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Xiangbo Gou
1. Tianjin Key Labortory of Drug Targeting and Bioimaging, Tianjin University of Technology, Tianjin, China
2. School of Chemistry and Chemical Engineering, Tianjin UniveKrsity of Technology, Tianjin, China

Haodong Zhao
1. Tianjin Tasly Pride Pharmaceutical Co., Ltd., Tianjin, China
2. Tianjin Key Laboratory of Safety Evaluation Enterprise of Traditional Chinese Medicine Injections, Tianjin, China

Meixu Wan
1. Tianjin Tasly Pride Pharmaceutical Co., Ltd., Tianjin, China
2. Tianjin Key Laboratory of Safety Evaluation Enterprise of Traditional Chinese Medicine Injections, Tianjin, China

Zhi Li
1. Tianjin Tasly Pride Pharmaceutical Co., Ltd., Tianjin, China
2. Tianjin Key Laboratory of Safety Evaluation Enterprise of Traditional Chinese Medicine Injections, Tianjin, China

Dekun Li
1. Tianjin Tasly Pride Pharmaceutical Co., Ltd., Tianjin, China
2. Tianjin Key Laboratory of Safety Evaluation Enterprise of Traditional Chinese Medicine Injections, Tianjin, China

Corresponding Author:
Xiangbo Gou
1. Tianjin Key Labortory of Drug Targeting and Bioimaging, Tianjin University of Technology, Tianjin, China
2. School of Chemistry and Chemical Engineering, Tianjin UniveKrsity of Technology, Tianjin, China

Yiqi Fumai Lyophilized Injection Ameliorates the Vasopressin-Induced Angina Pectoris Associated with the NF-κB Pathway

Xiangbo Gou, Haodong Zhao, Meixu Wan, Zhi Li and Dekun Li

Abstract
The aim of our study was to research the protective effect of YQFM on the vasopressin-induced rat anginal model and to explore the underlying pathway. The rat anginal model was established successfully by vasopressin injection. The cardiac function, tissue morphology and myocardial enzymes in the serum were detected to evaluate the cardiac injury. The pro-inflammatory factor such as TNF-α and IL-6, as well as the involved NF-κB pathway were detected through western blot. The anginal rats presented a depressed ST-segment in ECG accompanied with disordered cardiac function, tissue morphology and myocardial enzyme levels in the serum, which were all attenuated by the YQFM treatment. Moreover, YQFM can also inhibit the TNF-a and IL-6 protein levels, further down regulate the NF-κB signaling pathway in the anginal rats. These findings suggest that YQFM ameliorates the cardiac injury in the rat anginal model associated with the NF-κB signaling pathway.

Keywords: Angina pectoris, ST-segment depression, Yiqi Fumai Lyophilized Injection, Cardioprotection, NF-κB signaling

1. Introduction
Angina pectoris is a common cardiovascular disease at present, which is caused by an imbalance between the supply and demand of oxygen. During the development of angina pectoris, coronary artery vasospasm plays an important role in the pathophysiology of myocardial ischemic syndrome. In the clinical, angina pectoris is divided into angina of effort and stable angina according to the pathogenesis. Importantly, angina pectoris is frequently occured at daybreak or in the early morning, with an elevation or depression in the ST-segment on the electrocardiography (ECG) used as a hallmark to estimate the severity of the subendocardial artery ischemia [1]. As regards the drugs used for the treatment of angina pectoris, nitrates, β-adrenoceptor antagonists and calcium antagonists are commonly used in the clinical, because of their effect on the depression of oxygen consumption or the elevation of oxygen supply [2]. Although these drugs have a good effect on the angina pectoris treatment, they also have many adverse reactions. For instance, nitroglycerin may cause sinus tachycardia and acute myocardial infarction. Therefore, due to the reliable curative efficacy and long history of clinical trials, traditional Chinese medicines (TCMs) has been used in the prevention and treatment of angina pectoris, however, their potential molecular mechanisms remains unclear.

In the present study, the antianginal effects of Yiqi Fumai Lyophilized Injection (YQFM) were examined using an vasopressin-induced rat anginal model. Vasopressin is an antidiuretic hormone and a vasoconstrictor, which can produce vasoconstriction of small coronary arteries and increase total coronary resistance. The vasopressin-induced angina model is considered useful in evaluating antianginal effects of drugs *in vivo* [3]. After the vasopressin injection, a depression of the S-wave in the ECG was appeared, suggesting subendocardial artery ischemia [4]. The declining of the S-wave after the vasopressin injection was regarded as the depression of ST-segment in rats [5, 6]. The ST-segment changes were used as an index of ischemic severity. In this research, we use the vasopressin-induced rat anginal model to evaluate the YQFM effect on the treatment of angina pectoris.

