Amelioration by Quinapril of Myocardial Infarction Induced by Coronary Occlusion/Reperfusion in a Rabbit Model of Atherosclerosis

Possible Mechanisms

Shiro Hoshida, MD, PhD; Nobushige Yamashita, MD, PhD; Kiminori Kawahara, MS; Tsunehiko Kuzuya, MD, PhD; Masatsugu Hori, MD, PhD

Background—The increased severity of the myocardial injury produced by coronary occlusion-reperfusion in models of atherosclerosis is associated with an increase in leukocyte accumulation in the ischemic myocardium. Expression of P-selectin, an adhesion molecule involved in the interaction between leukocytes and endothelium, is increased in atherosclerotic vessels. Long-term angiotensin-converting enzyme (ACE) inhibition has been shown to reduce atherosclerotic vascular change in experimental models.

Methods and Results—We examined changes in the size of the infarct resulting from coronary occlusion/reperfusion in normally fed and cholesterol-fed rabbits that were chronically treated with quinapril. Infarct size was significantly larger in the cholesterol-fed versus normally fed rabbits. ACE activity in the ischemic and nonischemic myocardium was significantly reduced by quinapril. Chronic quinapril administration significantly ameliorated the increased myocardial injury in cholesterol-fed rabbits. Quinapril administration markedly increased the myocardial cGMP content and reduced the myeloperoxidase activity in the border region of the ischemic myocardium in cholesterol-fed rabbits. The enhanced expression of P-selectin in myocardial tissue of cholesterol-fed rabbits was also effectively reduced by quinapril treatment. The above effects of quinapril were eliminated by blockade of bradykinin B₂ receptors or inhibition of nitric oxide synthesis.

Conclusions—Chronic quinapril treatment ameliorated the severity of myocardial injury produced by coronary occlusion/reperfusion in cholesterol-fed rabbits, possibly because of reversal of the enhanced interaction between leukocytes and endothelium in the ischemic myocardium via a bradykinin-related pathway. (Circulation. 1999;99:434-440.)

Key Words: hypercholesterolemia n atherosclerosis n myocardial infarction n P-selectin

An impairment of coronary endothelium-dependent relaxation (EDR) increases the interaction between leukocytes and endothelium, leading to a progression of the myocardial infarct produced by coronary occlusion/reperfusion.¹,² In atherosclerotic coronary circulation, coronary EDR is known to be impaired but is effectively restored by chronic administration of the angiotensin-converting enzyme (ACE) inhibitor quinapril.³ ACE inhibitors block the degradation of bradykinin, thus increasing the production of nitric oxide (NO). These inhibitors significantly reduce the atherosclerotic area⁴–⁷ and restore EDR⁷,⁸ of the aorta in several atherosclerotic models.

The severity of myocardial injury has been shown to be exacerbated by acute hypercholesterolemia.⁹–¹¹ We previously reported that the size of the infarct produced by coronary occlusion/reperfusion is increased in cholesterol-fed rabbits or rabbits with hereditary hyperlipidemia versus normal rabbits.¹²–¹⁴ The reduction of infarct size by administration of an NO donor or an antioxidant in these rabbits is associated with a reduction in leukocyte accumulation of the ischemic myocardium. In rabbits with hereditary hyperlipidemia, the expression of P-selectin, an adhesion molecule involved in the interactions between the leukocytes and the endothelium, is increased in the coronary endothelium.¹⁴ P-selectin has been shown to be suppressed by NO¹⁵,¹⁶ but induced by oxidized low-density lipoprotein¹⁷ and oxygen radicals.¹⁸ Reduction of P-selectin expression may be important in the decrease in the infarct size through the reversal of the enhanced interactions between leukocytes and endothelium.

The purpose of the present study was to investigate the effects of chronic ACE inhibition on infarct size and leuko-
cyte accumulation in the ischemic myocardium of atherosclerotic tissue rabbits. The expression of P-selectin in the myocardial tissue, the content of cGMP in the myocardium of atherosclerotic rabbits, and the effects of blockade of the bradykinin B₂ receptor or inhibition of NO synthase were also examined.

