

Protective effects of Ping-Lv-Mixture (PLM), a medicinal formula on arrhythmias induced by myocardial ischemia-reperfusion

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Abstract

Ping-Lv-Mixture (PLM) is a Chinese medicinal formula. The present study aimed to determine the effects of PLM on myocardial ischemia-reperfusion (MI/R) induced arrhythmias in rats. Arrhythmia model was established by occlusion of the left arterial descending coronary artery and thereafter reperfusion. A lead II electrocardiogram was monitored throughout the experiment. The results showed that pretreatment of PLM to MI/R rats significantly reduced the incidence and duration of ventricular tachycardia and ventricular fibrillation. On induction of MI/R, the activities of creatine kinase and lactate dehydrogenase were increased in vehicle group. PLM (0.04–1.00 g/kg) administration prevented the increase of these enzymes. Moreover, a significant increase of myocardium superoxide dismutase and decrease of malondialdehyde contents were observed in rats of PLM groups. On the other hand, the expressions of platelet activating factor (PAF) receptor mRNA was down-regulated in a dose-dependent manner in the PLM-treated groups by RT-PCR. Thus, it can be concluded that pretreatment with PLM inhibited lipid peroxidation in rats through suppressing the expression of PAF receptor, which may contribute to its preventive effect on myocardial ischemia-reperfusion induced arrhythmias. © 2006 Elsevier Ireland Ltd. All rights reserved.

Keywords: Herbal formula; Myocardial ischemia-reperfusion; Platelet activating factor receptor; Lipid peroxidation

1. Introduction

Myocardial ischemia is one of the major causes of death in nowadays cardiac diseases. Reperfusion although is the only way to restore blood flow of coronary arteries and prevent the myocardium suffering from necrosis, it will lead to the occurrence of life-threatening arrhythmias which containing premature ventricular beats (PVB), ventricular tachycardia (VT) and ventricular fibrillation (VF) (Margit et al., 1996). Numerous mechanisms for the increase in tissue injury after reperfusion have been identified including the generation of oxygen-derived free radicals, calcium overload and dysfunction of myocardial energy metabolism (Pragada et al., 2004). Extensive studies show that platelet activating factor (PAF) is an important mediator of the inflammatory responses; it plays a main role in tissue injuries induced by myocardial ischemia-reperfusion (Katsuya et al., 2004). In recent years, many experimental studies have established the therapeutic benefits of PAF receptor inhibitor,

not only in limiting infarct size but also in reducing reperfusion arrhythmias. For example, it has been reported that RP59227, a kind of PAF receptor inhibitor, reduced infarct size (Serebruany et al., 1998) and the incidence of arrhythmias in dogs in vivo (Loucks et al., 2000). These effects of PAF receptor inhibitor have been attributed mainly to decrease oxygen free radical (Hu et al., 2002).

Ping-Lv-Mixture (PLM) is a medicinal formula containing *Glycyrrhiza inflata* Bat., *Sophora flavescens* Ait., *Belamcanda chinensis* (L.) DC., *Sophora tonkinensis* Gapnep. and *Schisandra chinensis* (Turcz.) Baill. There are evidences concerning the antiarrhythmic effects of some compositions of this formula such as *Sophora flavescens* Ait. and *Glycyrrhiza inflata* Bat. which were widely used in Chinese medicine (Jorg and Hermann, 1997). Besides these, *Belamcanda chinensis* (L.) DC. has been found to possess free radical scavenging properties. PLM is an antiarrhythmic drug under investigation with the clinical utilization for many years. Its ability to decrease mortality rate and frequency of serious arrhythmias has been demonstrated among other animal models induced by chloroform and CaCl₂. The aim of this study was to determine whether PLM influenced the reperfusion induced arrhythmias using the experimental coronary

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occlusion-reperfusion model in rats. Its possible mechanism was studied by assaying the expression of myocardial PAF receptor, the contents of malondialdehyde (MDA) and antioxidant enzymes activities.