YQFM provided by Tasly pride pharmaceutical Co., Ltd is prepared from a basic formula of three Chinese herbs, including red ginseng, radix ophiopogonis and schisandra chinensis. It is derived from Sheng-mai San (SMS), a well-known TCM formula, which is widely used for the treatment of cardiovascular and cerebrovascular diseases, while YQFM is freeze-dried powder

prepared by modern technology. It is possible because of the each different preparation process, there were previous study reported that the chemical compositions of YQFM are partly different from SMS [7]. It was reported that YQFM had beneficial effects on the treatment of myocardial ischemia/reperfusion [8], myocardial remodeling and heart failure [9], cerebral ischemia [10] and acute lung injury [11], because of its regulation on blood vessel function, immunity modulation and anti-lipid peroxidation. Both clinical and experimental studies demonstrated the prevention and treatment of YQFM on the cardioprotective diseases, including ischemia/reperfusion-induced myocardial apoptosis [8], chronic heart failure [12], myocardial remodeling and heart failure [9] as well as ischemic stroke [13]. Previous experiments have reported that YQFM exterted ameliorative effects on the rats with chronic heart failure through NF-κB inactivation and the suppression of pro-inflammatory factor, such as tumor necrosis factor-α (TNF-α), interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) [14]. Wang *et al.* [15] previously showed that the nuclear transcription factor-κB (NF-κB) pathway is closely associated with the effects of YQFM against cardio-cerebral ischemia diseases. In the clinical, YQFM are widely used in the treatment of angina pectoris. Nevertheless, the potential molecular mechanisms of YQFM against angina pectoris remain to be elucidated. Therefore, in this present study, we investigated the effects of YQFM on vasopressin-induced rat anginal model and explored the underlying pathways.

2. Materials and Methods

2.1 Animals and drugs

The male Sprague-Dawley (SD) rats weight about 180-200 g were bought from Beijing Vital River Laboratory Animal Technology Co., Ltd. (SCXK (Jing) 2016-006), which were housed in the animal house of Tasly pride pharmaceutical Co.,Ltd at a controlled temperature of 23-26℃ under a 12 h light-dark cycle with free access to food and water. All animals were received humane care in compliance with the ethical standards. All animal experiments are approved by The Tasly Animal Ethics Committee. The experimental procedures were compled with the the Principles of Laboratory Animal Care (NIH publication #85−23, revised in 1985). YQFM (Yiqi Fumai Lyophilized Injection, Tasly pride pharmaceutical Co., Ltd, TianJin, China) is consists of red ginseng, radix ophiopogonis and schisandra chinensis mainly. The drug powder dissolved with sterile water at the concentration of 0.2167 g·ml^{-1} was prepared for the study. Verapamil (43180301, Shanghai harvest pharmaceutical Co.,Ltd) was dissolved with sterile water at the concentration of 2.5 mg·ml^{-1} for ues. Vasopressin (HY-P0049, MedChemExpress) were prepared as a 1 mg·ml^{-1} stock solution in sterile water.

2.2 Establishment of angina model

After the SD rats were anesthetized with isoflurane, the polyethylene catheter filled with saline was inserted in the right lateral vein of the tail of rat. The ECG was recorded with a bioelectrical amplifier (Nanjing MedEase Science and Technology Co.,Ltd) and ECG processor (Nanjing MedEase Science and Technology Co., Ltd). After the ECG of rats was stabilized about 10 min, vasopressin was intravenously injected at a dosage of 0.05 mg·kg^{-1} through the catheter. The ECG was measured 10 min after the vasopressin administration. The amplitude of the ST-segment was measured 5 min after the vasopressin administration. The difference of the ST-segment amplitude before and after vasopressin administration was presented as the ST-segment depression.

2.3 Subgroup and administration

The rats were divided into high dose treatment group (H-YQFM, 1100 mg·kg^{-1}·d^{-1}), middle dose treatment group (M-YQFM, 550 mg·kg^{-1}·d^{-1}), low dose treatment group (L-YQFM, 275 mg·kg^{-1}·d^{-1}), verapamil treatment group (Verapamil, 2 mg·kg^{-1}·d^{-1}), angina group (Model) and control group (Control). The rats were administered intravenously with YQFM or verapamil once a day for 2 weeks before the rat anginal model establishment. Meanwhile, the angina group and control group rats was administered with water 10 ml·kg^{-1}·d^{-1}.

