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Effects of dauricine on transmembrane potential of ischemic and non–ischemic Purkinje fibers and ventricular muscles from infarcted canine hearts

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ABSTRACT Dauricine (Dau) 1 – 30 μmol / L produced the concentration–dependent depression of APA, V_{max}, MDP, and RP, and prolongations of APD_{90} of Purkinje fibers (PF) and epicardial ventricular muscles (VM) from both infarcted and non–infarcted zones. The ERP was lengthened only in non–ischemic PF and VM, and APD_{50} in non–ischemic PF, non– and ischemic VM. The prolonging effects of Dau on APD and ERP of ischemic PF were much less than those of non–ischemic ones, and its depressing effect on the V_{max} of ischemic VM was markedly greater than that of non–ischemic VM. The results suggest that Dau exerts its anti–arrhythmic effect through further depressing conduction of ischemic zone.

KEY WORDS dauricine; Purkinje fibers; action potentials; myocardial infarction; ischemia; electrophysiology

Dauricine (Dau) has been shown to be effective in treatment of various experimental and clinical tachyarrhythmias[1–3]. Its effect on the transmembrane potential of guinea pig papillary muscles has been reported[4]. Its effects on ischemic PF and VM have not been studied. Therefore, the present study was conducted to compare the effects of Dau on ischemic PF and VM surviving infarcted region and non–ischemic ones from normal region for a further understanding of its anti–arrhythmic effect.

MATERIALS AND METHODS

Eighteen adult mongrel dogs of either sex weighing 12 ± SD 2 kg were anesthetized with sodium pentobarbital (30 mg / kg iv). Under sterile condition, after opening the chest by a left thoracotomy the left anterior descending (LAD) coronary artery was ligated just distal to the first diagonal branch by the two–stage occlusion procedure[5]. Then the thorax was closed. After 3–5 d, the chest was reopened under sodium pentobarbital and the heart was excised to oxygenated Tyrode's solution. The ischemic and non–ischemic PF on the endocardial surface of left ventricle were carefully removed. The epicardial strips of left ventricle approximately 3 × 10 mm in size and 1 mm thick excised from both infarcted (IZ) and non–infarcted zones (NZ). The preparation were pinned to tissue bath and superfused with Tyrode's solution containing NaCl 149, KCl 4.0, $CaCl_2$ 1.8, $MgCl_2$ 0.5, Tris 10, dextrose 10 mmol / L, gassed with 100% O_2, pH 7.2–7.4 (37 ± 0.5℃).

The preparations were stimulated with square wave pulse of 1.5 time threshold intensity and 2 ms duration provided by stimulator (8303) and stimulus isolator made by Huayang Electronic Instrumental Factory. The basic frequency was 1 Hz. The premature stimulus (S_2) was introduced after every 8 basic stimulus (S_1) to determine the effective refractory period (ERP)[6].

The transmembrane potentials were recorded with glass microelectrodes filled with KCl 3 mol / L connected with a set of microelectrode amplifier (FW–2, made by Shanghai Institute of Physiology), double beam oscilloscope (SBR–1, made by Echoelectronic Instrumental Factory in Shantou) and electronic differentiator (SDW–1, made by Shanghai Institute of Physiology).

After all preparations had been stabilized

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in superfusion with Tyrode's solution for 2 h, action potential amplitude (APA), maximal rate of rise of phase 0 depolarization of the action potentials (V_{max}), maximal diastolic potential of PF (MDP), rest potential of VM (RP), action potential duratoin of 50% and 90% repolarization (APD_{50} and APD_{90}), and ERP were recorded during control period. Then, Dau (provided by the Faculty of Pharmacy in Tongji Medical University) was added to Tyrode's solution in a cumulative manner to achieve 1, 3, 10, 30 μmol / L for PF and VM, additional 100 μmol / L for VM only. All data were taken 30 min after superfusion with each concentration of Dau.

All values were expressed as $\bar{x} \pm SD$. Statistical analysis with F test of the date were perforemed.

