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Comparative study of propafenone and procainamide on canine ischemic ventricular tachyarrhythmias

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Abstract: AIM To observe the electrophysiologic effects of propafenone (Prop) on canine ischemic ventricular tachyarrhythmias and compared with those of procainamide (PA), so as to evaluate the effect and mechanism of Prop on ischemic ventricular tachyarrhythmias. **METHODS** A canine ischemic ventricular tachyarrhythmia model was established by the left anterior descending coronary artery occlusion for 2 h and reperfusion. Five to eight days later, open-chest dogs were given programmed electrical stimulation (PES), and electrophysiologic data were measured by electrocardiogram (ECG). **RESULTS** Both Prop and PA distinctly lengthened the QTc interval ($P < 0.01$) and effective refractory period (ERP) of normal and ischemic ventricular myocardium respectively ($P < 0.01$), decreased the dispersion of ERP in ischemic myocardium and in left ventricle ($P < 0.01$), and increased the diastolic excitability threshold of normal and ischemic ventricular myocardium remarkably ($P < 0.01$). Prop and PA effectively prevented PES- or ischemia-induced ventricular tachycardia or ventricular fibrillation ($P < 0.05$, or $P < 0.01$). **CONCLUSION** The canine model is a worthy and reliable one. Prop and PA may be effective in preventing the onset of ventricular tachycardia or ventricular fibrillation after myocardial ischemic damage. The antiarrhythmic effects of both drugs are similar.

Key words: propafenone; procainamide; arrhythmia; electrocardiography; myocardial ischemia

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During the last decade, testing serial drugs by the use of programmed electrical stimulation (PES) has become an important tool for the clinical assessment of antiarrhythmic drug effects[1]. Moreover animal models have been developed to allow preclinical evaluation of antiarrhythmic drug properties by this method[2-5]. Propafenone (Prop) and procainamide (PA) have been shown to be effective in antagonizing arrhythmias[6], but little is known about the comparative effects of Prop and PA on both normal and ischemic myocardium *in vivo* in case of ischemic ventricular tachyarrhythmias. The purpose of the present study was to observe the electrophysiologic effects of Prop on canine ischemic ventricular tachyarrhythmias and compared with those of PA, for PA is a typical and representative Ⅰ type antiarrhythmic drug in clinical electropharmacology, so as to evaluate the effect and mechanism of Prop on ischemic ventricular tachyarrhythmias.

1 MATERIALS AND METHODS

1.1 Drugs and animals

Prop was provided by Shanghai Xingyi Jingzhu Drug Company, PA was provided by Hongqi Pharmaceutical Factory of Shanghai Medical University. Twenty-four adult mongrel dogs, weighing 12 – 15 kg, were purchased from Animal Center of Jiangxi Medical College and maintained on a stand food and water.

1.2 Surgical preparation

The dogs were anesthetized with sodium pentobarbital (30 mg·kg^{-1}, iv), inserted with a cuffed endotracheal tube and ventilated with room air by a respirator. Surgical preparation was carried out according to the previous literatures[2-5].

In 18 dogs, the left anterior descending coronary artery (LAD) was occluded using an artery snare for 2 h, the occlusive snare was then removed and blood flow was restored through the stenosed artery. The chest was then closed and routine postoperative care was administered. Six sham-operated control dogs underwent identical procedures except for LAD occlusion.

1.3 Programmed electrical stimulation during the convalescent phase[2-5]

The dogs were anesthetized and ventilated at 5 – 8 d after the initial surgical operation, and the chests of the dogs were opened again as stated above, 8 – 10 unipolar plunge (hook) wire electrodes(0.2 mm in diameter) were placed in multiple intramyocardial sites within areas of both normal and ischemic ventricular myocardium. The electrodes were insulated except for the tip. The PES was performed by a XD-2A programmed electric stimulator, the current and the duration of the stimulus were held constantly at twice the excitability threshold and 2 ms respectively. The electrocardiogram (ECG) was monitored and recorded continuously by a SJ-41 polygraph.