2.4 Measurement of the vasopressin-induced ST depression

After anesthetized with isoflurane, the ECG of rats were monitored. The rats were intravenously injected with vasopressin 0.05 mg·kg^{-1} to induce the angina pectoris model after the baseline of ECG was stabilized. The depression of the ST-segment in the ECG was recorded 5 minutes after the vasopressin injection in all the group rats.

2.5 Measurement of cardiac function

The cardiac function of all the group rats were measured using echocardiographic system (GE logiq5 pro) after the vasopressin injection. The cardiac function parameters such as heart rate (HR), left ventricular end-systolic diameter (LVDs) and left ventricular end-diastolic diameter (LVDd) were all measured. The fractional shortening (FS) and ejection fraction (EF) were also calculated to evaluate the left ventricular systolic function.

2.6 Measurement of myocardial enzymes

After the measurements of cardiac function, the blood samples of all the rats were collected. Myocardial enzymes such as creatine kinase (CK), creatine kinase-MB (CK-MB), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in serum were estimated by automatic biochemical analyzer (Hitachi 7150, Japan).

2.7 Morphology observation

Then the cardiac was performed for morphology observation. Firstly, some of the hearts were taken for TTC staining, and then some of the hearts were fixed with 10% formaldehyde and stained with hematoxylin-eosin (HE). At last, the remaining left ventricular of rats were also fixed with 2.5% glutaral and 1% osmic acid for electron microscopy examination

2.8 Western Blot

The protein levels of TNFa, IL-6 and NF-κB of the left ventricular was evaluated by western blot analysis. The tissue was homogenized in ice-cold lysis buffer (RIPA and PMSF, 100:1) and then centrifuged at 12000 rpm for 30 min at 4℃. The protein concentration was measured by Bicinchoninic Acid (BCA) (Beyotime, China). Membranes were probed with the first antibody overnight at 4 ℃, then incubated by the secondary antibodies (Beyotime, 1:1000). Quantification of the signals was performed by Odyssey Infared Imaging System (Bio-Rad, USA). The first antibodies were used as

follows: anti-TNFa (Abcam, 1:1000), anti-NF-κB (BOATER, 1:500), anti-IL-6 (Abcam, 1:1000) and anti-GAPDH (Beyotime, 1:4000).

2.9 Statistical analysis
Data are expressed as means±SEM. The significance of differences between the groups was analyzed using unpaired Student's t tests and ANOVA with Dunnett's post hoc tests.

3. Results
3.1 The establishment of angina model
After anesthetized with isoflurane, the ECG of the rats before and after vasopressin injection was recorded. The rats were injected with 0.05mg·kg^{-1} vasopressin to make the rats angina model. After the vasopressin injection, the ECG of rats was continuously observed for at least 10min, then a depression of the S-wave in the lead ECG appeared (Fig.1), suggesting the subendocardiac ischemia. Changes in the ST-segment as an index of ischemic severity was recorded to evaluate the model. The results showed that the ST-segment decreased about 0.11mv after the vasopressin injection (P<0.01, Fig.1), which releaved that the myocardial angina model established successfully.

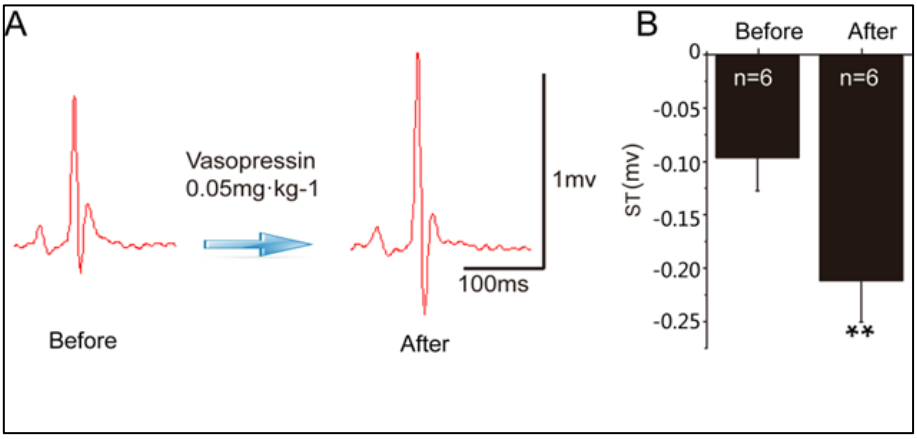

Fig 1: The establishment of the rats angina model. (A) A typical scheme of ECG changes in rats before and after vasopressin injection. (B) A summary of ST-segment of ECG in rats before and after vasopressin injection. **P<0.01 *vs*. Before value.