RESULTS

Effects on APA, V_{max}, MDP and RP Under control condition, the AP of PF and VM from the IZ displayed severe diminutions in APA, V_{max}, MDP and RP. The superfusion with Dau produced the concentration-dependent supressing effects on APA, V_{max} and MDP in all PF from both IZ and NZ. The results are summarized in Tab 1. Dau 3 μmol / L depressed V_{max} of PF markedly without significant changes in other parameters. Its depressing effects were exaggerated by increasing concentrations. During superfusion with Dau 30 μmol / L, APA and V_{max} of PF from NZ and IZ were reduced by 25 ± 5% and 82 ± 11%; those from IZ were reduced by 29 ± 8% and 77 ± 14%, respectively. The effects of Dau on APA and V_{max} of PF from both NZ and IZ did not show statistical differences at the same concentration.

The effects of Dau on APA, V_{max} and RP of epicardial VM from both NZ and IZ were similar to, but much weaker than, those of PF (Tab 1). The depressing effect of Dau on V_{max} of ischemic VM was greater than that of non-ischemic VM.

Effects on APD_{50} and APD_{90} Tab 1 shows the effects of Dau on action potential duration (APD) of PF in NZ and IZ. Under control condition, the APD_{90} of ischemic PF was significantly longer than that of non-ischemic ones. Dau prolonged the APD_{90} of PF from both NZ and IZ in a concentration-dependent manner. During superfusion with Dau 30 μmol / L, the APD_{90} of PF from both NZ and IZ were prolonged by 65 ± 26% and 26% ± 9%, respectively. The APD_{50} of PF was also prolonged by 73 ± 31% only in NZ. Undoubtedly, the prolonging effects of Dau on the APD_{50} and APD_{90} of ischemic PF were much weaker than those of normal PF at the same concentration. As a result, the dispersion of APD of PF from both NZ and IZ was diminished (Fig 1).

Similarly, Dau significantly increased the APD_{50} and APD_{90} of VM from both NZ and IZ (Tab 1). The effect of Dau on ischemic VM did not significantly differ from that on non-ischemic VM. The prolongating effects of Dau on APD_{50} and APD_{90} of VM were much weaker than that of PF.

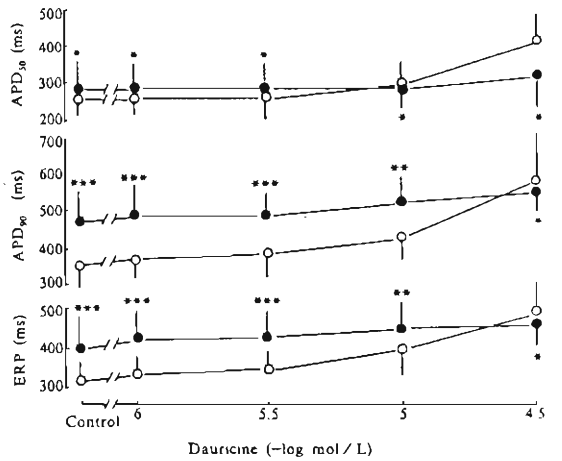

Fig 1. Effects of dauricine on APD_{50}, APD_{90} and ERP of non-infarcted (O, $n=8$) and infarcted, (●, $n=7$) canine Purkinje fibers. $\bar{x} \pm SD$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* infarcted Purkinje fibers.

Tab 1. Effects of dauricine on membrane potential of canine non-infarcted and infarcted Purkinje fibers and epicardial ventricular muscles. $\bar{x} \pm SD$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* control