The 18 dogs with LAD ischemia-reperfusion were divided into 3 groups, and given iv Prop 2 $mg \cdot kg^{-1}$, PA 25 $mg \cdot kg^{-1}$ and normal saline (NS) 40 mL, respectively. The PES was performed 10 min before and 10 min after drug administration in the same stimulating site and same PES protocol[2-5]. The dispersion of effective refractory period (ERP) was defined as the maximum difference between the longest and the shortest ERP of the myocardium[2-5]. The PES-induced sustained ventricular tachycardia (SVT) was terminated by a burst of rapid ventricular pacing. The PES-induced ventricular fibrillation (VF) was terminated by direct counterchock (3.59 – 4.78 cal).

1.4 Acute posterolateral ischemia during the convalescent phase[2-5]

After the completion of the PES, the left circumflex coronary artery (LCX) was isolated free from surrounding myocardium. A needle wire electrode with 4 mm noninsulated tip was inserted into the LCX. After another bolus Prop, PA or NS administration, an anodal direct current of 150 μA was applied to the electrode in order to initiate LCX intimal injury and thrombosis and acute posterolateral ischemia. The lead Ⅱ ECG was recorded continuously until spontaneous VF developed or for 6 h.

1.5 Postmortem examination[2-5]

At the completion of the experiment, the hearts of the dogs were isolated. The intravascular thrombi of the LCX were removed and weighed. The heart was sectioned transversely into 5 mm thick slices, histochemical staining was performed using 0.5% triphenyltetrazolium chloride (TTC) and 0.01% phosphate buffer(pH 7.4) to identify infarcted myocardium, and then, histopathologic staining was performed using hematoxylin-eosin.

1.6 Statistics

The data were presented as $\bar{x} \pm s$. Electrophysiologic data were analyzed using paired t test. Fisher′s exact test was used to analyze the differences in survival among the four groups of dogs.

2 RESULTS

2.1 Effects of propafenone and procainamide on electrophysiologic data

QTc intervals of ECG were measured in 18 dogs, significant increase in QTc intervals was observed after Prop and PA administration (Tab 1). Significant increases in excitability threshold and ERP both in normal and infarct myocardium were observed after Prop and PA administration (Tab 2, 3). The dispersion of ERP in ischemic myocardium and in left ventricle were decreased remarkably after Prop and PA administration (Tab 4).

2.2 Induction and termination of ventricular tachyarrhythmias

In sham-operated group, neither SVT nor VF was induced by PES in any dogs. Before medication, the SVT was reproducibly induced in 5/6 NS-group dogs, 5/6 Prop-group dogs (Fig 1) and 4/6 PA-group dogs respectively; the VF was induced in one of the NS-group dogs, one of the Prop-group dogs (Fig 1), and two of the PA-group

dogs respectively. There was no significant difference among these three groups ($P > 0.05$). After medication, the PES failed to produce VT or VF in any Prop-treated dogs (Fig 1) and in 5/6 PA-treated dogs. The PES produced non-sustained VT in only one PA-treated dog. There was a significant reduction in the induction of VT and VF in the Prop-treated group ($P < 0.01$) and the PA-treated group ($P < 0.05$). But in the NS-treated dogs, the PES induced VT or VF was reproduced again after iv NS ($P > 0.05$).

2.3 Effects of propafenone and procainamide on ventricular fibrillation induced by acute posterolateral ischemia in the convalescent phase

After the completion of PES, the application

Tab 1. Effects of propafenone (Prop) and procainamide (PA) on QTc intervals in dogs with left ventricle myocardial infarction

Group	QTc interval/ms	
	Before	After
NS	440 ± 40	450 ± 50
Prop 2	430 ± 36	530 ± 23$^{**\,\#\#}$
PA 25	410 ± 50	510 ± 50$^{**\,\#}$

Left ventricle myocardial infarction was produced by the left anterior descending coronary artery occlusion for 2 h and reperfusion, 5 – 8 d later, the electrophysiologic data were measured by electrocardiogram (ECG). Before, After: 10 min before and 10 min after Prop 2 mg·kg^{-1} or PA 25 mg·kg^{-1} iv. QT interval was measured by the lead Ⅱ ECG. $QTc = Q - T/\sqrt{R-R}$. $\bar{x} \pm s$, $n = 6$. $^{**}P < 0.01$, compared with before medication; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, compared with normal saline (NS).

