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Protective Effect of ACE Inhibitors on Ischemia-Reperfusion-induced Arrhythmias in Rats: Is this Effect Related to the Free Radical Scavenging Action of these Drugs?

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The antiarrhythmic effects of captopril, a sulphydryl-containing angiotensin converting enzyme (ACE) inhibitor, were compared with those of the non-sulphydryl-containing ACE inhibitor lisinopril and the sulphydryl-containing agent glutathione in an *in vivo* rat model of coronary artery ligation. To produce arrhythmia, the left main coronary artery was occluded for 7 min, followed by 7 min of reperfusion. Captopril (3 mg kg^{-1}) and lisinopril (0.1, 0.3 or 1 mg kg^{-1}) caused marked decreases in mean arterial blood pressure (BP) and heart rate, whereas glutathione (5 mg kg^{-1}) had no effect on them. The incidence of ventricular tachycardia (VT) on ischemia and reperfusion was significantly reduced by captopril and lisinopril. Captopril and 1 mg kg^{-1} lisinopril also significantly decreased the number of VEB during occlusion and the duration of VT on reperfusion, respectively. These drugs also attenuated the incidence of reversible ventricular fibrillation (VF) and the number of ventricular ectopic beats (VEB) during reperfusion. However, glutathione only reduced the incidence of VT on reperfusion, significantly. These results suggest that, in this experimental model, ACE inhibitors limit the arrhythmias following ischemia-reperfusion and free radical scavenging action of these drugs does not have a major contributory role in their protective effect.

Keywords: ACE inhibition, reperfusion arrhythmias, free radicals, Rat heart

INTRODUCTION

Life-threatening ventricular arrhythmias are known to occur on restoration of coronary flow after a period of myocardial ischemia.[1] Antiarrhythmic effects of calcium antagonists, Class I antiarrhythmics, beta-blocking agents and free radical scavengers (e.g. sulphydryl-containing agents) have been demonstrated in many reperfusion studies.[2,3] In addition, these arrhythmias were also shown to be attenuated by ACE inhibitors in dogs *in vivo*,[4] in isolated rat hearts[5–7] and in humans.[8–10] On the other hand, the different findings (i.e. effectiveness of a drug) obtained from ischemia-reperfusion studies have been reported, and factors such as species and even strain differences, *in vitro* versus *in vivo*

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models and the choice of anaesthetic agents may be important in explaining these discrepancies.[2,11,12] Recently, we demonstrated that captopril, a sulphydryl-containing ACE inhibitor, possessed similar protective effect against ischemia-reperfusion-induced arrhythmias *in vivo* in rats.[13] Free radical scavenging action of this drug had also been shown, previously.[14]

The aim of this study was to evaluate whether this protective effect of captopril was due to its free radical scavenging action. To examine this possibility, the effects of captopril on these arrhythmias were compared with those of the non-sulphydryl-containing ACE inhibitor lisinopril and the sulphydryl-containing agent glutathione.

MATERIALS AND METHODS

Male Wistar rats weighing 250–350 g were anaesthetised with urethane 1.2–1.4 g kg^{-1} administered intraperitoneally (i.p.). The jugular vein and the trachea were cannulated for drug administration and artificial respiration. Systemic blood pressure (BP) was monitored from the carotid artery by a Harvard model 50-8952 transducer and displayed on a Harvard Universal pen-recorder together with a standard lead-1 ECG.

The chest was opened by a left thoracotomy, followed by sectioning the fourth and fifth ribs, about 2 mm to the left of the sternum. Positive-pressure artificial respiration was started immediately with room air, using a volume of 1.5 ml/100 g body weight at a rate 60 strokes/min to maintain normal PCO_2, PO_2, and pH parameters.

After the pericardium was incised, the heart was exteriorized by a gentle pressure on the right side of the rib cage. A 6/0 silk suture attached to a 10-mm micropoint reverse-cutting needle was quickly placed under the left main coronary artery. The heart was then carefully replaced in the chest, and the animal was allowed to recover for 20 min. Any animal in which this procedure produced arrhythmias or a sustained decrease in BP to less than 70 mm Hg was discarded.