Methods

Protocol
A total of 60 male Japanese white rabbits (2.4 to 2.8 kg) were fed a diet of standard laboratory chow (normally fed; n=26) or chow that was supplemented with 1% cholesterol (cholesterol-fed; n=34) for 10 weeks. From the beginning of the diet regimen, 24 cholesterol-fed rabbits and 16 normally fed rabbits received 3 mg · kg⁻¹ · d⁻¹ quinapril in single oral doses for 10 weeks (treated groups). In a preliminary study, this dose of quinapril did not reduce mean arterial pressure in cholesterol-fed rabbits 24 hours after the last administration. Arterial blood samples for measurement of plasma total cholesterol were collected into tubes containing heparin immediately before the 10-week feeding period and at the end of the 10 week-period, 24 hours after the last dose of quinapril.

After 10 weeks on their respective diets and 24 hours after the last dose of quinapril, the rabbits were anesthetized with injections of sodium pentobarbital (30 mg/kg), intubated, and ventilated with the use of a small-animal respirator. The right femoral artery was used for the continuous measurement of heart rate and arterial blood pressure. The right femoral vein was used for drug administration. Experimental myocardial infarction was induced as reported previously.12,13 Briefly, a silk thread was passed around a branch of the left coronary artery with a tapered needle, and the ends of the thread were passed through a small vinyl tube. The snare was released after 30 minutes of coronary occlusion. The surgical wounds were repaired 60 minutes after reperfusion, and the animals were returned 30 minutes of coronary occlusion. 19 In some quinapril-treated, cholesterol-fed rabbits (n=6), a competitive NO-synthase inhibitor, N⁵-L-nitro-arginine methyl ester (L-NAME, 100 μg · kg⁻¹ · min⁻¹)20 was continuously infused beginning before coronary occlusion and lasting for 60 minutes. Forty-eight hours after the reperfusion, each rabbit received an intravenous injection of 1000 U of heparin and was then administered an overdose of pentobarbital. The aortic tissue and the heart were then removed for postmortem evaluation. Aseptic surgical techniques were employed throughout. Benzylpenicillin (30 000 U/kg) was injected intramuscularly as prophylaxis against infection. The snare was left in place for 48 hours. No rabbits received quinapril during the 10-day-period, 24 hours after the last dose of quinapril.

Assessment of Aortic Atherosclerosis
The surface area of the atherosclerotic lesions was determined in the thoracic aorta as previously described.7,14 Briefly, adventitial tissue was dissected from the aorta and any remaining blood was rinsed away. The surface area of the lesion and the total aortic surface area were measured by planimetry of photographic images.

To assess EDR, arterial rings 5 mm long were cut and suspended from strain gauges. The isometric circumferential force was measured using a small-animal respirator. The isometric circumferential force was measured as previously described.14 Relaxation was measured in rings precontracted by incubation with 1 μmol/L norepinephrine. Endothelial control of vascular tone was assayed by the addition of acetylcholine (ACh, 1 nmol/L to 10 μmol/L), and vasodilation of smooth muscle cells was assessed using sodium nitroprusside (SNP, 1 nmol/L to 10 μmol/L).

Measurement of Infarct Size
The size of the infarct was assessed as reported previously.12,13 Briefly, Evans blue dye (2%) was introduced after the reocclusion of the left coronary branch to estimate the ventricular mass perfused by the occluded artery (ischemic region). The left ventricle was cut perpendicular to the apex-base axis into 6 pieces. The slices were then incubated with 1% triphenyltetrazolium chloride to stain the noninfarcted region. The area at risk was defined as the ischemic region/left ventricular mass ratio and the infarct size as the infarct region/ischemic region mass ratio.

Assay of ACE Activity
ACE activity was determined spectrophotometrically by a method modified17 from that of Cushman and Cheung.21 After the 48-hour reperfusion phase, aortic tissues and myocardial samples obtained from nonischemic and ischemic tissues were homogenized on ice and were centrifuged for 20 minutes at 1500g (4°C). The supernant was incubated at 37°C for 60 minutes with hippuryl-L-histidyl-L-leucine in 10 mmol/L potassium phosphate buffer (pH 8.3) that contained 300 mmol/L sodium chloride. Hippurate was detected by absorbance at 228 nm. One unit of ACE activity was defined as the amount of enzyme that generated 1 nmol of hippurate per minute at 37°C.