3.2 The effects of YQMF on the vasopressin-induced ST-segment depression in angina pectoris rats
As Fig.2 shown, the ST-segment of the ECG reduced about 0.11 mv after the injection of vasopressin in the model group, which was significantly alleviated by the treatment of YQFM and verapamil (P<0.05 or P<0.01), indicating that YQFM had a significant therapeutic effect on angina pectoris with a dose-dependent. The results releaved that YQFM had a protective effect on the ST-segment depression induced by vasopressin, which may be the reason for the treatment of YQFM on angina pectoris rats. What is more, the rats in the model group showed a slower HR than the control group (P<0.01), but after the YQFM treatment, the rats exhibited a increased HR level in all the treatment groups (P<0.05 or P<0.01).

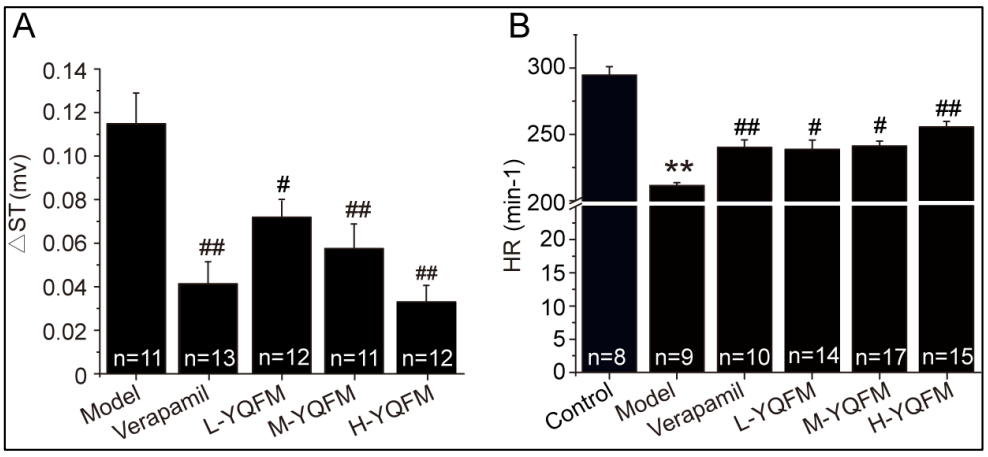

Fig 2: YQMF alleviated the vasopressin-induced ST-segment depression in angina pectoris rats. (A) A summary of vasopressin-induced ST-segment depression of ECG in all the group rats. (B) A summary of HR in all the group rats. **P<0.01 *vs.* Control value, $^{\#\#}P$<0.01 *vs.* Model value, $^{\#}P$<0.05 *vs.* Model value.

3.3 The effect of YQFM on cardiac function in angina pectoris rats
The cardiac function parameters of rats in all the groups were shown in Fig.3. The rats in model group showed the higher levels of LVDs and LVDd (P＜0.01), which were significantly attenuated by the YQFM treatment (P＜0.01 or P＜0.05). What is more, the EF and FE levels of the model rats decreased significantly (P＜0.01), while which were all alleviated by the YQFM treatment (P＜0.01 or P＜0.05). However, the low dose of YQFM had no effect on the protection of cardiac function (P>0.05). Our results revealed that YQFM could protect the angina pectoris by reducing the LVDs and LVDd levels and increasing the EF and FE levels.