A small plastic snare was threaded through the ligature and placed in contact with the heart. The artery could then be occluded by applying tension to the ligature, and reperfusion was achieved by releasing the tension.

Drug Administration

Captopril (Sigma, USA; 3 mg kg^{-1}) and lisinopril (kindly provided by Eczacibasi, Turkey; 0.1, 0.3 or 1 mg kg^{-1}) were administered by intravenous (i.v.) injection 10 min before occlusion. Glutathione (Sigma, USA; 5 mg kg^{-1}) was given intravenously just before reperfusion. Control animals received an equal volume (1 ml kg^{-1}) saline (0.09% NaCl wt/vol). Animals were randomly allocated to control (n = 25) or each drug treatment group (n = 15 in each group).

Evaluation on Arrhythmias

The artery was occluded for 7 min and then reperfused for 7 min more before the experiment was terminated. These durations of ischemia and reperfusion were previously used in the same experimental model successfully[13] and it was reported that this protocol produced ectopic activity in optimum number and severity.[1] ECG changes, BP, and heart rate (HR) were measured before and during the occlusion-reperfusion period.

Ventricular ectopic activity was assessed according to the diagnostic criteria advocated in the Lambeth Conventions.[11] The number of ventricular ectopic beats (VEB), the durations of ventricular tachycardia (VT) and ventricular fibrillation (VF) and the incidence of VT only in survivors were determined together with the incidences of reversible and irreversible VF.

Inclusion of data (i.e. the duration of VT or VF) only from survivors and the low incidence of VT/VF during occlusion period resulted in a dramatic reduction of the number of observations. When only one datum point was present, no statistical analysis were performed, the datum was

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presented with no transformation, and no standart error was indicated.

Statistics

Data are expressed as arithmetic means ± SEM of the number (n) of experiments; when $p < 0.05$, the difference was considered to be statistically significant. Differences in the incidences of arrhythmias were analysed by using Fisher's exact test. Group means were compared by Mann-Whitney U test. HR and BP values were analysed by repeated measures analysis of variance (ANOVA), and where F values permitted further analysis, individual treatment means were compared with respective control values by unpaired t-test.

RESULTS

Effects of the Drugs on Coronary Artery Occlusion and Reperfusion-induced Arrhythmias

After coronary artery occlusion, all animals exhibited cardiac arrhythmias, which occurred as ventricular ectopic beats, VT (defined as a run of four or more ectopic beats), or VF. In some animals, atrioventricular (A-V) block also occurred.

The incidence of occlusion-induced VT was reduced from 44% in control group to 6.7% ($p < 0.05$), 13.3% ($p < 0.05$), 13.3% ($p < 0.05$), 20% (NS), and 40% (NS) in groups treated with captopril (3 mg kg^{-1}), 0.1, 0.3 and 1 mg kg^{-1} lisinopril, and glutathione (5 mg kg^{-1}), respectively (Fig.1). During occlusion period, irreversible VF and mortality were not observed in any of the animals. Reversible VF occurred in one animal of each control, 0.3 mg kg^{-1} lisinopril and glutathione groups (Fig.2). Although captopril and lisinopril caused a marked reduction in the number of VEB (70.8 ± 25.5 in control group versus 14.3 ± 2.6, 28.9 ± 12, 18.6 ± 5.1, 22.6 ± 4.1, and 56.8 ± 26.9 in the same respective groups of captopril, lisinopril at doses of 0.1, 0.3 and 1 mg kg^{-1}, and glutathione), only captopril group was found significantly different from the control (Fig.3).

On subsequent reperfusion, VT developed in 100% of controls versus 42.8% ($p < 0.05$), 66.6% ($p < 0.05$), 80% (NS), 57.1% ($p < 0.05$), and 66.6% ($p < 0.05$) of captopril, 0.1, 0.3 and 1 mg kg^{-1} lisinopril, and glutathione-treated animals, respectively (Fig.1). Furthermore, lisinopril at dose of 1 mg kg^{-1} significantly reduced the duration of VT (Table I). 1 mg kg^{-1} lisinopril and 3 mg kg^{-1} captopril also caused significant decreases in the incidence of reversible VF (Fig.2) and the number of VEB (Fig.3).