Measurement of cGMP Content
The myocardial cGMP content was measured by ELISA (Amer sham). After 30 minutes of reperfusion, hearts were excised and tissue samples were homogenized in 0.1N hydrochloric acid; the supernatants obtained by centrifugation were assayed.

Assessment of Leukocyte Accumulation
Myeloperoxidase (MPO) activity was assayed as previously described.12 Myocardial tissue was obtained from the ischemic and nonischemic regions of hearts reperfused for 48 hours and from nonischemic and border regions of hearts reperfused for 30 minutes. These samples were frozen rapidly in liquid nitrogen. One unit of MPO activity was defined as the amount of enzyme required to degrade 1 μmol peroxide per minute at 30°C.

Immunohistochemistry
Immunohistochemical evaluation was performed as reported previously.14 The specimens of left ventricle were incubated with monoclonal mouse anti-human P-selectin (WAPS 12.2, Endogen Inc., Cambridge, Mass) for 60 minutes at room temperature; they were then exposed to peroxidase-conjugated affinity purified anti-mouse IgG (Kirkegaard & Perry Laboratories Inc., Gaithersburg, Md) for 60 minutes. Specific antigen-antibody complexes were visualized by development in 3-amino-9-ethylcarbazole (Aldrich-Chemie) and hydrogen peroxide in acetate buffer (0.05 mol/L, pH 5.0). The sections were counterstained with hematoxylin and then dehydrated. Controls were obtained by replacing the primary antibody with 10% nonimmune serum or phosphate-buffered saline. Additional controls were obtained by omitting the secondary antibody. All controls were negative.

Statistical Analysis
Values are expressed as mean±SEM. The significance of differences in infarct size, ACE activity, and hemodynamic changes were determined by analysis of variance (ANOVA) followed by Scheffe’s test as appropriate. ANCOVA was used to compare the regression lines of ischemic region mass versus infarcted tissue mass. A level of P<0.05 was accepted as statistically significant.

Results

Mortality and Characteristics
Two rabbits died of ventricular fibrillation during reperfusion, and 1 rabbit in each group died during coronary

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occlusion. The mortality rate did not differ significantly among the groups. There were no significant differences in body weight or plasma total cholesterol concentration among the groups at the beginning of the 10-week feeding period (Table 1). After the 10-week feeding period, there was no significant difference in the plasma total cholesterol concentration among the groups of cholesterol-fed rabbits or among the groups of normally fed rabbits.

**Effect of Chronic Quinapril on Aortic Atherosclerosis**

The chronic administration of quinapril effectively reduced the area of atherosclerotic plaque in the thoracic aorta of the cholesterol-fed rabbits (Figure 1). Aortic ACE activity was significantly higher in cholesterol-fed rabbits than in normally fed rabbits (Figure 1). The activity in both groups was markedly suppressed by the treatment with quinapril.

In aortic rings from normal-fed rabbits, ACh induced relaxation in a concentration-dependent manner (Figure 2). Maximal relaxation (complete elimination of norepinephrine-induced contraction) was observed at 10 μmol/L. In aortic rings obtained from the untreated cholesterol-fed rabbits, ACh was less efficacious, but the chronic administration of quinapril partially restored the response to ACh. In contrast, the vasodilatory response to the NO donor SNP was similar in the experimental groups.

**Hemodynamic Variables**

There was no significant difference in arterial pressure among the groups during ischemia and reperfusion (data not shown). The rate-pressure product, an index of myocardial oxygen consumption, was similar at all time points. The rate-pressure product in the 2 groups pretreated with HOE 140 or in the L-NAME-treated group did not differ from that of the other groups.

**Infarct Size**

The size of the infarct was significantly greater in the untreated cholesterol-fed rabbits than in the rabbits fed a normal diet (Figure 3). The size of the infarct in the quinapril-treated rabbits fed a normal diet did not differ significantly from that in the untreated group fed a similar diet. However, the size of the infarct in the quinapril-treated, cholesterol-fed rabbits was significantly smaller than that in the untreated, cholesterol-fed rabbits. The quinapril-induced reduction in the size of the infarct in cholesterol-fed rabbits was eliminated by administering a bradykinin B2 receptor blocker. The size of the infarct in the quinapril-treated, normally fed rabbits was not affected by pretreatment with HOE 140. Acute treatment with L-NAME during coronary occlusion and reperfusion also reversed the quinapril-induced reduction of infarct size in cholesterol-fed rabbits. There were no significant differences among the groups in the area at risk.