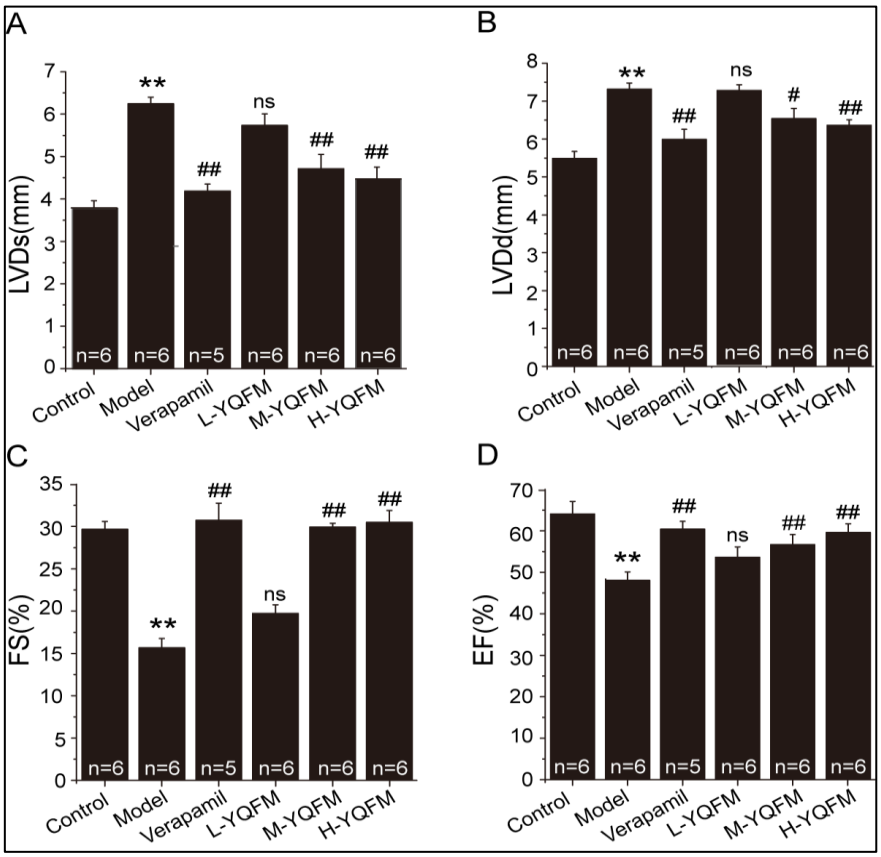

Fig 3: YQFM improved the cardiac function in the angina pectoris rats. (A-D) A summary data of cardiac function parameters in all the group rats, including LVDs, LVDd, FS and EF. ***P*<0.01 *vs* Control value, $^{\#\#}$*P*<0.01 *vs* Model value, $^{\#}$*P*<0.05 *vs* Model value, ns *vs* Model value.

3.4 The effect of YQFM on myocardial enzyme levels in angina pectoris rats

As shown in Fig.4, the AST, ALT, CK-MB, and CK levels in the model group rats were all increased compared with the control group rats (*P*<0.01 or *P*<0.05), which were all attenuated by the YQFM treatment (*P*＜0.01 or *P*＜0.05). Our results revealed that YQFM could protect the angina pectoris by reducing the AST, ALT, CK-MBmand CK levels.