4 of 25 (16%) control rats died due to the reperfusion-induced irreversible VF. Captopril (6.7%) and lisinopril at doses of 0.3 (0%) and 1 (6.7%)

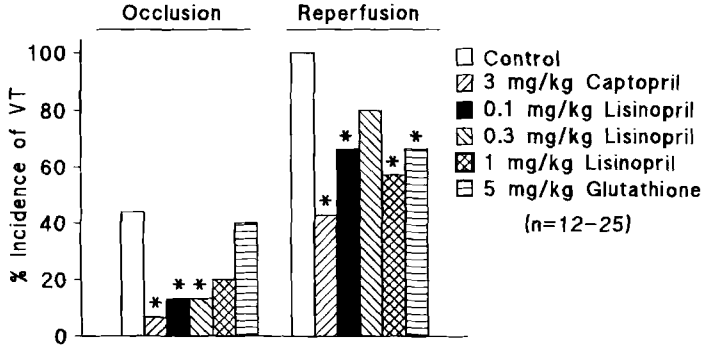

FIGURE 1 Percentage incidence of ventricular tachycardia (VT) that occurred in occlusion or reperfusion period in surviving rats pretreated with saline (control), captopril (3 mg kg^{-1}), lisinopril (0.1, 0.3 and 1 mg kg^{-1}) or glutathione (5 mg kg^{-1}). *$p < 0.05$, significant difference from saline-treated group.

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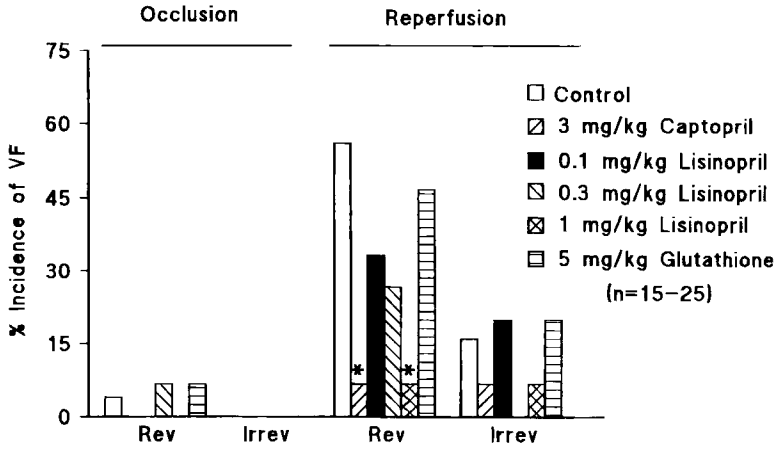

FIGURE 2 Percentage incidence of reversible (rev) and irreversible (irrev) ventricular fibrillation (VF) that occurred in occlusion or reperfusion period in rats pretreated with saline (control), captopril (3 mg kg^{-1}), lisinopril (0.1, 0.3 and 1 mg kg^{-1}) or glutathione (5 mg kg^{-1}). *$p < 0.05$, significant difference from saline-treated group.

mg kg^{-1} tended the reduce the incidence of irreversible VF, but these changes did not reach statistical significance (Fig.2).

Effects of the Drugs on Arterial BP and HR

Figure 4 summarizes the data obtained on the effects of lisinopril (0.1, 0.3 and 1 mg kg^{-1}) on mean arterial BP and HR before and after coronary artery occlusion and reperfusion. On shortly after the injection, lisinopril caused a sustained decrease of preocclusion values in the arterial BP and HR. Captopril also decreased these values significantly, whereas glutathione had no significant effect on either HR or arterial BP (Data not shown).

