Comparative Effects of Pretreatment With Captopril and Losartan on Cardiovascular Protection in a Rat Model of Ischemia-Reperfusion

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OBJECTIVES

We sought to assess the comparative effects of pretreatment with captopril and losartan on myocardial infarct size and arrhythmias in a rat model of ischemia-reperfusion.

BACKGROUND

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) inhibit the renin-angiotensin system in different ways. However, the comparative effects of pretreatment with ACE inhibitors or ARBs on acute myocardial infarct size and arrhythmias are unknown.

METHODS

We randomly assigned 117 female Sprague-Dawley rats into three groups: group N was the normal control; group C was given 40 mg/kg body weight per day of captopril in drinking water; and group L was given 40 mg/kg per day of losartan in drinking water. After 10 weeks of pretreatment, 25 rats in each group were subjected to 17 min of left anterior descending coronary artery occlusion and 2 h of reperfusion with hemodynamic and electrocardiographic monitoring. Fourteen rats in each group had blood samples drawn and aortic rings removed to study vascular reactivity.

RESULTS

Mortality during ischemia and reperfusion was lower in combined groups L and C than in group N (4.2% vs. 19.2%, p = 0.042). Rats treated with losartan had significantly higher levels of angiotensin II in their plasma. Hemodynamic variables were not significantly different among the three groups. The thresholds of ventricular fibrillation (VF) before occlusion and after reperfusion were significantly higher in groups L and C than in group N (1.99 ± 0.24 and 1.93 ± 0.27 vs. 1.23 ± 0.17 mA, p = 0.04; 2.13 ± 0.25 and 1.78 ± 0.22 vs. 0.95 ± 0.11 mA, p = 0.001). The average episodes of ventricular tachycardia (VT) and VF per rat were significantly less in groups L and C than in group N (0.96 ± 0.2 and 1.2 ± 0.3 vs. 2.8 ± 0.4 mA, p < 0.001). Myocardial infarct size was significantly smaller in groups L and C than in group N (34 ± 3% and 35 ± 3% vs. 44 ± 3%, p = 0.031, 0.043). Endothelium-dependent vasorelaxation induced by a calcium ionophore (A23187) was increased in both groups but was only statistically significant in group C (p = 0.020).

CONCLUSIONS

Losartan and captopril have similar cardiovascular protective effects in a rat model of ischemia-reperfusion. They increased the threshold of VF, decreased mortality and decreased episodes of VT and VF, as well as decreased myocardial infarct size. (J Am Coll Cardiol 2000;35:787–95) © 2000 by the American College of Cardiology

The renin-angiotensin system has an important role in the regulation of cardiovascular function. The primary active peptide hormone of this system is angiotensin II (Ang II). Angiotensin-converting enzyme (ACE) converts angioten-
activity and possibly other mechanisms (6). Angiotensin II receptor blockers (ARBs) block the effects of Ang II but do not increase bradykinin. They have similar beneficial effects and may improve hemodynamic data and coronary angiogenesis (7). However, the relative effects of ACE inhibitors and ARBs on myocardial infarct size and ischemic injury remain uncertain. The objective of this investigation was to explore the comparative effects of pretreatment with the ACE inhibitor, captopril, and the ARB, losartan, on myocardial infarct size, hemodynamic data, arrhythmias, ventricular fibrillation (VF) threshold and endothelial function in a rat model of ischemia–reperfusion.

**METHODS**

**Experimental groups.** We randomly assigned 117 female Sprague-Dawley rats (body weight 225 to 250 g) into three groups: group N was the normal control; group C was given 40 mg/kg body weight per day of captopril in drinking water for 10 weeks; and group L was given 40 mg/kg per day of losartan in drinking water for 10 weeks. The rats were housed in a room maintained at a constant temperature and kept on a 12-h light-dark cycle. All rats were fed a regular diet.

**Rat model of acute myocardial ischemia and reperfusion.** A rat model of left anterior descending coronary artery (LAD) occlusion and reperfusion was used as previously described (8). After induction of anesthesia (pentobarbital, 40 mg/kg intraperitoneally), a tracheostomy was performed, and the animal was ventilated on a Harvard Rodent Respirator (Model 683, Harvard Apparatus, S. Natick, Massachusetts). A reversible coronary artery snare occluder was placed around the proximal LAD through a midline sternotomy. Twenty-five rats in each group were subjected to 17 min of LAD occlusion and reperfusion as previously described (8). A plastic catheter (PE50) was inserted into the femoral artery to measure hemodynamic data. Heart rate, systolic pressure, diastolic pressure and the product of heart rate and systolic pressure were monitored by a MacLab/4S (Milford, Massachusetts).

