失常：应激8 h 反而抑制之. icv 乌头碱致心律失常的潜伏期在正常大鼠为4.1±0.9 min，但应激2 h 后缩短至2.9±0.9 min，应激8 h 后延长至9.3±3.8 min. 该双相反应可分别被预先肾上腺切除和迷走切断加 ip 氨茶碱削弱. 血中心肌特异酶活性随应激持续而上升. **结论**：急性制动应激使心脏电稳定性先降后升. 前者与儿茶酚胺释放有关，后者与 cAMP 适应性降低及迷走激动有关. 应激后心肌损伤与心脏电稳定性改变并不平行.

关键词 身体的约束；心律失常；乌头碱；氨茶碱；肾上腺切除术；迷走神经切断术；乳酸脱氢酶；肌酸激酶

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Effects of *Panax notoginseng* saponin Rg_1 on cardiac electrophysiological properties and ventricular fibrillation threshold in dogs

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AIM: To study the effects of Rg_1 isolated from saponins of *Panax notoginseng* on cardiac electrophysiological properties and ventricular fibrillation threshold (VFT). **METHODS**: Seventeen open-chest dogs were randomly allocated into a Rg_1 group (20 mg kg^{-1}, iv) and a control group. The electrophysiological variables and VFT were evaluated by standard electric stimuli and monophasic action potential (MAP) recording. **RESULTS**: Rg_1 prolonged sinus node recovery time (SNRT) by 19.1 %, AV conduction Wenckebach cycle length (AVWCL) by 7.1 %, and ventricular effective refractory period (VERP) by 7.9 %. It prolonged ventricular $MAPD_{30}$, $MAPD_{50}$, and $MAPD_{90}$ by 25.5 %, 24.2 %, and 13.5 %, respectively. VFT was increased by 19.2 %. **CONCLUSION**: Rg_1 prolonged ventricular refractoriness and repolarization, and increased VFT. It was indicated that cardiac electrophysiological effects of Rg_1 were similar to those of amiodarone.

KEY WORDS *Panax notoginseng*; panaxatriol saponins; anti-arrhythmia agents; electrophysiology; action potentials; ventricular fibrillation

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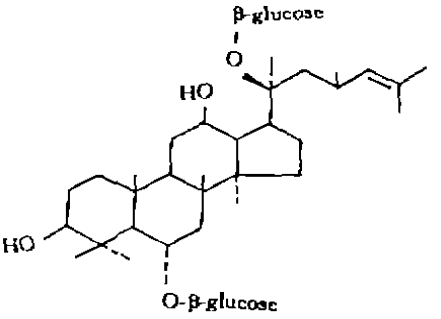
Extract of the root of *Panax notoginseng* (Burk) F H Chen mainly contains saponins (PNS). Panaxatriol saponins (PTS) are isolated from total saponins of PNS and PNS saponin Rg_1 is the product of further purification. The cardiac electrophysiological effects of PNS or PTS have been studied in mouse, rat, rabbit, or isolated guinea pig papillary muscles or sheep cardiac Purkinje fibers[1-6], as well as the *in vitro* studies on Rg_1[7]. In this paper, the effects of saponin Rg_1 on cardiac electrophysiological properties and ventricular fibrillation threshold (VFT) in dogs were evaluated by the technic of standard electric stimuli and monophasic action potential (MAP) recording.



Rg_2

MATERIALS AND METHODS

Rg_2 in the form of yellowish powder (purity >95 %) was kindly provided by Guangzhou Pharmaceutical Industrial Research Institute, and 1 % aqueous solution (10 g L^{-1}) was freshly prepared for iv injection. Healthy adult dogs (n=17) weighting 12.3±s 2.6 kg were allocated into 2 groups at random. One group (n=9) was given iv Rg_2, another group (n=8) iv normal saline (NS) solution. The dogs were anesthetized with ip 3 % sodium pentobarbital 30 mg kg^{-1}, intubated, and mechanically ventilated with humidified room air. A 6F catheter was inserted into the right femoral artery to monitor the blood pressure using a Spectramed P23XL transducer. Another catheter was placed in the right femoral vein for drug administration and maintenance infusion (about 1 L). The chest was opened by median sternotomy. The heart was suspended in a pericardial sling. Two pairs of stainless steel-wire electrodes (diameter 125 μm, 5 mm apart) were inserted into the right and left atrial appendages, and right ventricular anterior wall, respectively, for cardiac pacing and recording. Surface electrocardiogram lead II, right and left atrial and right ventricular bipolar electrograms, along with left ventricular MAP and arterial blood pressure were displayed simultaneously on an oscilloscope and recorded by Siemens Mingograf 7 recorder at a paper speed of 100 mm s^{-1}. Postoperatively, the dogs were stabilized for 10 min.