Tab 2. Effects of propafenone and procainamide on excitability threshold in dogs with left ventricle myocardial infarction

Group	Excitability threshold/V					
	Normal region			Ischemic region		
	n	Before	After	*n*	Before	After
Sham	48	1.5 ± 0.7	–			
NS	32	1.5 ± 0.5	1.6 ± 0.6	24	3.3 ± 2.2	3.4 ± 2.1
Prop 2	35	1.7 ± 0.5	2.9 ± 0.5$^{**\,\#\#}$	26	3.1 ± 0.6	4.5 ± 0.7$^{**\,\#\#}$
PA 25	31	1.6 ± 0.6	2.8 ± 0.6$^{**\,\#\#}$	31	3.0 ± 1.3	4.0 ± 1.1**

See Tab 1 for ischemia-reperfusion treatments. Sham: sham operation. Programmed electrical stimulation (PES) was performed 10 min before and 10 min after Prop or PA iv. $\bar{x} \pm s$, *n*: number of stimulated sites. $^{**}P < 0.01$, compared with before medication; $^{\#\#}P < 0.01$, compared with NS.

Tab 3. Effects of propafenone and procainamide on effective refractory period in dogs with left ventricle myocardial infarction

Group	Effective refractory period/ms								
	Right ventricle			Normal region			Ischemic region		
	n	Before	After	*n*	Before	After	*n*	Before	After
Sham	12	160 ± 22	–	48	165 ± 20	–			
NS	12	163 ± 22	162 ± 16	20	162 ± 20	162 ± 18	24	188 ± 23	186 ± 25
Prop 2	12	168 ± 12	195 ± 22$^{**\,\#\#}$	23	165 ± 16	194 ± 23$^{**\,\#\#}$	26	190 ± 18	225 ± 17$^{**\,\#\#}$
PA 25	12	164 ± 30	190 ± 24$^{**\,\#\#}$	19	165 ± 26	192 ± 23$^{**\,\#\#}$	31	185 ± 30	215 ± 30$^{**\,\#\#}$

See Tab 1 and 2 for ischemia-reperfusion and PES treatments. $\bar{x} \pm s$. *n*: number of stimulated sites. $^{**}P < 0.01$, compared with before medication; $^{\#\#}P < 0.01$, compared with NS.

Tab 4.　Effects of propafenone and procainamide on effective refractory period dispersion in dogs with left ventricle myocardial infarction

Group	Dispersion of effective refractory period/ms					
	Normal region		Ischemic region		Left ventricle	
	Before	After	Before	After	Before	After
Sham	15 ± 9	–	–	–	16 ± 12	–
NS	14 ± 9	14 ± 5	38 ± 24	42 ± 17	48 ± 17	52 ± 14
Prop 2	15 ± 6	13 ± 7	39 ± 11	21 ± 7$^{**\#\#}$	57 ± 17	43 ± 13$^{**\#}$
PA 25	15 ± 5	14 ± 6	44 ± 15	28 ± 9$^{**\#\#}$	48 ± 13	32 ± 11$^{**\#\#}$

See Tab 1 and 2 for ischemia-reperfusion and PES treatments. $\bar{x} \pm s$, $n = 6$. $^{**}P < 0.01$, compared with before medication; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, compared with NS.