DISCUSSION

We demonstrated that captopril and lisinopril attenuated the arrhythmias induced by coronary artery occlusion and reperfusion in anaesthetised rats. These ACE inhibitors reduced the incidence

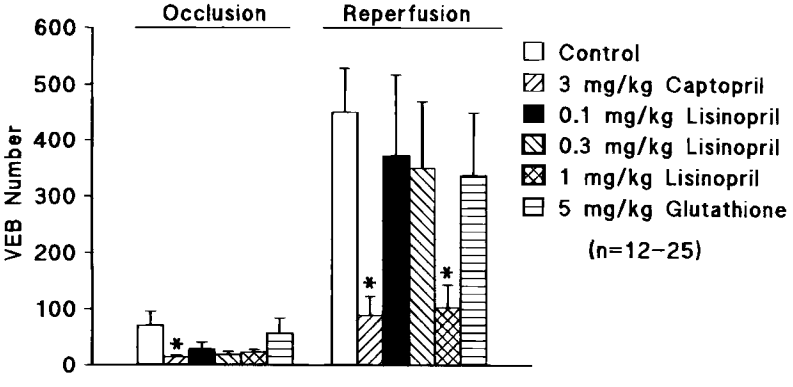

FIGURE 3 The numbers of ventricular ectopic beats (VEB) observed during occlusion or reperfusion period in surviving rats pretreated with saline (control), captopril (3 mg kg^{-1}), lisinopril (0.1, 0.3 and 1 mg kg^{-1}) or glutathione (5 mg kg^{-1}). *$p < 0.05$, significant difference from saline-treated group.

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TABLE I The durations (sec) of ventricular tachycardia (VT) and ventricular fibrillation (VF) in occlusion or reperfusion period in rats pretreated with saline (control), captopril (3 mg kg^{-1}), lisinopril (0.1, 0.3 and 1 mg kg^{-1}) or glutathione (5 mg kg^{-1})

	OCCLUSION		REPERFUSION	
	VT Duration	VF Duration	VT Duration	VF Duration
Control	10,73 ± 4,57 (n = 11)	45.00 (n = 1)	42,57 ± 7,81 (n = 21)	63.29 ± 10.78 (n = 14)
Captopril 3mg/kg	0,50 (n = 1)	—	15,75 ± 5,55 (n = 6)	72.00 (n = 1)
Lisinopril 0.1mg/kg	9,50 ± 3,50 (n = 2)	—	52,19 ± 18,14 (n = 8)	51.40 ± 16.05 (n = 5)
Lisinopril 0.3mg/kg	3,00 ± 1,00 (n = 2)	9.00 (n = 1)	35,83 ± 13,79 (n = 12)	59.50 ± 38.20 (n = 4)
Lisinopril 1mg/kg	2,00 ± 0,58 (n = 3)	—	13,25 ± 5,89* (n = 8)	4.50 (n = 1)
Glutathione 5mg/kg	8,83 ± 5,69 (n = 6)	57.00 (n = 1)	47,13 ± 13,36 (n = 8)	79.00 ± 14.99 (n = 7)

*$p < 0.05$, significant difference from saline-treated group.
n, refers to the number of observations.

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of VT on ischemia and reperfusion as well as the incidence of reversible VF and the number of VEB on reperfusion. 3 mg kg^{-1} captopril and 1 mg kg^{-1} lisinopril also significantly decreased the number of VEB during occlusion and the duration of VT on reperfusion, respectively. Mortality resulted from irreversible VF on reperfusion and it was reduced by captopril and lisinopril. However, this effect was not statistically significant. Both captopril and lisinopril caused sustained decreases in arterial BP and HR, whereas glutathione did not change these values and modified only the incidence of reperfusion-induced VT, significantly.

Consistent with our findings, protective effects of ACE inhibitors against reperfusion arrhythmias were shown *in vivo*[13] and *in vitro*[5–7] in rats and in dogs[4] and humans[8–10] *in vivo*.