**Thresholds and episodes of VF.** Electrocardiograms (ECGs, lead I or II) were obtained by subcutaneously inserting needle electrodes into the limbs and were monitored during the ischemia and reperfusion period. Ventricular fibrillation thresholds were measured before occlusion and after 1 h of reperfusion. Electrodes were inserted into the right ventricular surface about 1 mm at the upper, middle and lower parts. Electrical multiple stimuli (50/s for 2 s) were applied and intensified by 0.1 mA each time using a Stimulator (Model DTU, Bloom Associates, Ltd, Reading, Pennsylvania). The average threshold of VF from three parts of the right ventricle was used as the electrical intensity which induced VF. The episodes of paroxysmal ventricular tachycardia (VT) and VF were noted during the occlusion and reperfusion period. No rat received antiarrhythmic agents before and during the occlusion and reperfusion.

**Infarct size.** Infarct size was measured as described previously (8,9). The LAD was reclosed, and phthalocyanin blue dye was injected into the left ventricular (LV) cavity, allowing normally perfused myocardium to stain blue. The heart was then excised, rinsed of excess dye and sliced transversely from apex to base into 2-mm-thick sections. The sections were incubated in a 1% solution of triphenyltetrazolium chloride (TTC) for 10 to 15 min until viable myocardium was stained brick red. Infarct-related myocardium fails to stain with TTC. The tissue sections were then fixed in a 10% formalin solution and weighed. Color digital images of both sides of each transverse slice were obtained with a video camera (COHU Y/C 460 HTYL, 768 × 494 array, Leica, San Diego, California) connected to a microscope (Stereo Zoom 6 Photo, Leica) using the Rasterops Frame Grabber card and Frame Grabber 3.2 software (Rasterops, Santa Clara, California). The regions showing blue-stained (nonischemic), red-stained (ischemic but noninfarct-related) and unstained (infarct-related) tissue were outlined on each color image and measured using the National Institutes of Health program NIH Image 1.59 in a blinded fashion. On each side, the fraction of LV area representing infarct-related tissue (average of two images) was multiplied by the weight of that section to determine the absolute weight of infarct-related tissue. The infarct size for each heart was expressed as:

\[
\text{Infarct size/LV mass (％)} = \sum \frac{\text{Infarct weight in each slice}}{\text{Total LV weight}} \times 100%,
\]

\[
\text{Risk area/LV mass (％)} = \frac{\text{Total weight of unstained section}}{\text{Total LV weight}} \times 100%,
\]

Infarct size as percent risk area was then calculated as:

\[
\frac{\sum \text{Infarct weight in each slice}}{\sum \text{Risk area weight of each slice}} \times 100%
\]

**Ang II and renin levels in plasma.** After 10 weeks, a subset of rats in the three groups (14 rats selected at random...
from each group) was killed by a lethal injection of pentobarbital (130 mg/kg intraperitoneally). At the time of death, blood was taken for measurement of plasma Ang II and renin by radioimmunoassy. Plasma renin activity was measured using an Ang I antibody, expressed as nanograms of Ang I generated per milliliter of plasma during 2 h of incubation at 37°C and pH 6.5. Ang II concentration was measured after extraction on bentonite. Recovery of Ang II was 80% (10,11).

Vascular reactivity studies. Aortic ring segments (1 to 2 mm in diameter and 4 to 5 mm in length) were rapidly excised from the descending thoracic aorta for organ bath studies of vascular reactivity. Each ring was suspended horizontally between two parallel stainless-steel wires to measure isometric force in individual organ baths containing Krebs solution at 37°C. Isometric force generated by the ring segment was recorded continuously as previously described (12). Ring segments were stabilized at 1 g rest force for 60 min before being studied. Phenylephrine in increasing doses from 10^{-9} to 10^{-4} mol/liter was added to each organ bath. For each ring, the dose needed to achieve half-maximal effective contraction (EC_{50}) of phenylephrine was calculated. After the phenylephrine contraction series, the baths were washed out three times with fresh Krebs solution, and each ring was allowed to stabilize for 1 h.