	Dauricine (μmol / L)	APA (mV)	APD_{50} (ms)	APD_{90} (ms)	ERP (ms)	V_{max} (V / s)	MDP / RP (mV)
Non-infarcted PF($n=8$)	Control	134 ± 8	285 ± 25	348 ± 30	315 ± 32	599 ± 26	90 ± 4
	1	130 ± 8*	263 ± 30*	358 ± 36*	324 ± 32*	569 ± 25*	90 ± 4*
	3	123 ± 11*	281 ± 34*	377 ± 38*	349 ± 37*	510 ± 51**	88 ± 4*
	10	116 ± 9***	324 ± 57*	429 ± 41**	394 ± 35***	309 ± 72***	84 ± 3**
	30	101 ± 8***	463 ± 108***	596 ± 83***	503 ± 53***	108 ± 66***	75 ± 5***
Infarcted PF ($n=7$)	Control	106 ± 19	285 ± 61	465 ± 53	405 ± 62	333 ± 85	79 ± 4
	1	104 ± 21*	292 ± 65*	477 ± 58*	417 ± 66*	319 ± 87*	79 ± 4*
	3	101 ± 21*	299 ± 61*	489 ± 58*	428 ± 63*	216 ± 68*	77 ± 5*
	10	89 ± 20*	314 ± 80*	528 ± 43*	454 ± 55*	137 ± 67***	75 ± 4*
	30	75 ± 16**	323 ± 86*	556 ± 41**	469 ± 49*	73 ± 39***	70 ± 5**
Non-Infarcted epicardium ($n=6$)	Control	112 ± 7	219 ± 30	276 ± 33	241 ± 33	280 ± 34	87 ± 5
	1	108 ± 6*	220 ± 29*	276 ± 33*	246 ± 32*	270 ± 36*	87 ± 5*
	3	108 ± 8*	227 ± 31*	283 ± 35*	262 ± 36*	264 ± 27*	87 ± 5*
	10	107 ± 10*	243 ± 32*	301 ± 35*	274 ± 39*	248 ± 19*	85 ± 5*
	30	103 ± 12*	256 ± 44*	312 ± 44*	295 ± 46*	200 ± 34*	82 ± 6*
	100	91 ± 11***	293 ± 59**	353 ± 62***	319 ± 70**	132 ± 24***	76 ± 4***
Infarcted epicardium ($n=6$)	Control	103 ± 12	185 ± 44	273 ± 35	253 ± 44	210 ± 63	76 ± 6
	1	102 ± 13*	185 ± 44*	273 ± 34*	255 ± 45*	210 ± 63*	76 ± 6*
	3	99 ± 16*	195 ± 51*	296 ± 59*	278 ± 66*	168 ± 61*	75 ± 5*
	10	95 ± 14*	207 ± 58*	303 ± 60*	288 ± 63*	118 ± 26**	73 ± 6*
	30	86 ± 14*	245 ± 56*	310 ± 76*	325 ± 102*	84 ± 24***	69 ± 6*
	100	77 ± 14**	293 ± 60***	379 ± 77**	357 ± 93*	55 ± 18***	66 ± 5**

APA: action potential amplitude; APD_{50} and APD_{90}: action potential duration of 50 % and 90 % repolarization; ERP: effective refractory period; V_{max} : maximal rate of rise of potential; MDP / RP: maximal diastolic potential of PF and rest potential of epicardium, n = number of Purkinje fibers or epicardial ventricular muscles.

Effect on ERP During control superfusion, ERP of all ischemic PF were considerably longer than that of the normal PF, which caused severe dispersion of ERP between NZ and IZ. The Dau induced prolongation of APD as described above always accompanied by that of ERP. However, the prolonging effect of Dau on ERP of PF in NZ was markedly greater than that in IZ, and the dispersion of ERP between NZ and IZ was abolished after superfusion with Dau (Fig 1). The prolongation of Dau on ERP of VM from NZ did not differ from that from IZ, but was weaker than that of PF.

DISCUSSION

It has been shown that the PF and epicardium surviving infarcted region have abnormal electrophysiological characteristics including a lower membrane potential, decreased APA, depressed V_{max} and longer APD. These regions are thought to be the sites for genesis of arrhythmias following myocardial infarction[7,8]. It has also been reported that the arrhythmias occurring 3–5 d after coronary occlusion and reperfusion are nearly identical to the recurrent ventricular tachycardias that is often found in patients with old myocardial infarcts[9]. Its electrophysiological basis is thought to be reentry[10]. Dau decreases the APA and V_{max} of ischemic PF and VM, which suggests that Dau depresses conduction in infarcted region and eventually render unidirectional

block existing on infarcted region to bidirectional block. As a result, the reentrant pathway was disrupted.

