Journal of Pharmacological Reports

Research Article Open Access

Observation Study of Antiarrhythmic Effect of "Fuyun", a Multiherb Prescription for Ventricular Arrhythmias, in Isolated Rat Hearts

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Abstract

Background: Premature ventricular contractions (PVCs) are common in both patients with known heart diseases and healthy populations, and PVCs may decrease the quality of life and even lead to heart failure. "FuYun" is a multiherb prescription for arrhythmia. The present study was designed to observe its effects on ouabain-induced ventricular arrhythmia in isolated rat hearts.

Method: Thirty-two SD rats (male, 250 to 350 g) were divided into 4 groups randomly. The hearts, after isolated briefly, were excised and perfused retrogradely in Langendorff equipment at 37℃ with Krebs solution containing ouabain and "FuYun" extract. The electrocardiogram and the left ventricular tension were recorded isometrically with transducers on a Biopac recorder.

Results: With pre-administration of the isolated hearts, "FuYun" increased the time required to produce ventricular arrhythmias by ouabain, and decreased the quantity of arrhythmic beating in a concentration-dependent manner.

Conclusion: The present work has demonstrated that "FuYun" exhibited potential antiarrhythmic effects in isolated rat hearts.

Keywords: FuYun; Ouabain; Arrhythmia; Isolated rat hearts

Introduction

Premature ventricular contractions, also namely premature ventricular complexes, are common in both patients with known heart diseases and healthy populations [1]. The major causes of PVCs contain triggered activity (TA), early after-depolarization (EAD) and delayed after depolarization (DAD). It has been identified that the increased Ca^{2+} inward flow or the reactivated $I_{Ca,L}$ result in after-depolarization, while the EADs and DADs could be suppressed by inhibiting $I_{Ca,L}$ [2].

Patients with PVCs present various manifestations ranging from being asymptomatic to experiencing palpitations to feeling weak [3]. PVCs characterized by large quantity, short coupling interval, and wide QRS waves are more likely to develop PVC-induced cardiomyopathy, ventricular tachycardia, and even heart failure, decreasing the quality of life [4-7].The administration of PVCs usually include antiarrhythmic medical treatment and catheter ablation therapy for patients who are failed to medical treatment [8]. The currently first-line antiarrhythmic drugs (AADs) for frequent PVCs are beta blockers, class I or III antiarrhythmic agents. However these western AADs are relatively limited to their low efficacy and previously pro-arrhythmic effects [9]. Traditional Chinese Medicines (TCMs), which has a long history of use in China for diseases involved to arrhythmia, have been exploited to treat arrhythmia, such as Wenxinkeli and Shensong Yangxin capsule [10,11]. Due to the safety, these TCMs have been playing an increasingly important role in treatment for PVCs patients, especially for those suffering from AAD-induced discomfort. Despite the superiority in safety, the current TCMs may not satisfy all the patients with various patterns of PVCs because of a similar low cure rate with western AADs [12]. Thus we need to exploit new drugs of more efficacy to suppress PVCs itself and related diseases.

"FuYun", composed of *Polygala tenuifolia* Willd (PT), *Radix ophiopogonis* (RO), *Fructus schisandrae* (FS) and *Fructus gardeniae* (FG), is an ancient multiherb medicine for heart palpitations, which are described as uncomfortable sense of irregular beats of the heart. Any type of tachyarrhythmias can give rise to palpitations, no matter whether there is an structural heart disease or not. "FuYun" has showed a powerful suppression on palpitations during the past decades, but whether it exhibits any antiarrhythmic effects is unknown. The goal of present study is to testify the antiarrhythmic effect of "FuYun" in ouabain-induced arrhythmia in isolated rat hearts and discuss the probable underlying mechanism.

Materials and Method

Extraction of "FuYun"

The extraction procedure of "FuYun" as follow [13]: The proprietary standard operating procedures for "FY", the extract of "FuYun", used hot water extraction (80°C). The hot water extract was then spray dried with insoluble dextran into a granulated powder, packaged and stored at 4°C. The dried "FY" powder was dissolved in 80°C water (100 mg: 1 mL). The mixture was centrifuged for 1 min, and then placed in water bath at 80°C for 30 min with 1 min centrifuging for every 10 min. The sample was then cooled in an ambient temperature water bath for 5 min, centrifuged for 10 min at 10000 rpm. The sediment was filtered out sterilizedly (0.2 μm), reserving the supernatant for animal experiments.