For determination of endothelium-derived nitric oxide–mediated vasorelaxation, aortic rings which had been precontracted with the EC_{50} of phenylephrine were then exposed to acetylcholine (10^{-9} to 10^{-4.5} mol/liter). Acetylcholine induces vasorelaxation by release of nitric oxide, which is coupled to muscarinic receptor stimulation. For measurement of endothelium-derived nitric oxide–mediated vasorelaxation induced by a non–receptor-dependent mechanism, the aortic rings were exposed to the calcium ionophore (A23187) in increasing doses (from 10^{-9} to 10^{-4.5} mol/liter) after the rings had been precontracted by EC_{50} of phenylephrine and stable tension had developed. Lastly, each ring was precontracted and exposed to the endothelium-independent relaxation agent nitroglycerin (doses from 10^{-9} to 10^{-5} mol/liter). Vascular reactivity experiments were performed by an investigator who had no knowledge of the treatment groups.

Statistical analysis. All data are presented as the mean value ± SEM. The response to phenylephrine was expressed as the change in force from baseline (grams). Relaxation of the aortic rings is expressed as percent change of net developed force (measured force – baseline force)/(precontracted force – baseline force), EC_{50} and slope. Slope, expressed by the Hill coefficient, was calculated using commercially available software (Kaleidagraph, Abelbeck software, Reading, Pennsylvania) that resolved a curve of best fit to each ring’s dose-response relation. Slope was calculated to describe sensitivity to vasoactive substances. Differences in mortality during the occlusion and reperfusion period between the three groups were assessed by the Fisher exact test. The two treatment groups (captopril [C] and losartan [L]) were compared with the normal control group (N) using one-way analysis of variance (ANOVA), with the regression equation for multiple group comparison. All computations were done with the general linear model procedure in Minitab, version 7.2 (Minitab Statistical Software, State College, Pennsylvania) or Prime of Biostatistics: The program, version 3.03 (McGraw-Hill, New York, New York). Statistical significance was set at p < 0.05.

RESULTS

Body weight. After 10 weeks of feeding, the body weight of the three groups was the same (groups N, C and L: 248 ± 7, 247 ± 3 and 255 ± 10 g, respectively; p = 0.728 by ANOVA).

Hemodynamic data. There were no significant differences in heart rate, systolic pressure, diastolic pressure and rate–pressure product (an index of myocardial oxygen consumption) between the three groups at baseline, during coronary occlusion or during reperfusion, as displayed in Figure 1. The hemodynamic variables in all rats declined during the course of the experiment.

Threshold and episodes of VF. The VF thresholds before occlusion and after 1 h of reperfusion were significantly higher in groups L and C than in group N (1.99 ± 0.24 and 1.93 ± 0.27 vs. 1.23 ± 0.17 mA, p = 0.025 and 0.034, respectively; 2.13 ± 0.25 and 1.78 ± 0.22 vs. 0.95 ± 0.11 mA, p = 0.001 and 0.010, respectively), as displayed in Figure 2.

Average episodes of VT and VF per rat during the occlusion and reperfusion period were significantly lower in groups L and C than in group N (0.96 ± 0.2, 1.2 ± 0.3 vs. 2.8 ± 0.4, p < 0.001 and = 0.001, respectively), as displayed in Figure 3. The percentage of rats with VF was significantly lower in groups L and C than in group N (57% and 62% vs. 96%, p = 0.005 by the chi-square test), as displayed in Table 1.

There were negative correlations between the average episodes and threshold of VF before occlusion and after reperfusion (r = −0.40, p = 0.015 and r = −0.42, p = 0.011, respectively). There was a positive correlation between the thresholds of VF before occlusion and after reperfusion (r = 0.61, p < 0.001).

Mortality. Mortality during the occlusion and reperfusion period was lower in groups L and C than in group N (L + C vs. N: 4.2% vs. 19.2%, p = 0.04; L vs. N: 0% vs. 19.2%, p = 0.05; C vs. N: 7.4% vs. 19.2%, p = 0.25).

Myocardial infarct size. Infarct size was significantly smaller in groups L and C than in group N (34 ± 3% and 35 ± 3% vs. 44 ± 3%, p = 0.031 and 0.043, respectively), as displayed in Table 2.