On the other hand, there were considerable disparities in APA and ERP between NZ and IZ as well as within IZ itself, and highly heterogenous recovery of excitability throughout the conduction system, which are also important factors for initiation of reentrant arrhythmias after myocardial infarction[7,11]. Dau induces less prolongations in APD and ERP in the ischemic PF than in the normal ones, which significantly reduces disparities in APD and ERP between the normal and infarcted regions as well as throughout conduction system.

Based on the present results, it might be considered that the further depression of Dau on conduction of ischemic region and reducing of the extent of dispersion of APD and ERP between ischemic and normal tissues as well as within the IZ itself might be important mechanisms for its effective termination of ventricular reentrant tachyarrhythmias.

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REFERENCES

1 Li GR, HU CJ, Lü FH. Antagonistic effect of dauricine on experimental arrhythmias. *J Trad Chin Med* 1984; **4** : 25

2 冯克燕、周际安、龚培力、陈 汇、杨泽珈、胡崇家.蝙蝠葛碱治疗心律失常的临床观察.中华心血管病杂志. 1984; **12** : 265

3 Zhou JA, Feng KY, Leng DM, Yang ZJ, Gong PL, Hu CJ. Investigation of clinical efficacy and hemodynamic effects of dauricine in patients with arrhythmias. *Chin J Clin Pharmacol* 1987; **3** : 95

4 Zong XG, Jin MW, Zhao DY, Hu CJ, Lü FH. Effects of dauricine on electrical and mechanical activities in isolated guinea pig myocardium. *Acta Pharmacol Sin* 1985; **6** : 30

5 Harris AS. Delayed development of ventricular ectopic rhythms following experimental coronary occlusion. *Circulation* 1950; **1** : 1318

6 Nattel S, Zeng FD. Frequency-dependent effects of antiarrhythmic drugs on action potential duration and refractoriness of canine cardiac Purkinje fibers. *J Pharmacol Exp Ther* 1984; **229** : 283

7 Cardinal R, Sasyniuk B. Electrophysiological effects of bretylium tosylate on subendocardial Purkinje fibers from infarcted canine hearts. *Ibid* 1978; **204** : 159

8 Allen JD, Brennan FJ, Wit AL. Actions of lidocaine on transmembrane potentials of subendocardial Purkinje fibers surviving in infarcted canine hearts. *Circ Res* 1978; **43** : 470

9 Davis J, Glassman R, Wit AL. Method for evaluating the effects of antiarrhythmic drugs on ventricular tachycardias with different electrophysiologic characteristics and different mechanisms in the infarcted canine heart. *Am J Cardiol* 1982; **49**: 1176

10 El-Sherif N, Mehra R, Gough WB, Zeiler RH. Reentrant ventricular arrhythmias in the late myocardial infarction period. Interruption of reentrant circuits by cryothermal techniques. *Circulation* 1983; **68** : 644

11 Lazzara R, Scherlag BJ. Electrophysiologic basis for arrhythmias in ischemic heart disease. *Am J Cardiol* 1984; **53**: 1B

蝙蝠葛碱对犬心肌梗塞后缺血和非缺血浦氏纤维和心室肌跨膜电位的作用

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提要 蝙蝠葛碱(Dau) 1-30 μmol / L 浓度依赖性抑制梗塞区(IZ)和非梗塞区(NZ) PF 和 VM 的 APA、V_{max}, MDP 和 RP, 延长 APD_{90}, NZ 的 PF 和 VM 之 APD_{50} 和 ERP 及 IZ 的 VM 之 APD_{50} 亦明显延长.Dau 对缺血 PF 的 APD 和 ERP 的延长作用明显减弱, 使 IZ 和 NZ 之 APD 不匀一性减小, 而抑制 IZ 心肌 V_{max} 的作用强于其对 NZ 心肌的作用, 可能促使单向阻滞变为双向阻滞.这些药理效应可构成其抗缺血性室性心律失常的基础.

关键词 蝙蝠葛碱; 浦氏纤维; 动作电位; 心肌梗塞; 缺血; 电生理学