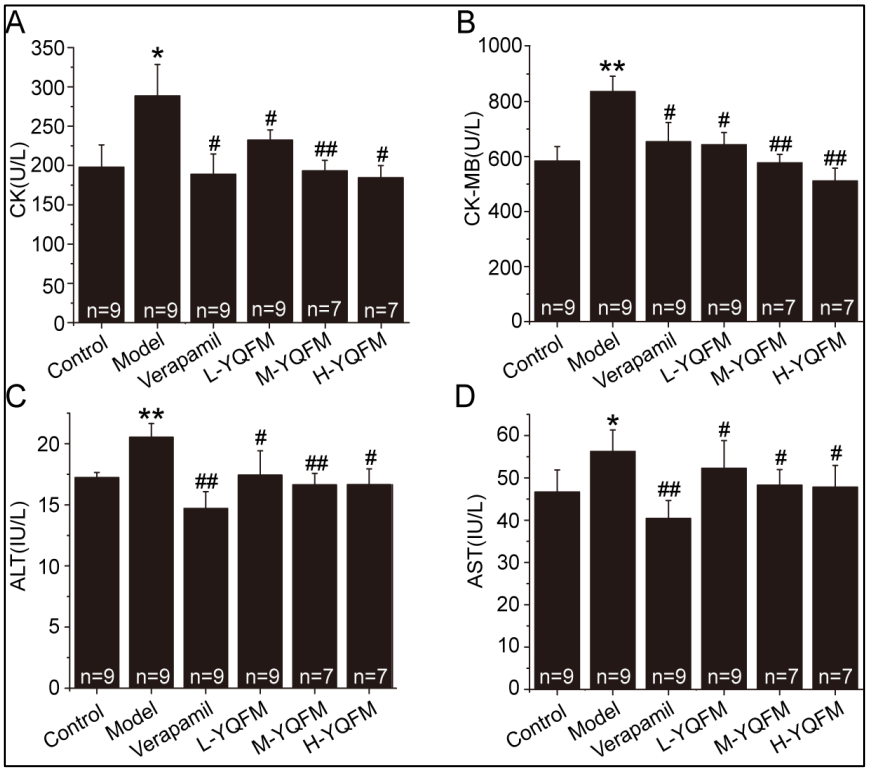

Fig 4: YQFM inhibited the myocardial enzyme levels in the angina pectoris rats. (A-D) A summary data of myocardial enzyme levels in all the group rats, including CK, CK-MB, ALT and AST. ***P*<0.01 *vs* Control value, **P*<0.05 *vs* Control value, $^{\#}$*P*<0.05 *vs* Model value, $^{\#\#}$*P*<0.01 *vs* Model value.

3.5 The effect of YQFM on cardiac morphology in angina pectoris rats

The cardiac structural was detected by TTC staining, HE staining and transmission electron microscope. As shown in Fig. 5A, the TTC staining showed that the infarct size was larger in the model group, and no myocardial infarction was observed in the H-YQFM group and the verapamil group. In Fig. 5B, cardiac muscle fibers of the control group rats arranged neatly and the morphological characteristics of myocardial cells were normal. But in the model group rats, the cardiac muscle fibers arranged in disorder, at the same time the myocardial was swelling and the fibroblasts was hyperplastic. Meanwhile, there were also inflammatory cell aggregation in the model group rats. All the symptoms in the model group rats can be alleviated by the YQFM treatment. In Fig. 6C, it could be seen that the constitution of the cardiac muscle fibril was very clear and the myofilament was well-arranged in the control group rats. The sarcomere Z-line was obvious and the mitochondrion constitution was integrated. But in the model group rats, there were lots of collagen fiber and the cardiac muscle cell was arranged confused. At the same time, the myofilament was disrupted and the mitochondrion was swelling. After the YQFM treatment, all the myocardium pathological changes were alleviated. The results above illustrated that the YQFM can improve the pathological damage in the vasopressin-induced angina pectoris rats.

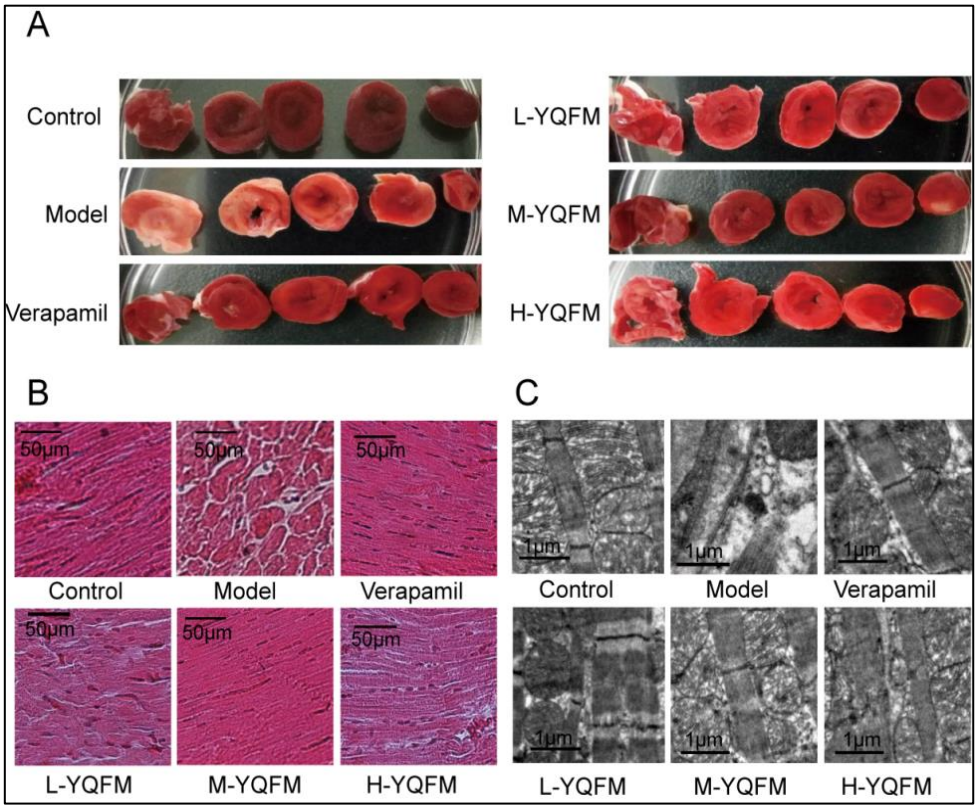

Fig 5: YQFM attenuated the pathological change of cardiac in the angina pectoris rats. (A) Representative pictures of myocardial tissue stained with TTC. (B) Representative pictures of myocardial tissue stained with HE (×400). (C) Representative transmission electron micrographs of left ventricular specimens.