A baseline three-step (electrophysiological, ventricular MAP duration and VFT) study was proceeded in sequence, which lasted 50—60 min. At least 30 min were allowed following the last defibrillation for recovery. Then, Rg_2 (20 mg kg^{-1}) or NS was injected iv 10 min before electrophysiological study on the basis of self-control.

Electrophysiological study [8] The variables measured were: sinus cycle length (SCL), QRS duration (QRSD), inter-atrial conduction time (IACT), and atrioventricular conduction time (AVCT) based on right atrial pacing at a cycle length of 300 ms. Sinus node recovery times (SNRT) and atrioventricular conduction Wenckebach cycle length (AVWCL) were evaluated by atrial incremental pacing. Sinoatrial conduction time (SACT) was estimated[8]. Atrial effective refractory period (AERP) and ventricular effective refractory period (VERP) were determined by programmed stimulation (Medtronic 5325) at twice diastolic threshold, with a duration of 1.8 ms at a based drive cycle length of 300 ms. The effective refractory period (ERP) is the longest S_1-S_2 interval not producing an atrial or ventricular depolarization.

Ventricular MAP duration (MAPD) [9] Epicardial MAPD was recorded by using nonpolarizable contact electrode probes. MAP signal through a DC-coupled, differential preamplifier was recorded by a 7-channel electrocardiographic recorder (Siemens, Mingograf 7). Ventricular MAPD was measured based on right atrial pacing at cycle length of 300 ms. MAPD was determined at repolarization of 90 %, 50 %, and 30 % ($MAPD_{90}$, $MAPD_{50}$, $MAPD_{30}$) of the total amplitude, which was defined as the distance from the baseline to the crest of the MAP plateau.

Ventricular fibrillation threshold (VFT) VFT was determined by a train of constant current pulses that scanned the T wave as previous study[3,10]. The minimal level of current successively evoking sustained ventricular fibrillation was defined as the VFT.

Statistical analysis All data were analyzed with paired t test.

RESULTS

All the results after iv NS did not show significant deviation from those in baseline study ($P>0.05$). Rg_2 prolonged AVWCL by 7.1 % (182±23 ms *vs* 195±31 ms, $P<0.05$). Rg_2 effected on SCL, IACT, AVCT, and QRSD without statistical significance. Rg_2 prolonged SNRT by 19.1 % (418±82 ms

vs 498±106 ms, $P<0.05$). SACT was insignificantly changed. Rg_1 prolonged VERP by 7.9 % (151±20 ms *vs* 163±25 ms, $P<0.01$). AERP was lengthened but without statistical significance. Rg_1 increased VFT by 19.2 % (27.1±6.6 mA *vs* 32.3±4.3 mA, $P<0.05$). Rg_1 markedly prolonged ventricular $MAPD_{10}$, $MAPD_{50}$, and $MAPD_{90}$ by 25.5 % (106±12 ms *vs* 133±21 ms, $P<0.01$), 24.2 % (128±17 ms *vs* 159±30 ms, $P<0.01$); and 13.5 % (170±23 ms *vs* 193±31 ms, $P<0.01$), respectively. Rg_1 did not significantly affect systolic or diastolic arterial blood pressure (Tab 1).

