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Anti-arrhythmic effects of captopril on coronary occlusion and reperfusion periods in pigs[1]

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ABSTRACT Anti-arrhythmic effects of captopril (Cap) were studied in the anesthetized pigs using a reversible balloon catheter. Results showed that Cap did not exert any influence on the weight percentage of ischemic area to the whole left ventricle, on the levels of serum creatine kinase (CK) and creatine kinase isozyme (CK-MB), nor on the incidence and duration of transient and persistent tachycardia, but reduced the incidence of ventricular fibrillation (2/12, 1/12 in high-dose group pigs treated with Cap 6 mg·kg^{-1} in the first 10 min, 25 μg·kg^{-1}·min^{-1} in the later 90 min and 12/21, 11/21 in control group treated with normal saline through the occlusion and reperfusion periods, respectively, $P < 0.05$). It was suggested that Cap did not exhibit direct (or non-specific, if any) effects on anti-arrhythmias.

KEY WORDS captopril; myocardial reperfusion injury; arrhythmia; creatine kinase; swine

Thrombolytic threapy may bring about limitation of infarct size, preservation of left ventricular function and a low complication and mortality rate[1], but may induce arrythmias during reperfusion[2,3]. The angiotensin converting enzyme (ACE) inhibitors may alleviate such arrhythmias[4]. Nevertheless, these protective effects remain controversial because of different research methods[5,6]. This study was to investigate whether Cap possessed any anti-arrhythmic effect upon reperfusion after ischemia was produced by reversible occlusion of the coronary artery with a balloon catheter in the closed-chest pigs.

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MATERIALS AND METHODS

Ukrainian swine (weighing 13.4±*s* 1.6 kg) was sedated with morphine (1 mg·kg^{-1}, sc). After 30 min, it was anesthetized with sodium pentobarbital (30 mg·kg^{-1}, iv), intubated with endotracheal tube and ventilated with air (16—20 times·min^{-1}, 150—200 ml/ventilation). Left jugular vein was exposed and a catheter with 2 polar rings and 2 poles was cannulated for recording dextrocardiogram and administering heparin (5 mg·kg^{-1}), Cap, and normal saline. Another catheter was cannulated into the left carotid artery to measure the intra-aortic pressure. The right carotid artery was cannulated with a modified 5 French Sones (5 F) Judkin's catheter containing an arterial embolectomy catheter (a balloon catheter). Acute regional myocardial ischemia was produced with 2 F balloon catheter, then a modified 5 F Judkin's catheter was inserted via the right carotid. Through the lumen of this catheter, the 2 F balloon catheter was inserted into the left anterior descending coronary artery.

Each pig was allowed to equilibrate until stable electro-cardiographic baseline values were obtained. After a control period of 20 min, ischemia was introduced by inflating the balloon lasting 20 min, then deflated. After the ischemic zone was reperfused for 60 min, the heart was stained with triphenyl tetrazolium chloride (TTC, 1% 5 ml) for 20 min in a dark place[7]. After removing both atria and right ventricular tissues, the interventricular septum and the left ventricle were cut into 10 thin transverse slices, parallel to the atrioventricular groove. These slices were fixed with formaldehyde solution (4% vol/vol) for 30 min. The ischemic area gradually turned into scarlet red whereas the non-ischemic area retained the original

color. The % of ischemic area to the total left ventricle was measured by weight.

Throughout the experiment, pig electrocardiography (V_1 and V_4), heart rate, and arterial pressure (diastolic and systolic) were continuously monitored by a pressure-electrocardiographic recorder.

Creatine kinase isozyme (CK-MB) and total creatine kinase (CK) levels were measured using enzyme assay ($U \cdot L^{-1}$, 30℃) at 10 min (control period), 40 min (the end of ischemic period), 45, 70, 90 min (reperfusion period), respectively.

Thirty-eight pigs were divided into 3 groups: (A) The control group: 21 pigs were infused with normal saline during the whole experiment; (B) The low-dose Cap group: 5 pigs were perfused with Cap 0.6 mg $\cdot kg^{-1}$ in the first 10 min and 2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during the next 90 min; (C) The high-dose Cap group: 12 pigs were perfused with Cap 6 mg $\cdot kg^{-1}$ in the first 10 min and 25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the following 90 min. The body weights in A, B, and C groups were 13.8±1.2 kg ($n=2$), 14±3 kg ($n=5$), 12.8±1.3 kg ($n=12$), respectively. The differences were non significant ($P>0.05$).

In order to prevent sudden death of the pig, a direct current cardioversion was applied in case ventricular fibrillation should occur within 30 s.