3.6 The effect of YQFM on the inflammatory factor expression in angina pectoris rats

As shown in Fig.6, compared with the control group, the expression of inflammatory factor (IL-6 and TNF-α) levels in the myocardial tissue of the model group rats were all significantly increased (P<0.05). After the YQFM treatment, all the inflammatory factor levels in the angina pectoris rats were decreased (P<0.01 or P<0.05). We next detected the NF-κB2 protein expression, which was elevated in the model group rats, but was decreased after the YQFM treatent. The results releaved that YQFM can inhibit the inflammatory factor expression elevation after the vasopressin injection, which maybe the target of YQFM preventing angina.

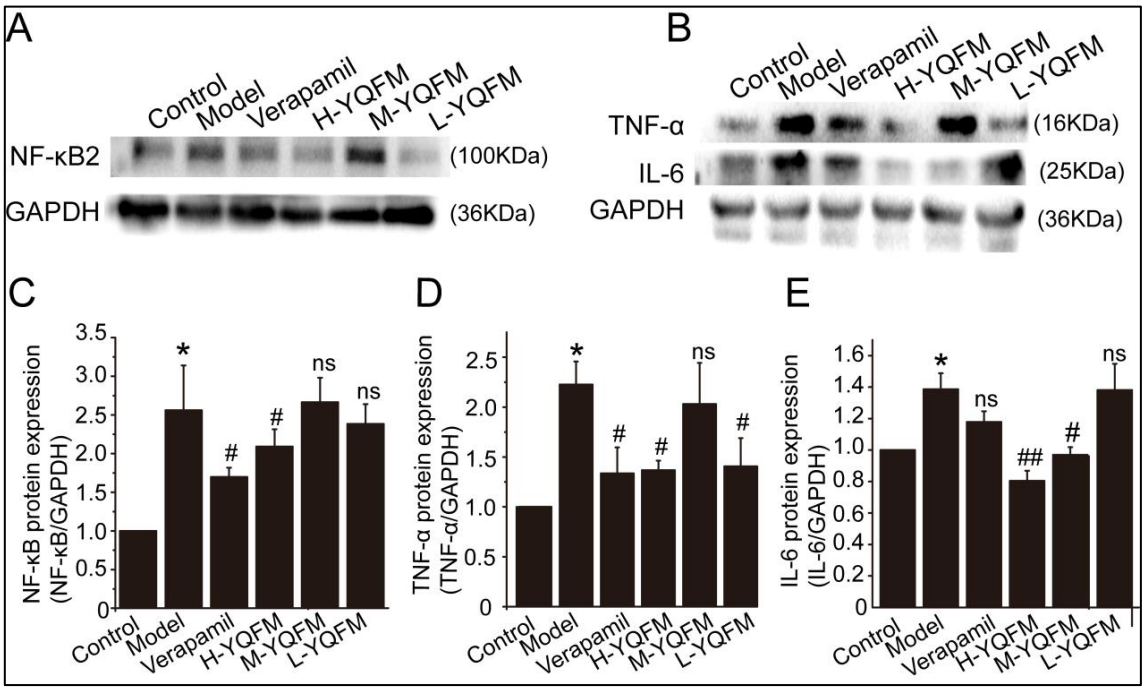

Fig 6: YQFM inhibited the TNF-α, IL-6 and NF-κB2 expression in the angina pectoris rats. (A.B) Representative western blot of TNF-α, IL-6 and NF-κB2 in the cardiac of all the group rats, GAPDH as a standard control. (C-E) The quantitive analysis of the TNF-α, IL-6 and NF-κB2 by western blot, **P*<0.05 *vs* Control value, #*P*<0.05 *vs* Model value, ##*P*<0.01 vs Model value, ns: *P*>0.05 vs Model value.