Although cardioprotective effect of ACE inhibitors has been demonstrated on ischemia and reperfusion injury, their mechanism of action is not clear. In addition to the systemic hypotensive activity of ACE inhibitors which may provide cardiac preservation through afterload reduction, a local action that interrupts regional cardiac tissue renin-angiotensin system (RAS) may participate in the protective effects of these drugs.[15] A recent study reported that increases in myocardial ACE activity and ACE mRNA levels occur after permanent coronary artery ligation in rats.[16] Paracrine and autocrine control of regional myocardial function and perfusion has been previously 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.[17] Bradykinin is tightly linked to the RAS because the bradykinin degradative enzyme, kininase II, has been determined to be identical to ACE.[18] Increases in bradykinin by ACE inhibition that stimulate EDRF or nitric oxide (NO) release and prostanoid production have been implicated as positive influences in reducing myocardial ischemia/reperfusion injury.[19] Vasodilatory activity of kinins and NO has already been implicated in the antihypertensive action of ACE inhibitors.[20] Both EDRF and prostacyclin, directly or indirectly, can elicit coronary vasodilatation and reduce platelet aggregation.[21] In isolated rat heart, captopril and ramiprilat each produced cardioprotection in ischemia that was abolished by the prosto-glandin synthesis inhibitor indomethacin.[22] In a similar preparation, ramiprilat protected the heart against reperfusion arrhythmias and reduced enzyme activities of lactate dehydrogenase and creatine kinase in the coronary effluent. This cardioprotective effects produced by both, ACE inhibitor and bradykinin, were completely abolished when the bradykinin antagonist was added to the perfusate, while a smaller inhibition was

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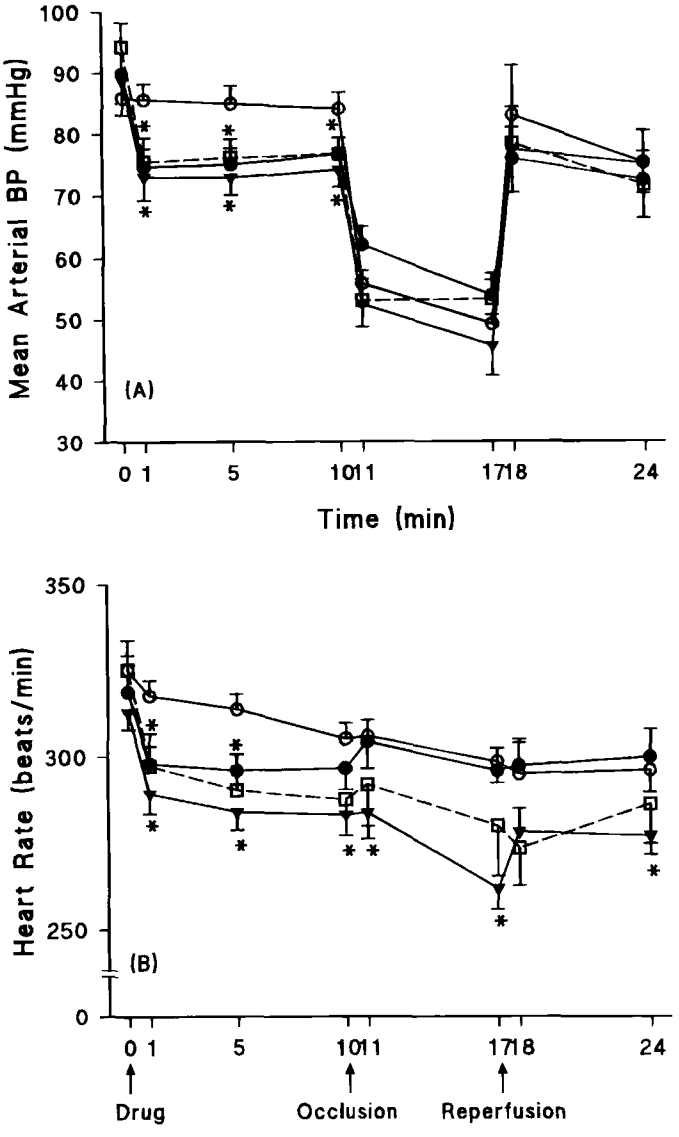

FIGURE 4 Mean arterial blood pressure (mm Hg) (**A**) and heart rate (beats min^{-1}) (**B**) in rats pretreated with saline (open circles) or lisinopril 0.1 (solid circles), 0.3 (solid triangles) and 1 (open squares with broken line) mg kg^{-1} before and after coronary artery occlusion and reperfusion. Drug or saline was injected intravenously at 0 min, occlusion was started at 10 min, and reperfusion was started at 17 min; n = 8–25, n refers to number of survivors which varied at each time point. *$p < 0.05$ indicates a lisinopril-induced significant difference.

