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Beneficial effects of enalapril on reperfusion arrhythmia and segmental contraction in anesthetized dogs [1,2]

LIU Li-Ying, CHEN Xiu, LI Kai, WU Wen-Jian

(*Department of Pharmacology, Hunan Medical College, Changsha 410008*)

ABSTRACT Left anterior descending (LAD) was occluded for 60 min followed by reperfusion in mongrel dogs. In control group (n = 14), 6 dogs died of ventricular fibrillation after LAD occlusion, another 4 out of 8 died of arrhythmia after reperfusion. While in enalapril pretreated group (n = 10) only 1 died after occlusion and none after reperfusion ($p<0.05$). Segmental shortenings (L) in both ischemic and normal areas were measured by ultrasonic crystals implanted in subendocardium and connected to sonomicrometer 120. Both end diastolic length (EDL) and end systolic length (ESL) were prolonged significantly in ischemic area, and in control dogs the ESL often surpassed that of EDL, implicates a passive protraction of ischemic area during systole. While in enalapril group, reduction of ΔL was significantly less than that in control group, indicating the improvement in segmental contraction during ischemia. Enalapril lowered the blood pressure, dP/dt-max and blood pressure × heart rate, hence reduced myocardial oxygen consumption, which might contribute partly to the mechanism of cardioprotection.

KEY WORDS enalapril; kininase II; coronary circulation; myocardial contraction; reperfusion arrhythmia; myocardial infarction; cardiac output

The renin-angiotensin system (RAS) is involved in the process of the development or aggravation of acute myocardial infarction[1,2]. Recently enalapril (MK-421), a new angiotensin converting enzyme (kininase II) inhibitor (ACEI), was shown to prevent reperfusion arrhythmia in anesthetized dogs[3], and enalaprilic acid (MK-422), the active form of enalapril was demonstrated to protect myocardial infarction against CPK release[2]. The present study was focused on the enalapril effect on cardiac performance in acute myocardial infarction, especially segmental contraction in ischemic myocardium and reperfusion arrhythmia in anesthetized dogs.

MATERIALS AND METHODS

24 mongrel dogs of either sex weighing 11.5 ± SD 1.8 kg, were anesthetized with iv sodium pentobarbital 30 mg/kg. Under artificial respiration, the heart was exposed via a left thoracotomy at the 5th intercostal space. A polyurethane nylon catheter was inserted into the apex of the left ventricle for measuring the left ventricular pressure and dP/dt_{max}. Electromagnetic flow probe of 12-13 mm diameter was placed at the root of aortic artery and connected to an electromagnetic blood flowmeter (NIHON KOHDEN) for measuring the cardiac output (CO). By ultrasonometric method[4], one pair of ultrasonic crystals (2.5 mm in diameter, 3 MHz in frequency) was placed in subendocardium of the left ventricle wall where blood was supplied by LAD for measuring the segmental contraction of the ischemic myocardium[4]. Another pair was implanted in the subendocardium of the left ventricle wall where blood was supplied by the left circumflex coronary artery for measuring segmental contraction of non-ischemic myocardium (Fig 1). The segmental contraction was monitored by sonomicro-

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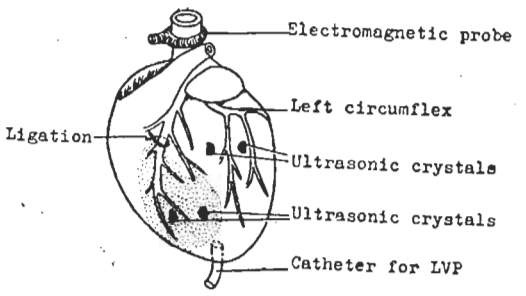

Fig 1. Crystal placements and ligation sites of LAD in dogs.

meter 120 (Triton Technology Inc, San Diego, CA, USA).