Vascular reactivity. Captopril supplementation significantly increased maximal A23187-induced endothelium-
dependent vasorelaxation, as well as slope (−79 ± 16% vs. −43 ± 7%, p = 0.020; −5.6 ± 2 vs. −1.2 ± 0.3, p = 0.029, respectively), as displayed in Figure 4. Losartan increased maximal A23187-induced endothelium-dependent vasorelaxation, although this was not statistically significant (−62 ± 8% vs. −43 ± 7%, p = 0.223). There were no significant differences in maximal vasorelaxation induced by acetylcholine or nitroglycerin between the three groups.

Ang II and renin levels in plasma. Rats treated with losartan for 10 weeks had significantly higher levels of angiotensin II in plasma (group L vs. C and N: 131 ± 47 vs. 42 ± 6 and 22 ± 3 pg/ml, p = 0.036 and 0.006, respectively). Rats treated with losartan and captopril for 10 weeks had higher levels of plasma renin activity (groups L and C vs. N: 103 ± 22 and 90 ± 14 vs. 28 ± 10 ng/ml, p = 0.005 and 0.022, respectively).

**DISCUSSION**

The primary findings of this study were that captopril and losartan had cardioprotective effects in this model of ischemia-reperfusion. The data with both agents was concordant, although there was not always statistical significance with both drugs for all end points. This may have been due to the small numbers in some groups. Results showed that: 1) both drugs decreased mortality during the ischemia-reperfusion period, although this was statistically significant for losartan only; 2) losartan and captopril significantly reduced myocardial infarct size; 3)
 losartan and captopril significantly decreased episodes of VT and VF and increased VF threshold; 4) hemodynamic data were not different in the three groups; 5) rats treated with losartan for 10 weeks had significantly higher levels of Ang II in plasma; and 6) both drugs increased endothelium-dependent vasorelaxation induced by a calcium ionophore (A23187), although this was statistically significant for captopril only.

**Figure 2.** The VF threshold before occlusion and after reperfusion in the three groups of rats. The VF threshold in groups L and C was statistically greater than that in group N, both before occlusion and after reperfusion. However, groups L and C were not statistically different (p = 0.861 and 0.238).

**Figure 3.** Average episodes of VT and VF per rat during ischemia and reperfusion in the three groups of rats. The episodes in groups L and C were statistically less than those in group N. However, groups L and C were not statistically different (p = 0.545).
Optimal dose and hemodynamic data. It is possible that the results of this study were influenced by the dose used. We attempted to use a dose that was effective but did not induce hypotension. In previous rat studies, the dose range for captopril or losartan was 50 to 60 mg/kg per day for 12 weeks (13,14) or 2 g/liter drinking water for three weeks to one year (15,16). A recent clinical study showed that a high dose of ACE inhibitor is superior to a low dose in chronic heart failure (17). We did a preliminary dose finding study. After one to two weeks of 60 mg/kg per day of captopril or losartan, hemodynamic data (heart rate and systolic and diastolic pressures) did not change significantly in the three groups. The lower dose, 40 mg/kg per day for 10 weeks, was then selected to have a safety margin in avoiding significant changes in hemodynamic data.

In the present study, 40 mg/kg per day of captopril or losartan for 10 weeks only decreased systolic pressure slightly (groups C and L vs. N: 118 and 113 vs. 128 mm Hg, p = 0.332). However, there were no significant differences in hemodynamic data between the three groups at any point during 17 min of ischemia and 2 h of reperfusion. Therefore, we conclude that captopril or losartan reduced infarct size independent of hemodynamic effects.

Myocardial infarct size. The ACE inhibitor, ramiprilat (50 µg/kg intravenously [IV]), reduced infarct size in a rabbit model of ischemia-reperfusion (5). This effect was abolished by pretreatment with the specific bradykinin-2 antagonist, HOE140 (1 µg/kg IV), or by inhibiting nitric oxide synthase (L-NAME [Nw-nitro-L-arginine methyl ester], 100 µg/kg IV) (5,18). This supports the role of improved endothelial function during reperfusion, which would limit infarct size. Furthermore, it would suggest that bradykinin and nitric oxide play a pivotal role, consistent with our findings that only captopril (and not losartan) statistically improved vascular relaxation. However, because losartan reduced infarct size, bradykinin cannot be the only mechanism of benefit. Reducing the adverse effects of angiotensin II must also play a role. The ACE inhibitors also suppressed the temporal increase in infarct zone collagen and attenuated infarct zone expansion, thinning and bulging, as well as LV enlargement and aneurysm formation during healing after acute myocardial infarction (19). The angiotensin II Type I receptor (AT₁) blocker, losartan, was associated with a significant decrease in cardiac fibrosis in rats treated after myocardial infarction (20).