Tab 1. Cardiac effects of iv Rg_1 (20 mg kg^{-1}) in dogs. $\bar{x}\pm s$. **[a] $P>0.05$, [b] $P<0.05$, [c] $P<0.01$ *vs* before injection.**

	Drug	*n*	Before	After	Change/%
SCL/ms	Rg_1	9	357±76	371±67	3.9[a]
	NS	8	364±66	385±68	5.8[a]
IACT/ms	Rg_1	9	44±12	44±14	0.0[a]
	NS	8	53±14	55±16	3.8[a]
AVWCL/ms	Rg_1	9	182±23	195±31	7.1[b]
	NS	8	199±44	210±37	5.5[a]
AVCT/ms	Rg_1	9	121±18	121±26	0.0[a]
	NS	8	118±16	120±41	1.7[a]
QRSD/ms	Rg_1	9	64±14	63±15	−1.6[a]
	NS	8	66±18	68±20	3.0[a]
SNRT/ms	Rg_1	9	418±82	498±106	19.1[b]
	NS	8	503±117	502±108	−0.2[a]
SACT/ms	Rg_1	9	28±11	32±11	14.3[a]
	NS	8	37±24	43±21	16.2[a]
AERP/ms	Rg_1	9	125±18	132±19	5.6[a]
	NS	8	130±21	128±15	−1.5[a]
VERP/ms	Rg_1	9	151±20	163±25	7.9[c]
	NS	8	158±27	161±24	1.9[a]
VFT/mA	Rg_1	9	27.1±6.6	32.3±4.3	19.2[b]
	NS	8	23.3±6.9	21.6±94	−7.3[a]
$MAPD_{10}$/ms	Rg_1	9	106±12	133±21	25.5[c]
	NS	8	112±21	104±22	−7.1[a]
$MAPD_{50}$/ms	Rg_1	9	128±17	159±30	24.2[c]
	NS	8	139±31	133±26	−4.3[a]
$MAPD_{90}$/ms	Rg_1	9	170±23	193±31	13.5[c]
	NS	8	196±34	192±30	−2.0[a]
SBP/kPa	Rg_1	9	15.9±1.1	17.6±3.1	10.7[a]
	NS	8	16.3±3.7	15.7±2.1	−3.7[a]
DBP/kPa	Rg_1	9	12.0±1.3	13.1±3.7	9.2[a]
	NS	8	11.3±2.1	11.5±2.4	1.8[a]

DISCUSSION

Present study demonstrated the effects of Rg_1 on cardiac electrophysiological properties and VFT in dogs *in vivo*. It showed Rg_1 produced a picture very similar to those of PNS or PTS, such as lengthening of VERP, ventricular MAPD, and increasing of VFT. On the contrary, a few results of previous studies showed Rg_1 did not affect the configuration of action potential[7], and even PNS shortened action potential duration in isolated guinea pig papillary muscles[11]. Controversy in results could be explained on account of differences between animal experiments *in vivo* and *in vitro*. Because PTS might depress the central sympathetic nervous system in rats, which is important for its antiarrhythmic effects[8]. Moreover, consistency of experimental results was disturbed by other factors, such as different doses of drug administrated, different species of animals, and others.

Some investigations suggested that cardiac effects of PTS were similar to those of amiodarone[3,4]. In this study, the results showed that Rg_1 obviously lengthened ventricular MAPD in dogs. Furthermore, $MAPD_{30}$ and $MAPD_{50}$ were more prolonged than $MAPD_{90}$. It suggested that Rg_1 mainly lengthened earlier phase of ventricular repolarization facilitating the prolongation of voltage-dependent ERP, by which antiarrhythmic effects were exerted. It has been considered that difference between the actions of intravenous and oral amiodarone on cardiac effects were observed in previous study[12]. Oral amiodarone resulted in a marked prolongation in VERP and MAPD, but introvenous amiodarone did not. As a result, our animal data indicated that cardiac electrophysiological effects of Rg_1 were more similar to those of oral amiodarone.

The results of pharmacokinetic study of Rg_1 in animals lacked consistency[13-15]. So intravenous Rg_1 was repeatedly administrated before each step of experiment designed in this study. However, relationship between the effects and dosage of Rg_1 *in vivo* remained to be confirmed.

In conclusion, present study showed that Rg_1 prolonged ventricular refractoriness and repolarization, and increased VFT. It was suggested that cardiac electrophysiological effects of Rg_1 were similar to those of amiodarone.

REFERENCES

1 Liu S, Chen JX. Anti-arrhythmic effects of total saponins of *Panax notoginseng*.
Acta Pharmacol Sin 1984; **5**: 100-3.