All of the hemodynamic data and segmental contractions of the left ventricles were recorded on polygraph system (NIHON KOHDEN). Enalapril (Merck-Sharp Dohme Research Lab) 1 mg/kg or equivalent volume of normal saline were given iv to experimental and control groups, respectively. 15 min after iv, LAD was ligated at the level distal to the 2nd branch or at a similar level to generate comparable area of infarction. After 60 min, occlusion was released and perfusion was restored upto 15 min, or until the dog died of ventricular fibrillation which usually occurred within 3 min.

After the experiment, the heart was removed, LAD was ligated again at the original ligating site, and Evan's blue was injected via the coronary orifice. The size of myocardial ischemia was estimated by the weight of ischemic (nonstained) part/total weight of the left ventricle.

Measurement of segmental contraction[4,5] Segmental contraction was represented by segmental shortening(ΔL), calculated as the difference in mm between end diastolic length (EDL) and end systolic length (ESL). The EDL was identified at the point just before the onset of the positive dP/dt signal, and ESL was defined as the maximal systolic excursion occurring at 20 ms prior to the negative dP/dt_{max}. Segmental shortening percentage ($\%\Delta L$) during systole was calculated as follows: (EDL - ESL) $\times$ 100/EDL.

RESULTS

Effect on incidence of ventricular fibrillation (VF) In control group, 6 out of 14 dogs (42%) died of VF within 10-40 min after LAD occlusion and 4 out of the rest 8 dogs (50%) died of VF within 3 min after reperfusion. However, in enalapril group, 1 out of 10 dogs (10%) died of VF within 20 min after LAD occlusion and neither VF nor death occurred in the rest 9 dogs after reperfusion. The difference between the two groups was statistically significant ($p<0.05$).

Effect on changes of segmental contraction As shown in Tab 1 and Fig 2, in non-ischemic region there were no significant changes in EDL, ESL, ΔL and $\%\Delta L$ of the two groups. However, in ischemic area, both EDL and ESL were significantly prolonged. The prolongation of ESL surpassed that of EDL in control dogs, hence ΔL turned to negative; while in enalapril group, the reduction of ΔL was significantly less than that in control (Tab 1). The difference of ΔL reduction between control and enalapril pretreated dogs was statistically significant ($p<0.05$) at 30 min as well as 60 min after occlusion. In addition, EDL returned to normal promptly after reperfusion in both groups. However, ESL were improved insignificantly in both groups.

Effect on heart performance and hemodynamics As shown in Tab 2, the control group showed no prominent changes of all the indices except $+dP/dt_{max}$ decreasing after ligation and reperfusion of LAD and $-dP/dt_{max}$ decreasing 30 min after ligation of LAD. In enalapril group, mean arterial pressure (MAP) and $\pm dP/dt_{max}$ decreased markedly 15 min after medication. The MAP, heart rate (HR), HR $\times$ MAP, as well as dP/dt_{max} further reduced after LAD

Tab 1. Effects of enalapril on regional segmental contraction in myocardial ischemia and after reperfusion in dogs. *$p>0.05$, **$p<0.05$, ***$p<0.01$ *vs* before ligation of LAD (15 min after medication); †$p>0.05$, ††$p<0.05$ enalapril *vs* control groups; ‡$p>0.05$ *vs* before medication in enalapril group. $\bar{x}\pm SD$