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**Table 1. Characteristics of Experimental Groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Body Weight, kg</th>
<th>Plasma Total Cholesterol, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Normally fed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated (n=8)</td>
<td>2.6±0.1</td>
<td>3.2±0.1*</td>
</tr>
<tr>
<td>Quinapril† (n=9)</td>
<td>2.6±0.1</td>
<td>3.3±0.1*</td>
</tr>
<tr>
<td>Quinapril+HOE 140‡ (n=5)</td>
<td>2.6±0.1</td>
<td>3.2±0.1*</td>
</tr>
<tr>
<td>Cholesterol-fed§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated (n=9)</td>
<td>2.6±0.1</td>
<td>3.2±0.1*</td>
</tr>
<tr>
<td>Quinapril (n=9)</td>
<td>2.6±0.1</td>
<td>3.2±0.1*</td>
</tr>
<tr>
<td>Quinapril+HOE 140 (n=7)</td>
<td>2.6±0.1</td>
<td>3.1±0.1*</td>
</tr>
<tr>
<td>Quinapril+L-NAME¶ (n=5)</td>
<td>2.6±0.1</td>
<td>3.2±0.1*</td>
</tr>
</tbody>
</table>

Body weight and total plasma cholesterol concentration were determined immediately before and after the 10-week feeding period.

*P<0.05 versus before the 10-week feeding period.
†Rabbits received quinapril (3 mg · kg⁻¹ · day⁻¹) during the 10-week feeding period.
‡A bolus injection (IV) of HOE 140 (26 μg/kg) was administered 15 minutes before occlusion.
§Laboratory chow was supplemented with 1% cholesterol.
¶L-NAME (100 μg · kg⁻¹ · min⁻¹) was administered immediately before occlusion for 60 minutes.
The infarct tissue mass was significantly correlated with the mass of the ischemic region in all groups. The regression line of data from the untreated, cholesterol-fed rabbits was significantly different from that for the untreated, normally fed rabbits or the 2 quinapril-treated groups (Figure 4). Although not shown, the regression line for the quinapril-treated, cholesterol-fed rabbits given HOE 140 or L-NAME was similar to the line for the untreated, cholesterol-fed rabbits.

ACE Activity in Myocardial Tissue
ACE activity in ischemic myocardium of the untreated groups was significantly greater than activity in the nonischemic myocardium (Figure 5). ACE activity in ischemic and nonischemic myocardium from cholesterol-fed rabbits was also higher than activity in the corresponding tissue from normally fed rabbits. Treatment with quinapril significantly reduced the ACE activity of the ischemic and nonischemic myocardium in both the normally fed and cholesterol-fed rabbits.

cGMP Content in Myocardial Tissue
cGMP content in nonischemic myocardium after 30 minutes of reperfusion did not differ significantly among the groups

Accumulation of Leukocytes
In all groups, MPO activity was significantly higher in the ischemic versus the nonischemic myocardium. The MPO activity in the ischemic myocardium after 48 hours of reperfusion was significantly higher in the untreated cholesterol-fed rabbits than that in normally fed rabbits. Treatment with quinapril significantly reduced the ACE activity of the ischemic and nonischemic myocardium in both the normally fed and cholesterol-fed rabbits (Figure 6). The content in the border region of the ischemic myocardium was significantly reduced, compared with the nonischemic myocardium in both normally fed and cholesterol-fed rabbits. Chronic quinapril treatment restored the cGMP content in the border region in cholesterol-fed rabbits, although HOE 140 pretreatment eliminated the effect of quinapril. Acute treatment with L-NAME also reversed the effect of quinapril on the cGMP content in cholesterol-fed rabbits.

Figure 2. Relaxation of rabbit arterial rings. Thoracic aorta were harvested from normally fed (open symbols) and cholesterol-fed (filled symbols) rabbits treated (squares) or untreated (circles) with quinapril. Data expressed as mean±SEM. Symbols as in Figure 1.