2 Chen JQ, Zhang YG, Xiong C, Zhang SZ, Zeng Q, Rong MZ. Effects of *Panax notoginseng* saponins on monophasic action potentials of heart and automaticity and contractility of isolated atria.
Acta Pharmacol Sin 1992; **13**: 538-40.

3 Li XJ, Zhang BH. Studies on the antiarrhythmia effects of panaxatriol saponins (PTS) isolated from *Panax notoginseng*. Acta Pharm Sin 1988; **23**: 168-73.

4 Li XJ, Fan JS, Liu YW, Zhang BH. Effects of panaxatriol saponins (PTS) isolated from *Panax notoginseng* on the action potential and delayed rectifier current (Ix) in sheep cardiac Purkinje fibers.
Acta Pharm Sin 1993; **28**: 81-4.

5 Li XJ, Zhang BH. The sympathetic nervous mechanism of antiarrhythmic effects of panaxatriol saponins isolated from *Panax notoginseng*.
Chin J Pharmacol Toxicol 1990; **4**: 161-3.

6 Cao BY, Li XJ, Liu L, Zhang BH. Effect of panaxatriol saponins isolated from *Panax notoginseng* (PTS) on myocardial ischemic arrhythmia in mice and rats.
Acta Pharm Sin 1992; **27**: 641-4.

7 Xiong ZG, Sun JJ. Effects of *Panax notoginseng* saponin Rb_1 and Rg_1 on myocardial action potential and slow inward current.
Acta Pharmacol Sin 1989; **10**: 520-2.

8 Fisher JD. Role of electrophysiologic testing in the diag-

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nosis and treatment of patients with known and suspected bradycardias and tachycardias.
Prog Cardiovasc Dis 1981; **24**: 25—90.

9 Franz MR. Method and theory of monophasic action potential recording.
Prog Cardiovasc Dis 1991; **33**: 347—68.

10 Lu F, Zhang XM, Mei BY.
Effects of propafenone, quinidine, and their combination on ventricular fibrillation threshold in dogs.
Acta Pharmacol Sin 1992; **13**: 364—7.

11 Xiong ZG, Chen JX, Sun JJ. Effects of *Panax notoginseng* saponins on cardiac action potentials and slow inward current. Acta Pharmacol Sin 1989; **10**: 122—5.

12 Kadish A, Morady F. The use of intravenous amiodarone in the acute therapy of life-threatening tachyarrhythmias. Prog Cardiovasc Dis 1989; **31**: 281—94.

13 Huo YS, Zhang SC, Zhou D, Yao DL, You GY, Zhang HW, *et al*. Pharmacokinetics and tissue distribution of [^{3}H]ginsenoside Rg_1.
Acta Pharmacol Sin 1986; **7**: 519—21.

14 Odani T, Tanizawa H, Takino Y. Studies on the absorption, distribution, excretion and metabolism of ginseng saponins. II. The absorption, distribution and excretion of ginsenoside Rg_1 in the rat.
Chem Pharm Bull 1983; **31**: 292—8.

15 Ma YQ, Xiao JC, Li T, Shen BL, Huang YJ. Pharmacokinetics studies of ^{3}H-sanchi ginseng saponin-Rg_1 in rats. Chin Trad Herb Drugs 1987; **18**: 21—4.

三七皂甙 Rg_1对犬心电生理特性及心室纤颤阈值的影响

R965.2

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目的：研究三七皂甙 Rg_1对心肌电生理特性及室颤阈值（VFT）的影响. **方法**：17只正常犬被随机分为生理盐水对照组和 Rg_1组（20 mg kg^{-1}, iv）. 麻醉后沿正中开胸，暴露心脏. 应用心脏电刺激及单相动作电位（MAP）记录技术，测量心肌电生理参数及 VFT. **结果**：Rg_1延长窦房结恢复时间19.1 %；延长房室传导文氏阻滞周长 7.1 %；延长心室有效不应期 7.9 %；延长心室 MAP 时程（MAPD），其中 $MAPD_{30}$延长25.5 %，$MAPD_{50}$延长24.2 %，$MAPD_{90}$延长13.5 %；提高 VFT 19.2 %. **结论**：Rg_1延长心室不应性及复极化时程，提高 VFT，提示 Rg_1的作用与胺碘酮的效应类似.

关键词 三七；人参三醇甙；抗心律失常药；电生理学；动作电位；心室纤颤