Index (mm)	Groups	Before medication	Before ligation	After ligation of LAD 2 min	30 min	60 min	Reperfusion for 2 min
		Non-ischemic area					
EDL	Control		12.3±2.3	12.4±2.4*	12.0±2.8*	11.9±2.6*	11.1±3.3*
	Enalapril	11.9±2.5	11.0±2.2‡	10.9±2.4*†	10.9±2.4*†	11.0±2.4*†	10.9±2.3*†
ESL	Control		10.6±1.8	10.5±2.0*	10.4±2.2*	10.3±2.1*	9.8±2.4*
	Enalapril	9.8±2.4	9.8±2.2‡	9.7±2.4*†	9.7±2.3*†	9.7±2.3*†	9.7±2.2*†
ΔL	Control		1.6±0.7	1.8±0.7*	1.5±0.9*	1.6±0.8*	0.93±0.49*
	Enalapril	1.3±0.5	1.3±0.5‡	1.1±0.4*†	1.2±0.4*†	1.2±0.4*†	1.2±0.6*†
%ΔL	Control		13.0±4.3	15.0±3.0*	13.0±4.1*	13.0±4.5*	10.5±5.1*
	Enalapril	11.5±5.1	11.6±6.1‡	11.1±5.5*†	11.3±3.9*†	11.4±4.7*	10.8±5.3*†
		Ischemic area					
EDL	Control		14.3±2.0	15.7±1.8**	15.8±2.1***	15.7±1.8***	14.2±2.6*
	Enalapril	12.2±3.3	12.0±3.0‡	13.2±3.6*†	14.4±3.3***†	13.9±2.9**†	13.3±3.2*†
ESL	Control		11.4±1.6	15.8±2.3***	16.1±2.1***	15.6±2.3***	13.1±2.3**
	Enalapril	10.3±3.0	10.2±2.9‡	13.3±3.6**†	13.9±3.2***†	13.4±3.0***†	12.8±3.5**†
ΔL	Control		3.0±1.5	−0.2±1.9**	−0.5±1.3***	0.2±0.9***	1.5±0.8*
	Enalapril	1.9±1.2	1.9±1.0‡	−0.1±0.9***†	0.4±1.4**††	0.5±1.2**††	0.8±0.6**†
%ΔL	Control		18.7±9.2	−1.3±12.9***	−3.2±8.3***	4.0±9.3**	6.6±2.8**
	Enalapril	16.2±8.2	16.4±8.9‡	−1.7±8.9***†	3.9±8.4**†	2.9±9.1**†	4.1±5.4***†

Tab 2. Effects of enalapril on hemodynamics and indices of heart function in myocardial ischemia and postreperfusion dogs. *$p>0.05$, **$p<0.05$, ***$p<0.01$ *vs* before ligation of LAD (15 min after medication); †$p>0.05$, ††$p<0.05$ enalapril *vs* control groups; ‡$p>0.05$, ‡‡$p<0.05$, ‡‡‡$p<0.01$ *vs* before medication in enalapril group. $\bar{x}\pm SD$

Index	Unit	Groups	Before medication	Before ligation	After ligation of LAD 2 min	30 min	60 min	Reperfusion for 2 min
MAP	kPa	Control		10.2±2.7	9.6±2.4*	9.2±2.8*	9.6±3.1*	9.3±4.3*
		Enalapril	10.8±2.5	9.0±2.7‡‡‡	8.4±2.8**†	8.0±2.7***††	8.9±3.1*†	8.6±2.8*†
HR	beats/min	Control		177±27	176±29*	182±28**	181±24*	182±26*
		Enalapril	186±17	184±20‡	183±18*†	179±14*†	179±14*†	182±14*†
MAP×HR	kPa·beats /min	Control		1837±699	1702±721*	1739±756*	1816±802*	1847±1160*
		Enalapril	2011±591	1591±672‡‡‡	1515±577**††	1449±543**††	1591±567*†	1558±490*†
CO	l/min	Control		1.1±0.29	1.06±0.28*	1.1±0.18*	0.9±0.27*	0.93±0.28*
		Enalapril	1.1±0.2	0.9±0.3‡	0.9±0.3*†	0.9±0.3*†	0.9±0.4*†	0.87±0.35*†
$+dP/dt_{max}$	kPa	Control		258±84	224±59**	225±67**	204±58**	217±69**
		Enalapril	269±92	215±82‡‡‡	187±78**†	185±62*†	176±45*†	179±68*†
$-dP/dt_{max}$	kPa	Control		168±71	147±88*	142±88**	153±89*	182±121*
		Enalapril	166±55	129±55‡‡‡	104±44***†	104±31**†	119±54*†	122±52*†