4. Discussion

In the present study, we compared the anti-anginal effect of YQFM *in vivo* by using a well-established vasospastic angina model of rats [16], which was achieved by constricting small coronary arteries and causing subendocardial ischemia through administration of vasopressin [17]. We used verapamil as the positive control since it was the most frequently used anti-angina agent in clinical as a calcium channel blocker. The vasopressin-induced ST-depression model is caused by the imbalance between the oxygen supply and demand due to the coronary constriction or systemic vascular constriction by the vasopressin injection. In our experiment, the intravenous injection of vasopressin induced a transient ST-segment depression in rats and the degree of maximal ST-segment depression observed was similar to previous reports [2, 3]. As a result of the intravenous administration of YQFM, the angina rats exhibited dose-dependent suppressive effects on the ST-segment depression, where these effects occurred parallel to the suppressive effect on the HR level (Fig. 2).

Echocardiography is clinically applied to detect cardiac structure and function.The EF and FS levels were used to evaluate cardiac contractile capabilities both in basic and clinical researches [18]. It was reported that vasopressin has been reported to increase the left ventricular end-diastolic pressure in a dose-dependent in the pentobarbital sodium-anesthetized dogs [19]. The elevation of the preload can increase the ventricular wall stress, which can result in the aggravation of subendocardial ischemia, the effect of a drug on the preload to the left ventricle may have some potential to affect its anti-anginal effects. It has been shown that YQFM could significantly decrease the left ventricular end-diastolic pressure in coronary artery ligation (CAL)-induced HF rats [12]. Thus, the pretreatment of YQFM might have ameliorated the vasopressin-induced increase of the left ventricular end-diastolic pressure, which could also contribute to the anti-anginal effect. In our research, the ECG results revealed that YQFM could protect the cardian funtion through decreasing the LVDs and LVDd levels, and increasing the FS and EF levels of the angina rats (Fig. 3).

For the angina patients, a large number of studies have highlighted on the risk of ECG variation caused by subendocardial ischemia, in contrast very few of researches focusing on the relationship involving myocardial enzyme in the serum. CK-MB is found mainly in myocardium, but serum CK-MB content increase following myocardial injury [20]. Further, an increase of serum AST and ALT reflect myocardial damage and infarcted myofilaments. In the angina rats, the CK, CK-MB, ALT and AST levels were all ellivated, which were all attenuated by the YQFM treatment, proving the cardiac protection of YQFM on the angina rats (Fig. 4). The histopathological study confirmed that YQFM can decrease the infarct size of the cardiac in the angina rats and ameliorated heart damages (Fig. 5). All these results of echocardiography and the cardiac injury biomarkers all illuminated the beneficial effects of YQFM on vasopressin-induced angina rats.

YQFM, a Traditional Chinese Medicine prescription, has been used in the treatment of angina and heart failure in clinical practice [9]. YQFM are extracted from three traditional medicinal herbs: panax ginseng, schisandra chinensis and ophiopogonjaponicas. It has been used for patients with cardiovascular disease and hepatopathy. In this study, we demonstrated that YQFM could inhibit the ST-segment depression and improve the cardiac funtion in angina pectoris rats induced by vasopressin. YQFM significantly inhibited the vasopressin-induced subendocardial ischemia, which was not observed by the vehicle, indicating that YQFM may possess an anti-ischemic effect. It was reported that intraperitoneal administration of YQFM could ameliorate cerebral ischemia by inhibiting endoplasmic reticulum stress-mediated neuronal apoptosis in the permanent middle cerebral artery occlusion-injured mice [10]. Previous studies have also suggested that the NF-κB pathway is associated with the YQFM treatment of ischemic cardio-cerebral ischemic diseases [21], attenuating NF-κB phosphorylation can inhibit inflammatory response after tissue ischemia [22]. Interleukin-6 (IL-6) and tumor

necrosis factor-α (TNF-α), the two leading mediators of inflammatory response, are synthesized under the influence of pathogenic stimuli due to the increase of NF-kB level [23]. The possible mechanism that YQFM used is to reduce the expression of the pro-inflammatory cytokines TNF-α and IL-6 to block the inflammation progress associated with the NF-κB/p65 signaling pathways. Our research was consistent with previous reports that YQFM suppressed the mRNA levels of TNF-α, IL-1β and IL-6 in the brain microvascular endothelial barrier dysfunction [24]. In this present study, we confirmed that YQFM inhibited NF-κB activation and the expression of IL-6 and TNF-α (Fig. 6).

5. Conclusion
Our findings suggest that YQFM could ameliorate vasopressin-induced angina through the NF-κB/p65 signaling pathways. These findings provide pharmacological evidence supporting the clinical use of YQFM for treating angina.

6. Declarations of interest
None

7. Acknowledgment
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