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obtained by indomethacin perfusion.[6] ACE inhibitors were also shown to reduce myocardial necrosis associated with acute coronary occlusion-reperfusion by a bradykinin-dependent mechanism.[23]

Increased endogenous catecholamine levels during and after myocardial ischemia worsen reperfusion injury by exacerbating arrhythmias, decreasing the cardiac supply/demand ratio, and increasing systemic vascular resistance to increase cardiac work further.[24] ACE inhibitors captopril, enalaprilat, and ramiprilat attenuate norepinephrine (NE) and creatine kinase release from globally ischemic, isolated hearts on reperfusion.[22,25] In intact anesthetized pigs, myocardial release of creatine kinase and NE were concomitantly decreased after ischemia/reperfusion by pretreatment with captopril.[26] These *in vitro* and *in vivo* studies imply that ACE inhibition may protect myocardial tissue by attenuating adrenergic activity in it under conditions of ischemia/reperfusion.

On the other hand, oxygen derived free radicals known to be produced during reperfusion after a short period of ischemia have been suggested to be responsible for ischemia-reperfusion injury, as well.[27] Depletion of tissue glutathione content was also demonstrated during myocardial ischemia.[28] In addition, some studies showed that free radical scavengers such as sulphydryl-containing agents attenuated the reperfusion damage[27,29] In *in vitro* rat model, glutathione protected the heart against ischemia-reperfusion-induced arrhythmias in one study[30] but the other.[31] Furthermore, in some studies,[32–34] only the ACE inhibitors having sulphydryl residues possessed cardioprotective effect against ischemia-reperfusion injury, whereas in the other studies,[7,23,25] non-sulphydryl containing ACE inhibitors were also found to be effective. These discrepancies may be due to the differences between models (e.g. *in vitro* versus *in vivo*) and the different experimental protocols.

In this study, we demonstrated that captopril (a sulphydryl-containing ACE inhibitor) and lisinopril (a non-sulphydryl-containing ACE inhibitor) had similar protective effect against ischemia-reperfusion-induced arrhythmias but glutathione (a sulphydryl-containing agent) did not have a major influence on them.

In conclusion, our data suggest that ACE inhibitors exert protective effect during myocardial ischemia and reperfusion by reducing serious ventricular arrhythmias and this effect does not seem to be related their free radical scavenging action but may be due in part to their marked hemodynamic effects.

References

[1] Manning, A. S. and Hearse, D. J. (1984). Reperfusion-induced arrhythmias: Mechanisms and prevention. *Journal of Molecular and Cellular Cardiology*, **16**, 497–518.

[2] Hearse, D. J. (1990). Ischemia, reperfusion, and the determinants of tissue injury. *Cardiovascular Drugs and Therapeutics*, **4**, 767–76.

[3] Huang, T. F. (1992). Drug effects on the ischemia- and reperfusion-induced arrhythmias in the conscious rats. *Chinese Journal of Physiology*, **35**, 9–19.

[4] Westlin, W. and Mullane, K. (1988). Does captopril attenuate reperfusion-induced myocardial dysfunction by scavenging free radicals? *Circulation*, **77**, 130–39.

[5] Di Napoli, P., Di Gregorio, G., De Sanctis, F., Gallina, S., E. Di Girolamo, G. P. Trevi and A. Barsotti (1993). The myocardial protective effects of cardiac tissue ACE inhibition in experimental ischemia-reperfusion in isolated rat hearts. *Cardiologia*, **38**, 107–12.

[6] Scholkens, B. A. and Linz, W. (1988). Local inhibition of angiotensin II formation and bradykinin degradation in isolated hearts. *Clinical and Experimental Hypertension, A*, **10**, 1259–70.

[7] Van Gilst, W. H., De Graeff, P. A., Wesseling, H. and De Langen, C. D. J. (1986). Reduction of reperfusion arrhythmia in the ischemic isolated rat heart by angiotensin converting enzyme inhibitors: A comparison of captopril, enalapril and HOE 498. *Journal of Cardiovascular Pharmacology*, **8**, 722–28.