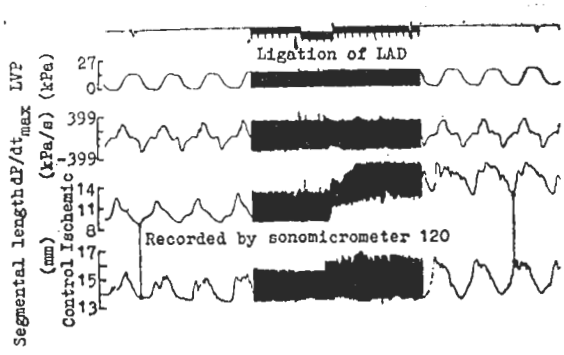

Fig 2. Segmental length recording from left ventricular myocardium before and after ligation of LAD in ischemic and nonischemic areas in (♂, 15 kg) dog.

occlusion. However, CO maintained stable.

DISCUSSION

The present study showed that pretreatment with enalapril (1 mg/kg iv) prevented reperfusion arrhythmia and hence reduced mortality of dogs with concomitant improvement of segmental contraction in ischemic region. It was documented that the incidence of VF correlates with the size of ischemic myocardium at risk[6]. However, little is known about the correlation between ischemic heart performance and reperfusion arrhythmia. Our results indicate that the protective effect of enalapril on ischemic local segmental contraction during occlusion parallels with its beneficial hemodynamic effect. Reduction of HR × MAP may contribute to the amelioration of reperfusion arrhythmia. The present results also reconcile with our previous observation[7] which concluded that ACEI could protect both myocardial ischemia and reperfusion damage in rats. In our experiment, the incidences of VF in control dogs were 42% (6/14 died of VF) during occlusion and 50% (4/8 died of VF) during reperfusion, quite comparable to 30-57% during LAD occlusion and 40-67% during reperfusion in the literature[3]. Considering the determinant influence of size of risk myocardium and the big variation of canine coronary arteries, we carefully adjusted the level of ligation of LAD in different dogs, so as to produce comparable size of ischemia in different groups. The size of ischemia identified by infusion of Evan's blue after experiments were 18±3% and 17±4% of the left ventricle in control and enalapril groups, respectively.

In the present experiment, new and accurate ultrasonic technique and equipment were used to measure the segmental contraction change in ischemic and normal myocardium. The results indicate that sonomicrometer is capable of differentiating minute change in mm and enable us to estimate the early functional damage in local ischemic myocardium and to evalute the protective effect of drugs on myocardium. The results showed that after LAD ligation, there were no significant changes of ΔL in nonischemic area in both groups. However, in ischemic area ΔL reduced remarkably even turned to negative, that is, EDL was smaller than ESL, implicated a passive protraction in ischemic area during systole. Detrimental changes of ΔL in enalapril pretreated dogs were significantly less than that in control, indicating the improvement of segmental contraction in ischemic myocardium. It is important to notice that there was no correlation between the recovery of segmental contraction and VF. In fact, VF often occurred as EDL recovered in the control group. This indicates that different mechanisms operate in reperfusion arrhythmia and functional damage of segmental shortening. Actually many vasodilators (captopril, nifedipine, felodipine, ketanserin) can protect dogs against ischemic VF, but only enalapril can save dogs from VF[3].

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依那普利对麻醉犬再灌注心律失常和节段收缩的有益作用

刘立英、陈　修、李　凯、邬文建　（湖南医学院药理教研室　长沙 410008）

提要　麻醉犬结扎前降支形成心肌梗塞，扎后 1 h 再灌注，用超声测微计测量扎前降支前后缺血区域和非缺血区域心肌的节段收缩。对照组 6/14 犬死于缺血期，生存的 4/8 犬在再灌注 3 min 内发生室颤死亡；给药组 1/10 犬死于梗塞期。余 9 犬在扎前降支前 15 min iv 依那普利 1 mg/kg 无室颤死亡。两组犬缺血局部心肌的节段收缩均显著减弱。表现为收缩期的缩短减少，但依那普利组的减少显著轻于对照组。结果显示对心肌缺血和再灌注室颤有保护作用。

关键词　依那普利；激肽酶Ⅱ类；冠状动脉循环；心肌收缩；再灌注心律失常；心肌梗塞；心输出量

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