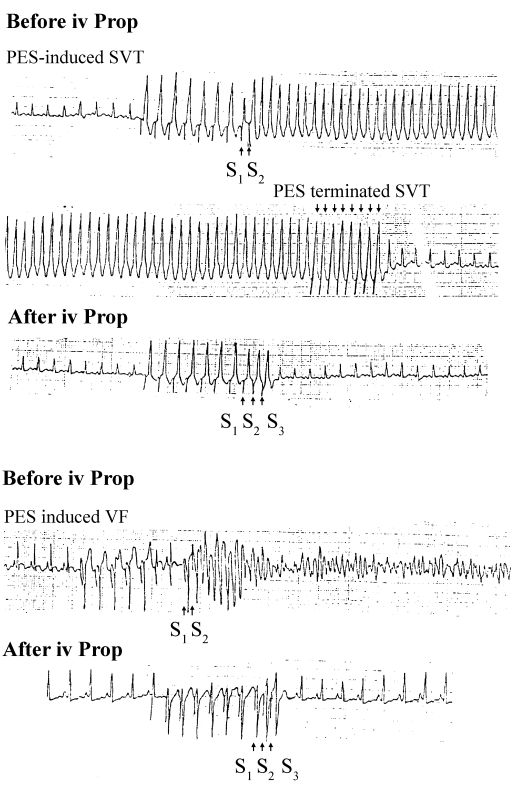

Fig 1.　Effect of propafenone on sustained ventricular tachycardia and ventricular fibrillation (VF) induced by programmed electrical stimulation in dogs. See Tab 1 and 2 for ischemia-reperfusion and PES treatments. Before iv Prop, SVT and VF were reproducibly induced and terminated by the PES. After iv Prop, the PES failed to produce SVT and VF. S_1: basic ventricular drive beats; S_2: the 1st extrastimulus; S_3: the 2nd extrastimulus.

of 150 μA anodal direct current to the electrode previously inserted into the LCX was followed by ECG evidence of posterolateral ischemia in leads

Tab 5.　Effects of propafenone and procainamide on ventricular fibrillation induced by acute posterolateral ischemia in the convalescent phase

Group	Time of ST elevation/min	Thrombus /mg	Infarct size/%	No. with VF
Sham	104 ± 30	22 ± 11	0	0/6
NS	104 ± 30	18 ± 9	31 ± 8	6/6
PA 2	110 ± 40	23 ± 16	32 ± 7	1/6*
Prop 25	104 ± 26	23 ± 5	31 ± 4	1/6*

After completion of PES, dogs were given another bolus of Prop, PA or NS, 5 min later, an anodal direct current of 150 μA was applied for 6 h by a needle wire electrode with 4 mm noninsulated tip inserted into the left circumflex coronary artery (LCX) to initiate LCX intimal injury, thrombosis and acute posterolateral ischemia. The lead Ⅱ ECG was recorded continuously until spontaneous VF developed or for 6 h. The infarct size was determined gravimetrically as a percentage of the total left ventricular mass. $\bar{x} \pm s$, $n = 6$. $^{*}P < 0.05$, compared with NS group.

Ⅱ, Ⅲ, aVF and aVL at similar time intervals for all dogs (Tab 5, Fig 2). Within 30 min of the onset of ischemia, all of the NS-treated dogs developed spontaneous VF (Fig 2), but only one Prop-treated dog and one PA-treated dog developed spontaneous VF, indicating that the Prop and PA treatments significantly increased dog survival when compared to the NS treatment (Tab 5).

2.4　Postmortem examination

All dogs had intimal injury and thrombus formation in the LCX. In all 18 dogs subjected to occlusion and reperfusion of the LAD, histochemical

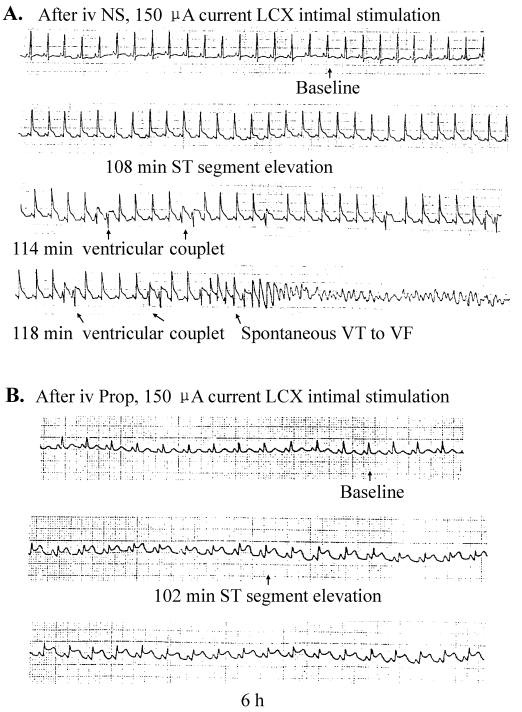

Fig 2. Effect of propafenone on ischemia-induced ventricular fibrillation. See Tab 5 for dog treatments. Within 30 min of the onset of acute posterolateral ischemia, all of the six NS-treated dogs developed ventricular couplet and spontaneous VF (A). But in five of the six Prop-treated dogs failed to develop spontaneous VF (B).

staining was performed using TTC to identify infracted myocardium, Histopathologic staining and microscopic examination confirmed marked interspersing of normal, abnormal, necrotic and hemorrhagic myocardium and mononuclear cell infiltration. The infarct size and the weight of the thrombus mass were similar among the three LAD occluded groups (Tab 5).