RESULTS

Myocardial damage The weight % of ischemic area were 46%±6% in group A, 49%±8% in group B, and 44%±10% in group C. There were no differences among them ($P>0.05$).

CK and CK-MB levels Serum CK and CK-MB levels did not show statistically significant differences among the 3 groups (Tab 1).

Electrocardiography and arterial pressure The heart rates became slower and the arterial pressure became lower in the 2 Cap groups, especially in group C. The incidences of ventricular fibrillation in group C were 2/12 during occlusion and 1/12 during reperfusion which were lower than those in group A (12/21 and 11/21, respectively, $P<0.05$). There was no significant difference between those in group B (4/5, and 2/5, respectively) and in group A during both periods. The incidence and durations of transient plus persistent ventricular techycardia and the elevated ST segment showed no significant difference among these 3 groups either during occlusion and reperfusion periods.

DISCUSSION

All measurable parameters in our experiments except the incidences of ventricular fibrillation did not show any statistical differences among the control, low-dose, and high-dose groups. Cap could neither improve the blood circulation of the coronary ischemic region, nor exert any sepcific effect electrocardiographically, nor possess any direct antiarrhythmic effects. The exact mechanisms by

Tab 1. Serum total creatine kinase (CK) and creatine kinase isozyme (CK-MB) levels ($U \cdot L^{-1}$) in pigs treated with captopril by a arterial catheter. $\bar{x} \pm s$. 'P>0.05.

Enzyme	Group	n	Control 10 min	Occlusion 20 min	Occlusion 5 min	Reperfusion 30 min	Reperfusion 60 min
CK	A	8	384±138	463±198	639±191	871±315	1 225±827
	B	5	322±116'	353±203'	444±141'	474±66'	739±82'
	C	12	332±124'	438±272'	523±270'	738±396'	842±440'
CK-MB	A	8	300±48	288±22	321±82	349±200	436±279
	B	5	254±33'	290±43'	337±93'	440±188'	478±270'
	C	12	248±40'	293±90'	350±143'	432±247'	464±272'

which Cap reduced the incidences of ventricular fibrillation while did not reduce the incidences and durations of transient and persistent ventricular tachycardia remained to be elucidated. It was supposed that Cap could reduce the heart rate and arterial pressure of pigs, thus cause a reduction of myocardial oxygen consumption due to a decrease in pre- and after-load. However, this protection could by means be no specific.

REFERENCES

1 Van de Werf F, Arnold AER. Intravenous tissue plasminogen activator and size of infarct, left ventricular function, and survival in acute myocardial infarction. *Br Med J* 1988; 297 : 1374—9.

2 Zwerner PL, Gore JM. Thrombolytic therapy in acute myocardial infarction. *J Intens Care Med* 1986; 1 : 302—18.

3 Maras P, Della Grazia E, Klugmann S, Morgera T, Salvi A, Pandullo C, *et al*. Reperfusion ventricular arrhythmias during intracoronary thrombolysis. *Eur Heart J* 1986; 7 Suppl A : 23—30.

4 Edwards CRW, Padfield PL. Angiotensin-converting enzyme inhibitors; past, present, and bright future. *Lancet* 1985; 1 : 30—4.

5 Hemsworth PD, Pallandi RT, Campbell TJ. Cardiac electrophysiological actions of captopril; lack of direct anti-arrhythmic effects. *Br J Pharmacol* 1989; 98 : 192—6.

6 de Graeff PA, van Gilst WH, Bel K, de Langen CDJ, Kingma JH, Wesseling H. Concentration-dependent protection by captopril against myocardial damage during ischemia and reperfusion in a closed chest pig model. *J Cardiovasc Pharmacol* 1987; 9 Suppl 2 : 37—42.

7 Karageuzian HS, Liu ZY, Yao FX, Fishbein MC, Mandel WJ. Suppression of reperfusion ventricular fibrillation by metoprolol-quinidine combination. *Revue Europeenne de Technologie Biomedicale* 1990; 12 : 81.

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猪冠状动脉阻塞及再灌注期卡托普利的抗心律失常作用

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摘要 本文用可逆性气囊导管阻塞猪冠状动脉来研究卡托普利抗心律失常、改善心肌血供及阻止酶释放作用。结果表明：卡托普利能减少高治疗组猪（前10分钟用6 mg·kg^{-1}，后90分钟用25 μg·kg^{-1}·min^{-1}）室性颤动发生率（阻塞期、再灌注期分别为2/12，1/12；对照组为12/21，11/21，$P<0.05$）。对其它观察指标无明显影响。提示卡托普利有非特异性抗心律失常作用。

关键词 卡托普利；心肌再灌注损伤；心律失常；肌酸激酶；猪