[8] Di Pasquale, P., Paterna, S., Cannizzaro, S., Albano, V., Valdes, L., Licata, G. and Barone, G. (1992). Captopril and glutathione before thrombolysis in acute myocardial infarction: a pilot study. *Drugs under Experimental and Clinical Research*, **18**, 401–6.

[9] Muller, C. A., Opie, L. H., Peisach, M. and Pineda, C. A. (1994). Chronic oral pretreatment with the angiotensin converting enzyme inhibitor, trandolapril decreases ventricular fibrillation in acute ischemia and reperfusion. *European Heart Journal*, **15 (7)**, 988–96.

[10] Kingma, J. H., van Gilst, W. H., Peels, C. H., Dambrink, J. H., Verheugt F. W., and Wielenga, R. P. (1994). Acute intervention with captopril during thrombolysis in patients with first anterior myocardial infarction. *European Heart Journal*, **15 (7)**, 898–907.

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[11] Walker, M. J. A., Curtis, M. J., Hearse, D. J., Campbell, R. W. F., Janse, M. J., Yellon, D. M., Cobbe, S. M., Coker, S. J., Harness, J. B., Harron, D. W. G., Higgins, A. J., Julian, D. G., Lab, M. J., Manning, A. S., Northover, B. J., Parratt, J. R., Riemersma, R. A., Riva, E., Russell, D. C., Sheridan, D. J., Winslow, E. and Woodward, B. (1988). The Lambeth Conventions: guidelines for the study of arrhythmias in ischaemia, infarction, and reperfusion. *Cardiovascular Research*, **22**, 447–55.

[12] Iskit, A. B. and Guc, M. O. (1996). Comparison of sodium pentobarbitone and urethane anaesthesia in a rat model of coronary artery occlusion an reperfusion arrhythmias: interaction with L-NAME. *Pharmacological Research*, **33 (1)**, 13–18.

[13] Olmez, E., Birincioglu, M., Aksoy, T. and Acet, A. (1995). Effects of captopril on ischemia-reperfusion-induced arrhythmias in an *in vivo* rat model. *Pharmacological Research*, **32 (1/2)**, 37–41.

[14] Chopra, M., McMurray, J., Stewart, J., Dargie, H. J. and Smith, W. E. (1990). Free radical scavenging: a potentially beneficial action of thiol-containing angiotensin converting enzyme inhibitors. *Biochemical Society Transactions*, **18**, 1184–1185.

[15] Dzau, V. J. (1988). Circulating versus local renin angiotensin system in cardiovascular homeostasis. *Circulation*, **77**, 113–14.

[16] Hirsch, A. T., Talsness, C. E., Shunkert, H., Paul, M. and Dzau, V. J. (1991) Tissue-spesific activation of cardiac angiotensin converting enzyme in experimental heart failure. *Circulation Research*, **69**, 475–82.

[17] van Wijngaarden, J., Tio, R. A., van Gilst, W. H., de Graeff, P. A., de Langen, C. D. J. and H. Wesseling (1990). Basic pharmacology of ACE inhibitors with respect to ischeamic heart disease : prostaglandins and bradykinin. *European Heart Journal*, **11**, 84–93.

[18] Bhoola, K. D., Figueroa, C. D. and Worthy, K. (1992). Bioregulation of kinins: kallikreins, kininogens, and kininases. *Pharmacological Reviews*, **44**, 1–80.

[19] Linz, W. and Scholkens, B. A. (1992). Role of bradykinin in the cardiac effects of angiotensin-converting enzyme inhibitors. *Journal of Cardiovascular Pharmacology*, **20**, 83–90.

[20] Cachofeiro, V., Sakakibara, T. and Nasjletti, A. (1992). Kinins, nitric oxide, and the hypotensive effect of captopril and ramiprilat in hypertension. *Hypertension*, **19**, 138–45.