2. Materials and methods

2.1. Preparation of PLM

PLM consists of five medicinal plants as shown in Table 1. Five herbal materials used in this work were purchased from Wuhan Herbal Materials Company, Hubei Province, China, and identified by Dr. Mingxi Jiang, Wuhan Botanical graduate institute, The Chinese Academy of Sciences. The five voucher specimens of the herbs, 04-06-21, 04-06-22, 04-06-23, 04-06-24, and 04-06-25 were conserved at the herbal herbarium of Department of pharmacology, Medical collage, Wuhan University. Aqueous extract of PLM was prepared as following procedure: the roots of *Glycyrrhiza inflata* Bat., *Sophora flavescens* Ait., *Belamcanda chinensis* (L.) DC., *Sophora tonkinensis* Gapnep. and *Schisandra chinensis* (Turcz.) Baill. were mixed in proportion and were extracted at 80 °C under stirring for 1 h with 10 times (v/m) distilled water. The resultant extract was then centrifuged at 1500 × g to at room temperature to obtain the supernatant and concentrated under reduced pressure at 70 °C to obtain the semisolid form of PLM solution. The percentage yield was 18.75%. PLM was suspended in 0.9% saline to obtain three groups of different dose. The aqueous extract was further diluted with five parts distilled water and was filtrated to obtain the working solution for high-performance liquid chromatography (HPLC). The working conditions used for the HPLC analysis were as follows: column: Cromasil C18 (5 μm, 250 × 4.6 mm); mobile phase: methanol (A), phosphate buffer saline (B), a linear gradient of 20% A and 80% B changing over 40 min to 100% A and 0% B was used; detection: UV, 200–400 nm; flow rate: 1.0 ml/min. The reference compounds mainly including oxymatrine, matrine, schisandrin, deoxyschisandrin, glycyrrhizin, liquiritigenin, isoliquiritigenin were purchased from Sigma Chemical Co. The HPLC trace of PLM is shown in Fig. 1.

2.2. Animals and treatments

Laboratory bred Sprague–Dawley rats of either sex weighing 200–300 g were purchased from the Experimental Animal Center of Wuhan University. The rats were maintained under standard laboratory condition at 25 ± 2 °C, relative humidity 50 ± 15% and normal photo period (12-h dark/12-h light) were

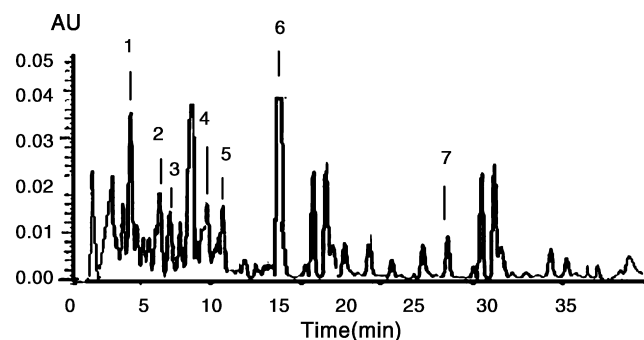


Fig. 1. HPLC chromatogram of PLM. 1: oxymatrine; 2: matrine; 3: schisandrin; 4: glycyrrhizin; 5: liquiritigenin; 6: deoxyschisandrin; 7: isoliquiritigenin.

used for the experiment. The animals were fed normal diet and water ad libitum. All study protocols were approved by internationally accepted principles and the Guidelines for the Care and Use of Wuhan University, Wuhan, China. Rats were randomly divided into four groups, each consisting of 10 animals. Group-I was the sham group; Group-II were treated with 0.9% normal saline orally and served as a vehicle control. Group-III, -IV and -V were treated with PLM at doses 0.04, 0.20 and 1.00 g/kg by oral gavages every day for 7 days. On the seventh day, 1 h after the above treatments, the rats were subjected to the following evaluation tests.

2.3. In vivo studies of myocardial ischemia-reperfusion surgical preparation

Rats of all experimental groups were anaesthetized intraperitoneally with pentobarbitone sodium (60 mg/kg). The neck was opened with a ventral midline incision, and a tracheotomy was performed, the rats were ventilated with room air from a positive pressure ventilator (Crompton Parkinson Ltd., England) using compressed air at a rate of 50 strokes/min and a tidal volume of 15 ml/kg. A left thoracotomy was performed and the pericardium was opened to expose the heart. The left arterial descending coronary artery (LAD) was ligated 2 mm from its origin by a 5-0 silk suture with a traumatic needle and ends of this ligature were passed through a small vinyl tube to form a snare. Myocardial ischemia was induced by one stage occlusion of the LAD. Electrocardiographic leads were attached subcutaneous electrodes to monitor limb lead II. The animals then underwent 15 min of ischemia. Then the myocardium was reperfusion by releasing the snare gently for a period of 2 h.

2.4. Evaluation of arrhythmias

Before and during ischemia and reperfusion period, ECG changes were recorded. Number of PVB and the incidence and duration of ventricular tachyarrhythmia, including VT and ventricular fibrillation VF, in surviving animals were determined.

2.5. Measurements of plasma LDH and CK

The enzyme activity lactate dehydrogenase (LDH) of was measured by the method of Werthamer et al. (1973). Plasma

Table 1
Recipe of Ping-Lv-Mixture (PLM)

Components	Ratio
1. Gan Cao (<i>Glycyrrhiza inflata</i> Bat., root)	2
2. Ku Shen (<i>Sophora flavescens</i> Ait., root)	2
3. She Gan (<i>Belamcanda chinensis</i> (L.) DC., root)	2
4. Dou Gen (<i>Sophora tonkinensis</i> Gapnep., root)	1
5. Wu Wei Zi (<i>Schisandra chinensis</i> (Turcz.) Baill., fruit)	1

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