3 DISCUSSION

3.1 Animal model

The canine model of ischemic ventricular tachyarrhythmias described here has some advantages: ① Because of preconditioning a stenosis in the LAD, the mortality of dogs in the acute stage is much lower than that occurring after routine occlusion techniques[3-5]. ② The infarct size produced are large with low variability (Tab 5). ③ Because the canine model presents stably more detailed electrophysiologic data *in vivo*, excitability threshold and refractoriness are able to evaluate at multiple sites. ④ The VT and VF may be reproducibly initiated for 5 – 8 d after acute myocardial infarction in open-chest dogs by PES. ⑤ The spontaneous VF may also be induced by acute myocardial ischemia at a site distant to a previous myocardial infarction. These may provide a model which closely resembles the development of VT and VF in humans and is suitable for the evaluation of both the mechanisms of arrhythmias and the effects of antiarrhythmic drugs[1-5]. The results of the present study suggest that PES-induced VT and VF are highly reproducible and reliable, and this canine model is a worthy and reliable one.

3.2 Effects of propafenone and procainamide on ventricular tachyarrhythmias

Previous studies have provided strong evidence that PES induced VT is reentrant in mechanism[2]. Our experiments showed that Prop and PA were effective in antagonizing ventricular tachyarrhythmias induced by PES and acute myocardial ischemia in dogs. This action was probably responsible for the significant lengthening of the QTc interval and the ERP of both normal and ischemic myocardium, and for the decreasing of the dispersion of ERP in ischemic myocardium and left ventricule so as to discontinue the reentrant cycle, and to increase the excitablilty threshold of both normal and infarct myocardium and thus to increase the electrophysiologic stability of the heart to prevent arrhythmia. The results of the present study suggest that both Prop and PA be effective in preventing the onset of VT and VF reentrant ventricular tachyarrhythmias after myocardial ischenic damage, and deserve further attention as antifibrillatory agents. The antiarrhythmic effects of both drugs are similar.

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普罗帕酮和普鲁卡因胺抗犬缺血性快速室性心律失常的对比研究

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摘要：目的　观察普罗帕酮对犬在体心脏缺血性快速室性心律失常的心电生理影响并与普鲁卡因胺对比，以探讨其抗缺血性快速室性心律失常的效果及作用机制。**方法**　用冠状动脉左前降支结扎并部分再灌注法造成犬急性前壁心肌梗死，5～8 d 后，辅以心室程控电刺激（PES）技术及冠状动脉内恒定微量直流电刺激技术，并诱发与终止持续性室性心动过速和心室纤颤，制备成犬急性心肌缺血再灌注后可控性快速室性心律失常的在体心脏心电模型，心电图对比观察普罗帕酮及普鲁卡因胺的抗心律失常作用。**结果**　普罗帕酮及普鲁卡因胺均能显著地延长心肌梗死犬的心电图 QTc 间期（$P < 0.01$）及正常和缺血心肌的有效不应期（$P < 0.01$），降低缺血心肌和左室心肌的有效不应期离散度（$P < 0.01$），提高正常心肌和缺血心肌的舒张期兴奋阈值（$P < 0.01$），抑制 PES 诱发的持续性室性心动过速和心室纤颤（$P < 0.01$），并能预防犬急性心肌梗死后再次缺血所致的自发性室性心动过速和心室纤颤（$P < 0.05$）。**结论**　①该犬在体心脏心电药理学实验模型具有较好的重复性、可靠性及临床相关性，是一种有价值的心电药理学实验研究模型。②普罗帕酮及普鲁卡因胺均具有抗缺血性快速室性心律失常的心电生理作用，是有效的抗颤药物，两药效果相似。

关键词：普罗帕酮；普鲁卡因胺；心律失常；心电描记术；心肌缺血

（本文编辑　董立春）