Groups and solutions

A total of 32 SD rats were randomly divided into four groups. Group 0, control group, hearts received no pre-administration with

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Received January 31, 2016; **Accepted** March 07, 2016; **Published** March 10, 2016

Citation: Liu Y, Hou Q, Yi J, Lin K, Wang X, et al. (2016) Observation Study of Antiarrhythmic Effect of "Fuyun", a Multiherb Prescription for Ventricular Arrhythmias, in Isolated Rat Hearts. J Pharma Reports 1: 113.

"FY" before perfusion with ouabain. The perfusion procedure was as follows, normal Krebs solution for 20 min, and then Krebs solution with ouabain (1 mM) for 30 min. Group 1, Low-"FY" group, hearts received pre-administration with "FY" of low concentration. The perfusion procedure was as follows, normal Krebs solution for 20 min, Krebs solution with "FY" of low concentration (20/9 mL extract in 1000 mL Krebs solution) for 30 min, and then Krebs solution with "FY" of low concentration and ouabain (1 mM) for 30 min. Group 2, Mid-"FY" group, hearts received pre-administration with "FY" of middle concentration. The perfusion procedure was as follows, normal Krebs solution for 20 min, Krebs solution with "FY" of middle concentration (20/3mL extract in 1000 mL Krebs solution) for 30 min, and then Krebs solution with "FY" of middle concentration and ouabain (1 mM) for 30 min. Group 3, High-"FY" group, hearts received pre-administration with "FY" of high concentration. The perfusion procedure was as follows, normal Krebs solution for 20 min, Krebs solution with "FY" of high concentration (20 mL extract in 1000 mL Krebs solution) for 30 min, and then Krebs solution with "FY" of high concentration and ouabain (1 mM) for 30 min. The composition of Krebs solution was as follows (mM): NaCl 118.0, KCl 3.5, KH_2PO_4 1.0, $NaHCO_3$ 25.0, glucose 11.1, EDTA 0.004, $MgCl_2$ 1.6, $CaCl_2$ 1.8. The Krebs solution was oxygenated modified before perfusion, and 36-37°C and pH 7.4.

Heart isolation and langendorff

Hearts were isolated from rats conforming to previous studies [14,15]. SD rats (male, 250-350 g) were anesthetized with intraperitioneal injection of sodium pentobarbital (0.01 ml/g, 1%) after heparin injection (3.0 mg/300 g). Briefly, the chest was opened, and the heart was excised and suspended on the pipe through ascending aorta, to receive retrograde perfusion in Langendorff equipment.

Statistical analysis

Data are expressed as mean ± S.D. Statistical differences are evaluated by analysis of variance using SPSS statistical software (version 17.0; SPSS Inc., Chicago, IL). $P<0.05$ is considered as statistical significance.

Results

Effect on the time of onset of arrhythmia

Ouabain alone (1 mM) in group 0, produced PVCs after 3.46 ± 1.31min and VTs after 5.00 ± 2.49 min in isolated rat hearts. Pre-administration with "FY" caused a significant prolongation in the meantime of onset of PVCs and VTs in a concentration-dependent manner ($P<0.05$, versus control group, Figure 1). Especially, the pre-administration with "FY" of high concentration helped prolong the time of onset of PVCs to 15.44 ± 10.44 min ($P=0.001$, versus group 0), and VTs occurred at 18.96 ± 10.49 min ($P=0.009$, versus group 0).

Effect on the quantity of arrhythmic beats

During 30 min retrograde perfusion with ouabain, the mean numbers of PVCs in "FY" groups were less than that in control group ($P<0.05$, versus control group, Figure 2). The number of PVCs was 2032 ± 1050 beats/30 min in control group, 955 ± 794 beats/30 min in Low-"FY" group, 166 ± 178 beats/30 min in Mid-"FY" group, and 25 ± 35 beats/30 min in High-"FY" group, respectively. In addition, this effect was concentration-dependent.