[21] Radomski, M. W., Palmer, R. M. J. and Moncada, S. (1987). The antiaggregating properties of vascular endothelium: interactions between prostacyclin and nitric oxide. *British Journal of Pharmacology*, **92**, 639–46.

[22] van Gilst, W. H., Graeff, de P. A., Wesseling, H. and de Langen, C. D. J. (1986). Reduction of reperfusion arrhythmias in the ischemic isolated rat heart by angiotensin converting enzyme inhibitors: A comparison of captopril, enalapril, and HOE 498. *Journal of Cardiovascular Pharmacology*, **8**, 722–8.

[23] Hartman, J. C., Wall, T. M., Hullinger, T. G. and Shebuski, R. J. (1993). Reduction of myocardial infarct size in rabbits by ramiprilat: reversal by bradykinin antagonist HOE 140. *Journal of Cardiovascular Pharmacology*, **21**, 996–1003.

[24] Opie, L. H. (1991). *The heart, physiology and metabolism.*: Raven Press, New York.

[25] Carlsson, L. and Abrahamsson, T. (1989). Ramiprilat attenuates the local release of noradrenaline in the ischemic myocardium. *European Journal of Pharmacology*, **166**, 157–64.

[26] de Graff, P. A., van Gilst, W. H., Bel, K., de Langen, C. D. J., Kingma, J. H. and Wesseling, H. (1987). Concentration-dependent protection by captopril against myocardial damage during ischemia and reperfusion in closed chest pig model. *Journal of Cardiovascular Pharmacology*, **9**, 37–42.

[27] Ferrari, R., Ceconi, C., Curello, S., Cargnoni, A., Alfieri, O., Pardini, A., Marzollo, P. and Visioli, O. (1991). Oxygen free radicals and myocardial damage: protective role of thiol-containing agents. *American Journal of Medicine*, **91**, 95S–105S.

[28] Arduini, A., Mezzetti, A., Porreca, E., Lapenna, D., DeJulia, J., Marzio, L., Polidoro, G. and Cuccurullo, F. (1988). Effect of ischemia and reperfusion on antioxidant enzymes and mitochondrial inner membrane proteins in perfused rat heart. *Biochimica et Biophysica Acta*, **970 (2)**, 113–21.

[29] Koerner, J. E., Anderson, B. A. and Dage, R. C. (1991). Protection against postischemic myocardial dysfunction in anesthetized rabbits with scavengers of oxygen-derived free radicals: superoxide dismutase plus catalase, N-2-mercaptopropionyl glycine and captopril. *Journal of Cardiovascular Pharmacology*, **17**, 185–91.

[30] Bernier, M., Hearse, D. J. and Manning, A. S. (1986). Reperfusion induced arrhythmias and oxygen-derived free radicals. Studies with "anti-free radical" interventions and a free radical-generating system in the isolated perfused rat heart. *Circulation Research*, **58 (3)**, 331–40.

[31] Coetzee, W. A., Owen, P., Dennis, S. C., Saman, S. and Opie, L. H. (1990). Reperfusion damage: free radicals mediate delayed membrane changes rather than early ventricular arrhythmias. *Cardiovascular Research*, **24 (2)**, 156–64.

[32] Grover, G. J., Sleph, P. G., Dzwonczyk, S., Wang, P., Fung, W., Tobias, D. and Cushman, D. W. (1991). Effects of different angiotensin-converting enzyme (ACE) inhibitors on ischemic isolated rat hearts: relationship between cardiac ACE inhibition and cardioprotection. *Journal of Pharmacology and Experimental Therapeutics*, **257 (3)**, 919–29.

[33] Kilgore, K. S., Homeister, J. W., Sato, P. S. and Lucchesi, B. R. (1994). Sulfhydryl compounds, captopril, and MPG inhibit complement-mediated myocardial injury. *American Journal of Physiology*, **266 (1–2)**, H28–35.

[34] Tanaka, M., Ishibashi, T. and Imai, S. (1990). Effects of two angiotensin converting enzyme inhibitors on the mechanical function and energy metabolism of isolated rat hearts. A nuclear magnetic resonance study with an active form of benazeprilat and captopril. *Arzneimittelforschung*, **40 (10)**, 1082–6.

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