Several studies showed that long-term therapy with captopril (2 g/liter of drinking water for 10 months) produced a marked regression of LV hypertrophy and prevented the development of severe cardiac dysfunction in the spontaneously hypertensive rat (21–23). However, ACE inhibition and AT₁ receptor blockade were equally effective in limiting the increase in ventricular mass, suggesting that myocyte hypertrophy, the major determinant of ventricular mass, was strongly influenced by activation of the AT₁ receptor (24).

Our study demonstrated that either losartan or captopril can significantly reduce myocardial infarct size in a rat model of ischemia-reperfusion. This supports the concept of a significant role of the cardiac renin-angiotensin system in myocardial ischemia-reperfusion injury (6).

Episodes of VF and VF threshold. Ischemia-reperfusion injury is associated with expansion of the infarct area and the occurrence of life-threatening arrhythmias (25). Using

### Table 1. Percentage of Rats With Ventricular Fibrillation in the Three Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>No. With VF</th>
<th>No. Without VF</th>
<th>Percentage</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (n = 24)</td>
<td>23</td>
<td>1</td>
<td>95.8%</td>
<td>0.005*</td>
</tr>
<tr>
<td>C (n = 26)</td>
<td>16</td>
<td>10</td>
<td>61.5%</td>
<td>0.002*</td>
</tr>
<tr>
<td>L (n = 23)</td>
<td>13</td>
<td>10</td>
<td>56.5%</td>
<td>0.005†</td>
</tr>
</tbody>
</table>

*By the Fisher exact test. †By the chi-square test.

C = captopril-treated group; L = losartan-treated group; N = normal control group; VF = ventricular fibrillation.

### Table 2. Myocardial Infarct Size in the Three Groups of Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Inf/LV</th>
<th>RA/LV</th>
<th>Inf/RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (n = 21)</td>
<td>26.3 ± 1.9%</td>
<td>59.6 ± 1.4%</td>
<td>44.3 ± 3.0%</td>
</tr>
<tr>
<td>C (n = 25)</td>
<td>20.4 ± 2.0%</td>
<td>58.0 ± 1.3%</td>
<td>35.2 ± 3.2%</td>
</tr>
<tr>
<td>L (n = 23)</td>
<td>20.3 ± 1.8%</td>
<td>58.8 ± 1.8%</td>
<td>34.4 ± 3.0%</td>
</tr>
</tbody>
</table>

0.046* 0.759* 0.057*

C vs. N 0.030† C vs. N 0.043†

L vs. N 0.029† L vs. N 0.031†

C vs. L 0.960† C vs. L 0.847†

*By analysis of variance. †Using regression equation for multiple group comparison. Data are presented as the mean value ± SEM.

Inf = infarct size; LV = left ventricle; RA = right atrium; other abbreviations as in Table 1.
isolated perfused rat hearts, ACE inhibitors decreased the incidence of VF and cardiac enzymes and increased glycogen, adenosine triphosphate, creatine phosphate, LV pressure and coronary flow (26). These effects of ACE inhibitors have been attributed to both a blockade of Ang II synthesis and a decrease in breakdown of bradykinin, which may stimulate the production of prostaglandin and nitric oxide.

Using Ang II type 1a receptor (AT\textsubscript{1a}) knockout mice, one study found that during ischemia and reperfusion, Ang II is involved in the induction of ventricular arrhythmias through AT\textsubscript{1}, and both genetic deletion of the AT\textsubscript{1a} gene and treatment with the AT\textsubscript{1} antagonist CV-11974 significantly attenuated reperfusion arrhythmias (27). Reperfusion-induced arrhythmias are postulated to be associated with major alterations in Ca\textsuperscript{2+} levels. It is well known that Ang II not only increases Ca\textsuperscript{2+} influx through the 1-type Ca\textsuperscript{2+} channel but also induces Ca\textsuperscript{2+} release from intracellular stores through AT\textsubscript{1}. Losartan, as an AT\textsubscript{1} antagonist, has been reported to attenuate ventricular tachyarrhythmias during reperfusion (28).