Discussion

"FuYun" is a multiherb formula for palpitations in China. And it has showed outstanding efficacy on palpitations during the past decades. It

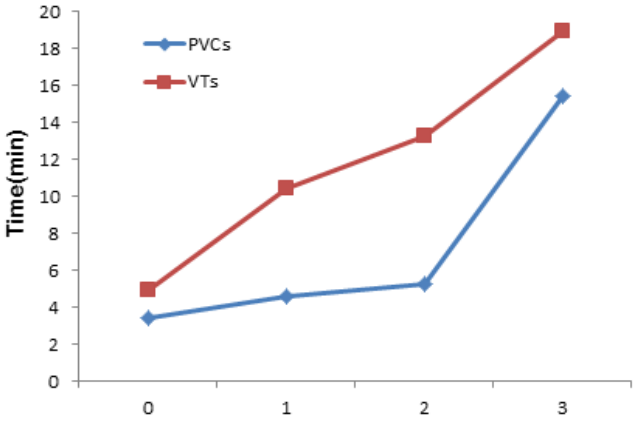

Figure 1: The time of onset ventricular arrhythmia, results are mean ± S.D.

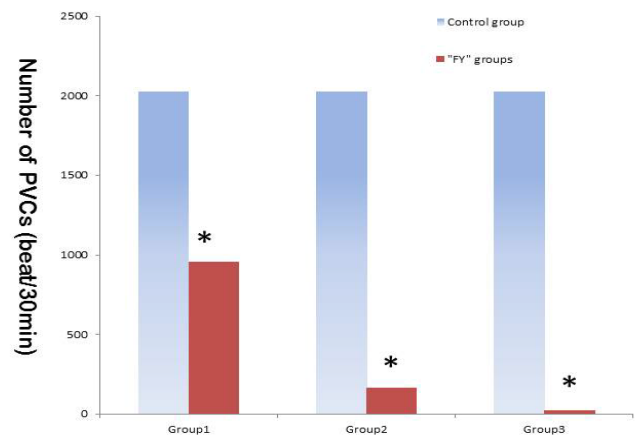

Figure 2: The total number of PVCs in every group. *$P<0.05$ *vs.* control group.

was observed in our study that "FuYun" not only significantly prolonged the time of onset of ouabain-induced ventricular arrhythmia, but also produced an unexpected decrease in the proportion of arrhythmic beats.

Ouabain is widely used to produce steady arrhythmic models for screening novel antiarrhythmic drugs. Toxic dosage ouabain inhibits Na^+/K^+-ATPase on the myocardial membrane, elevating intracellular Na^+ concentration. The excess intracellular Na^+ concentration disturbs the normal Na^+-Ca^{2+} exchange, causing intracellular Ca^{2+} overload, which leads to another Ca^{2+} overload in sarcoplasmic reticulum (SR). The SR-Ca^{2+} overload are linked to after-depolarization, which, if sufficiently strong, may approach threshold and produce spontaneous action potentials, leading ventricular arrhythmias [16-18].

The effect of "FuYun" on the suppression of ouabain-induced arrhythmia may lie in inhibiting certain ionic currents, like Ca^{2+} current, and then preventing the Ca^{2+} overload in both intracellular and SR. Moreover, it may perform some capacity to stabilize the action of myocardial membrane through underlying mechanisms.

It has been demonstrated that Methyl 3,4,5-trimethoxycinnamate (M-TMCA)-a bioactive extract from roots of PT, which is the major component of "FuYun"-showed some potential anti-arrhythmic effects. M-TMCA significantly attenuated action potential duration

(APD) of cardiomyocytes through inhibition of L-type calcium current ($I_{Ca,L}$) without affecting outward K^+ currents in a reversible and a dose-dependent manner. In addition, M-TMCA inhibits the intracellular Ca^{2+} transient induced by Isoprenaline and BayK8644, and thus may abolished the positive staircase effect of Ca^{2+} transient [19].

"FuYun" is a multiherb medicine and contains a multiple of components. It is a hard work to distinguish the exact antiarrhythmic components and the underlying antiarrhythmic mechanism, but it deserves further explorations because of its active antiarrhythmic effects.

Several limitations in the present study should be mentioned. Firstly, it failed to further exploration on a cellular and ionic level. The exact antiarrhythmic mechanism of "FuYun" has not been demonstrated. We just take SD rats as arrhythmic models; moreover, the number of samples was insufficient. We have designed another related study to explore the underlying antiarrhythmic mechanism of "FuYun".

Conclusion

The present work has indicated that "FuYun" performed some potential antiarrhythmic effects by prolonging the time of onset of arrhythmia and decreasing the arrhythmic beating times induced by ouabain.

Competing Interests

There are no potential conflicts of interest to declare.

Acknowledgement

This work was supported by grants from the Clinical Research Supportive Fund General Hospital of Chinese People's Liberation Army (No. 2013FC-CXYY-300).

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