Figure 3. Infarct size and area at risk affected by occlusion/reperfusion. Groups are described in Table 1. Infarct size (necrotic tissue mass/ischemic region mass) and area at risk (ischemic region mass/left ventricle mass) were evaluated after 48 hours of reperfusion. Data expressed as mean±SEM of values from n rabbits. *P<0.05 (ANOVA and Scheffe’s test) versus normally fed rabbits; †P<0.05 versus without quinapril; and ‡P<0.05 versus quinapril without HOE 140 or L-NAME.

Figure 4. Correlation between the ischemic region mass and infarcted tissue mass in rabbits. Data from normally fed rabbits are represented by open circles (untreated; line a; \( y = 0.69x - 0.22; r = 0.943 \)) or open squares (quinapril-treated; line b; \( y = 0.65x - 0.26; r = 0.671 \)). Data from cholesterol-fed rabbits are represented by filled circles (untreated; line c; \( y = 0.88x - 0.23; r = 0.939 \)) or filled squares (quinapril-treated; line d; \( y = 0.73x - 0.35; r = 0.862 \)).

Figure 5. Myocardial angiotensin-converting enzyme (ACE) activity. Data expressed as mean±SEM of values from n rabbits. *P<0.05 versus normally fed rabbits; †P<0.05 versus nonischemic; and ‡P<0.05 versus without quinapril. All results obtained by ANOVA and Scheffe’s test.
The activity of the border region of cholesterol-fed rabbits was further increased compared with normally fed rabbits and was significantly suppressed by chronic quinapril. Pretreatment with HOE 140 eliminated the quinapril-induced suppression of MPO activity of the border region in cholesterol-fed rabbits (Figure 7 bottom). Treatment with L-NAME also reversed the effect of quinapril in cholesterol-fed rabbits.

Expression of P-Selectin

After 30 minutes of reperfusion, P-selectin in the border region of the ischemic tissue was localized on coronary endothelium with leukocytic emboli in untreated cholesterol-fed rabbits (Figure 8B), although the expression of P-selectin on intravascular platelets could not be ruled out. In contrast, little or no specific staining for P-selectin was observed on the myocardium in chronically quinapril-treated cholesterol-fed rabbits (Figure 8C). Pretreatment with HOE 140 reversed the reduced expression of P-selectin in quinapril-treated cholesterol-fed rabbits (Figure 8D). Although not shown, acute treatment with L-NAME also increased the expression of P-selectin in the treated, cholesterol-fed rabbits. Rabbits fed a normal diet did not express P-selectin in postischemic myocardial tissue (Figure 8A), and the chronic quinapril treatment did not affect the expression of P-selectin (data not shown).

Discussion

Atherosclerosis in ACE Inhibition

We recently reported that ACE activity increases during the process of atherosclerotic lesion formation in the aorta and that chronic ACE inhibition with enalapril effectively reduces aortic atherosclerotic lesion area in association with a significant reduction of aortic ACE activity. Results of the present study are consistent with these previous observations. Moreover, chronic administration of quinapril, which is a more potent inhibitor of ACE activity than enalapril in several tissues, reduced both the atherosclerotic lesion area and ACE activity in aorta more effectively than enalapril (compared with data from reference 7).

Mechanism for Limitation of Size of Infarct

Chronic quinapril treatment reduced the severity of myocardial injury in the cholesterol-fed rabbits to the level observed in the normally fed rabbits, except during bradykinin B2 receptor blockade or NO synthase inhibition. Under these conditions, chronic quinapril ameliorated the reduction of cGMP content and the increased MPO activity and reduced the increased expression of P-selectin in the border region of the ischemic myocardium in cholesterol-fed rabbits. P-selectin has been shown to be induced by oxidized low-density lipoprotein and/or lysophosphatidylcholine and to be suppressed by NO. The restoration of cGMP content of the border region by chronic quinapril may reflect the increased production of NO. Furthermore, a competitive NO-synthase inhibition effectively increased the size of the infarct associated with the augmentation of myocardial MPO activity in quinapril-treated, cholesterol-fed rabbits. These results suggest that the efficacy of chronic quinapril in limiting the size of the infarct in cholesterol-fed rabbits may be related to the reduction of leukocyte-induced myocardial injury by suppressing the expression of P-selectin. A reduction in P-selectin expression would result from an increased production of NO because of a reduction in the degradation of bradykinin. However, one cannot rule out a more direct effect of bradykinin on adhesion between leukocytes and endothelium. The expression of other important adhesion molecules involved in the interaction between leukocytes and endothelium remains to be investigated.