The results of the present study are consistent with the previously cited studies. Either losartan or captopril significantly attenuated VT and VF and increased the threshold of VF during ischemia and reperfusion. Both losartan and captopril may suppress the release of catecholamines and decrease calcium overload. The AT\textsubscript{1} receptor antagonists and ACE inhibitors appear to attenuate fibrous tissue formation and suppress endogenous endothelin secretion, which may account for less ventricular dysfunction and ventricular arrhythmias (29,30).

**Mortality during ischemia and reperfusion.** The mortality resulting from reperfusion-induced irreversible VF in a control group decreased from 43% to 8% (p < 0.05) at a dose of 3 mg/kg of captopril given intravenously 10 min before coronary artery ligation in rats (31). Long-term therapy with captopril reduced peri-infarction mortality in spontaneously hypertensive rats (32). This study suggests that regression of myocardial hypertrophy or long-term normalization of arterial systolic blood pressure, or both, are major determinants of very early mortality (within 1 h after infarction).

The results of our present study showed that captopril (40 mg/kg per day for 10 weeks) reduced mortality (19.2% to 7.4%, p = 0.25), although this was not statistically significant. Losartan (40 mg/kg per day for 10 weeks) significantly reduced mortality (19.2% to 0%, p = 0.05). Several studies showed that losartan decreased sudden death after acute myocardial infarction, achieved normalization of excessive cardiovascular morbidity and mortality (33) and even prevented stroke (34).

**Endothelial function.** Hypertension is associated with endothelial dysfunction characterized by decreased endothelium-dependent relaxation and increased endothelium-dependent contraction. A study in spontaneously hypertensive rats showed that both captopril and losartan improved endothelial function in aortic rings, not only by enhancing endothelium-dependent relaxation but also by reducing contractions in response to an endothelium-derived contracting factor (14).

Another study showed that losartan did not modify the relaxing responses to either acetylcholine or sodium nitroprusside in phenylephrine-preconstricted aortic rings. Furthermore, losartan did not alter isometric tension in either basal or phenylephrine-precontracted conditions (35). Long-term AT\textsubscript{1} blockade alone does not affect endothelium-dependent relaxation and increases contractions to AT\textsubscript{2} in the rat aorta (36). Long-term treatment with captopril partially normalizes endothelium-dependent relaxation responses in the rat aorta (37). Early and long-term treatment with captopril can prevent alterations in endothelial function, even after ACE inhibitor therapy has been stopped (38).

The results of vascular reactivity in the present study showed that both drugs improved endothelium-dependent relaxation induced by A23187, although this was only statistically significant with captopril (p = 0.020). This suggests a role for bradykinin in the response to captopril.

**Clinical implications.** Our study suggests that if acute myocardial infarction (ischemia-reperfusion) occurs, long-term pretreatment with captopril or losartan may reduce infarct size and arrhythmias. In elderly patients with heart failure, the Evaluation of Losartan In The Elderly (ELITE) study found that losartan (at dose of 50 mg/day) was
superior to captopril, 50 mg three times daily, in terms of its effects on total mortality and/or hospital admission for chronic heart failure (39). The reduction in mortality was principally due to a reduction in sudden death. That result is concordant with our findings that losartan decreased arrhythmic death more than captopril. It is self-apparent, however, that an anesthetized rat model may be significantly different from patients. The ACE inhibitors have been extremely beneficial after myocardial infarction. We do not yet have the same data with ARBs. Studies like OPTIMAAL (Optimal Trial in MI with All Antagonist Losartan) with losartan are currently evaluating this question.

Conclusions. Captopril and losartan both have cardiovascular protective effects in a rat model of ischemia-reperfusion. Pretreatment with either losartan or captopril for 10 weeks increased the VF threshold, decreased episodes of VT and VF and reduced myocardial infarct size. Both drugs decreased mortality, although this was statistically significant only with losartan. Both drugs also improved endothelial function, although this was statistically significant only with captopril. These effects were independent of hemodynamic variables.

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