathy.

It should be noted, however, that in contrast to the wall hypertrophy, Notoya and coworkers have shown that the remodeling of renal afferent arterioles is reversed by long-term ACE inhibition.

The presence of structural changes in pre-glomerular arteries and afferent arterioles before the development of hypertension, and the persistence of these structural changes despite normalization of arterial pressure (with antihypertensive treatment), strongly suggest that these changes are not due to elevated arterial pressure but may instead be involved in the pathogenesis of hypertension. Consistent with this hypothesis, Norrelund and coworkers found a correlation between the lumen diameter of the afferent arteriole at 7 weeks of age in an F2-generation SHR/Wistar-Kyoto cross and the extent of subsequent development of hypertension. Long-term studies have demonstrated that both Ang-II antagonists and ACEIs have comparable efficacy in terms of blood-pressure reduction at trough. Myocardial antioxidants are dynamic in nature and have been reported to change in various physiological and pathological conditions, including hypertrophy, exercise and adriamycin-induced cardiomyopathy. It is also known that different enzymatic and non-enzymatic antioxidants respond uniquely in a variety of oxidative stress conditions. For example, hypoxia resulted in a reduction in MnSOD and glutathione peroxidase (GSHPx) activities with no change in catalase activity. In the pressure-overload-induced model of heart failure, only SOD activity was significantly less, with no changes in the GSHPx and catalase activities. More recently, studies have reported unique regional differences in non-enzymatic antioxidants in hearts subjected to ischemia reperfusion. The exact stimulus for the altered activity of these enzymes is not known; however, increased free radical formation and/or lipid peroxidation during stress condition may act as a signal. Using the rat coronary artery ligation model, studies have reported depressed myocardial endogenous antiox-
dant reserve and increased oxidative stress associated with poor cardiac function.\textsuperscript{41,43-44} Furthermore, some ACEIs having sulphydryl residues, such as captopril, are known to act as free-radical scavengers, a property which may also play a contributory role in their cardioprotective action.\textsuperscript{45}

It is important to protect the target organs from damage induced by hypertension. This study demonstrates that ACEIs prevent the histological damage caused by hypertension induced by AAB in rats. The mild perivascular fibrosis, edema, and mild lymphocytic infiltration observed in the hypertensive rats were found to be consistent with those reported by Chen and coworkers,\textsuperscript{46} along with defragmentation of cardiac fibers, mild to moderate degree of hemorrhage, congestion, mild vacuolations and focal areas of necrosis in 1-2 areas. All these changes indicate the extent of damage to the heart due to hypertension in this model.

As described in the results, treatment with ACEIs brings about a decrease in the intensity of the cardiac damage, as shown by the mild degree of hemorrhage, mild perivascular fibrosis, defragmentation of cardiac fibers, congestion, edema, and mild vacuolations. The studies by Kumiko and coworkers demonstrated that early and transient treatments with angiotensin receptor blockers are effective in the prevention of hypertension induced end-organ damage.\textsuperscript{47}

Liver sections in the untreated AABIH group showed congestion, multifocal areas of necrosis, and dilation of the central vein. There was also a moderate degree of degeneration and vacuolations restricted to border areas below the hepatic capsule, indicating the initial stages of ischemia.

Endothelial dysfunction is one of the most important mechanisms involved in the development of atherosclerosis and is present in patients with various cardiovascular risk factors, including hypertension, hypercholesterolemia, and type II diabetes, as well as in patients with coronary artery disease. Endothelial dysfunction has important prognostic implications in patients.\textsuperscript{48-49} In one elegant study,\textsuperscript{50} resistance arteries obtained from gluteus subcutaneous biopsies from a small group of hypertensive patients and normotensive controls were studied by measuring the endothelium-dependent and independent responses and the cross-sectional area. The histological sections of the thoracic aorta in the untreated AABIH group showed a mild accumulation of foam cells in between the fibers. Following treatment with ACEIs there was no significant change in the vascular tissue, which shows that treatment with captopril and ramipril prevents the histopathological changes (prevention of end-organ damage) induced in the thoracic aorta observed in the hypertensive group. This may be attributed to the protective effect of ACEIs on the endothelial dysfunction of the vascular endothelium seen in hypertension-induced damage to the vasculature.

Conclusions

Our study demonstrates that ACE inhibition with captopril and ramipril causes an improvement in the myocardial antioxidant reserve and a decrease in oxidative stress, and also prevents pathophysiological alterations associated with hypertension in rats, as evidenced by the protection from histological changes observed in the treatment groups. The study also emphasizes that modulation of the RAS by ACE inhibition is beneficial in preventing target organ damage in hypertension.

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References


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