Inhibition of Myocardial ACE

Although myocardial ACE activity was suppressed by chronic quinapril more completely in the present study than...
in previous studies with enalapril, the infarct-limiting effect of quinapril did not differ significantly from that of enalapril in cholesterol-fed rabbits.\textsuperscript{24} The suppression of myocardial ACE activity to some threshold level may be sufficient to reduce the size of the infarct. A threshold level of bradykinin in myocardial tissue may be all that is needed to reduce leukocyte accumulation and infarct size. Because myocardial ACE activity was completely suppressed 3 days after the last dose of quinapril in the present study, left ventricular remodeling after myocardial infarction may be inhibited sufficiently even when treatment with quinapril commences 2 days after the onset of myocardial infarction in patients that had received chronic quinapril treatment before onset of infarction.

ACE Inhibition in Normal Rabbits

Adhesion molecules such as P-selectin and intercellular adhesion molecule-1 are expressed in the coronary bed of the reperfused myocardium in normal cats;\textsuperscript{25} antibodies against these adhesion molecules have reduced myocardial injury in normal dogs.\textsuperscript{26} However, there may be species differences in the expression of P-selectin in the ischemic myocardium. P-selectin was not expressed in the coronary vasculature of the ischemic/reperfused myocardium and chronic quinapril treatment did not modulate its expression in normally fed rabbits. Therefore, quinapril could not further reduce leukocyte accumulation in the border region of the ischemic myocardium, consistent with the inability to limit infarct size in normally fed rabbits in the present study. Several investigators have reported infarct-limiting effects of acute treatment with ACE inhibitors and its reversal by bradykinin receptor blockade in normal animals.\textsuperscript{27,28} The reason for the discrepancy may lie in differences in experimental design, such as the timing of infarct size assessment or ACE inhibitor administration. Failure of limitation of infarct size by ACE inhibitors has also been reported in normal dogs\textsuperscript{29} and rabbits.\textsuperscript{30}

Study Limitations

Although coronary EDR was not measured in all groups, quinapril has been shown to restore coronary EDR in humans.\textsuperscript{5} Myocardial cGMP content and P-selectin expression were determined after 30 minutes of reperfusion, but examination of the time course of these parameters may be important in elucidating the precise mechanism for infarct size-limitation in cholesterol-fed rabbits. Little work has been done on the effect of ACE inhibition on platelet function. Furthermore, changes in healing or collagen deposition at longer time points following myocardial injury in an ACE inhibitor-treated, cholesterol-fed rabbits remain to be elucidated. It is interesting to know how long ACE inhibitors should be administered to obtain favorable effects on infarct

Figure 8. Expression of P-selectin in cardiac tissue. Photomicrographs of the border region in the ischemic myocardial tissue sections incubated with anti-P-selectin from normally fed rabbits and cholesterol-fed rabbits. A, Normally fed rabbits; B, Untreated, cholesterol-fed rabbits; C, Quinapril-treated, cholesterol-fed rabbits; and D, Cholesterol-fed rabbits treated with quinapril and HOE 140. All specimens were counterstained with hematoxylin and are displayed at the same magnification. Bar shows 50 μm.
size in cholesterol-fed rabbits, although short-term treatment with quinapril for 1 week did not reduce infarct size in our preliminary study (data not shown).

Conclusions
Chronic quinapril treatment ameliorated the severity of myocardial injury that resulted from coronary occlusion/reperfusion in cholesterol-fed, but not normally fed, rabbits. The improvement was associated with a reduction in the myocardial accumulation of leukocytes possibly because of an inhibition of myocardial expression of P-selectin. Bradykinin receptor blockade or NO-synthase inhibition effectively reversed the favorable effects of chronic quinapril treatment, suggesting that reduction of bradykinin degradation may enhance NO production, thus leading to the reduction of P-selectin expression and the reduction of infarct size only in the cholesterol-fed rabbits. Chronic inhibition of ACE may exert favorable effects especially in pathophysiological conditions that result from an impaired EDR and an increased expression of P-selectin, conditions commonly observed in patients with atherosclerosis.

References
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