Qiliqiangxin Attenuates Adverse Cardiac Remodeling after Myocardial Infarction in Ovariectomized Mice via Activation of PPARγ

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Key Words
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Abstract
Background/Aims: This study was designed to investigate the therapeutic effect of traditional Chinese medication Qiliqiangxin (QLQX) on adverse cardiac remodeling after myocardial infarction (MI) in bilateral ovariectomized (OVX) female mice. Methods: Eight-week old female C57BL/6 mice were operated to ligate the left anterior descending coronary artery seven days after bilateral ovariectomy and were orally administered either QLQX or vehicle. 21 days after ligation, echocardiography was performed to evaluate the heart function of all mice. Masson’s Trichrome staining was applied to evaluate myocardial fibrosis. Collagen deposition was determined by the mRNA level of Collagen I, Collagen III and α-SMA using real-time quantitative polymerase chain reaction (qPCR). Myocardial apoptosis was examined by the protein level of Bax, Bcl2 and the Bcl2/Bax ratio using western blotting. Results: These mice displayed a significant reduction in heart function, increased myocardial fibrosis and apoptosis, and decreased expression of peroxisome proliferator activated receptor γ (PPARγ) in the heart tissue, which could be reversed by QLQX treatment. Inhibition of PPARγ reduced QLQX-mediated cardio-protective effects, while PPARγ activation did not further enhance the beneficial effect of QLQX. Furthermore, QLQX upregulated 9 genes (Cd36, Fatp, Pdk4, Acadm, S. Shen, H. Jiang and Y. Bei contributed equally to this work.

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Acadl, Acadvl, Cpt1a, Cpt1b and Cpt2) facilitating energy metabolism in the MI hearts of the OVX mice and 5 (Acadm, Acadl, Cpt1a, Cpt1b, Cpt2) of the 9 genes were the downstream targets of PPARγ. **Conclusion:** The present study indicates that QLQX has a treatment effect on pathological remodeling post MI in bilateral OVX female mice via activation of PPARγ, suggesting that QLQX may be a promising prescription for the treatment of postmenopausal women suffering from MI.

**Introduction**

The risk of cardiovascular diseases (CVDs), mainly coronary heart disease, significantly increases after the menopausal transition and continues to be the leading cause of mortality in women older than 65 years of age [1, 2]. In addition, large observation studies and meta-analysis have also revealed that women who underwent surgical menopause (surgical removal of both ovaries before the natural age of menopause) were significantly more likely to develop CVDs compared with premenopausal age-matched women [3-5]. Moreover, the year after natural or surgical menopause is found to be an independent risk factor for cardiovascular mortality [6-9]. Although it has been widely accepted that the increased cardiovascular risk in postmenopausal women is attributed to the decline of estrogen and secondary factors induced by decreased estrogen such as increased lipid, lipoprotein and glucose level [7, 10-15], hormone replacement therapy (HRT) is still controversial because of its serious side effect such as venous thromboembolism [16]. Thus, identification of a safe and effective treatment is needed for postmenopausal women with CVDs, mainly coronary heart disease such as myocardial infarction (MI).

Qiliqiangxin (QLQX) is a traditional Chinese medication extracted from 11 distinct herbs including astragaliradix, ginseng radix et rhizoma, aconiti lateralis radix preparata, salvia miltiorrhizaradix et rhizoma, semen descurainiae lepidii, alismatis rhizoma, polygonati odorati rhizoma, cinnamomi ramulus, carthamiflos, periploca cortex, and citri reticulatae pericarpium [11]. And QLQX has been proven to be effective in heart failure patients based on a multicenter randomized double-blind study [11]. Moreover, QLQX has been reported to attenuate cardiac hypertrophy, remodeling and dysfunction induced by pressure overload and spontaneous hypertension [17-20]. In addition, our previous studies revealed that QLQX could protect against cardiac ischemia-reperfusion injury and phenylephrine-induced cardiac hypertrophy [21, 22]. Recently, we reported that QLQX could attenuate heart failure after acute myocardial infarction (AMI) by activation of PPARγ [19]. Interestingly, PPARγ is a regulated target of estrogen in several tissues and plays a role in cardiovascular protection [22-24]. However, it is unclear whether QLQX could attenuate adverse remodeling after MI in ovariectomized mice and, if so, whether this protective effect is achieved by the activation of PPARγ.

**Materials and Methods**

This study was conducted in accordance to the Guidelines on Human Use and Care of Laboratory Animals for Biomedical Research published by the National Institutes of Health (NIH publication number 85-23, revised in 1996). The study protocol was approved by the ethical animal committees of Nanjing Medical University.

**Animals and treatment protocol**

Eight-week-old C57BL/6j female mice were obtained from the Model Animal Research Center of Nanjing University and were employed in this study. QLQX was obtained from Shijiazhuang Yiling pharmaceutical CO., LTD (Shijiazhuang, Hebei, China). All mice were ovariectomized (OVX) and seven days later, they were divided into groups as follows: i) Sham + vehicle, ii) MI + vehicle, iii) Sham+QLQX iv) MI+QLQX, v) MI + QLQX...
+ PPARγ activator (Rosiglitazone), and vi) MI + QLQX + PPARγ inhibitor (T0070907). MI was induced by the permanent ligation of the left anterior descending coronary artery (LAD) in mice as previously described [25]. All animals were raised in the animal research institute of Nanjing Medical University. They were kept on a 12 h light/dark cycle and had free access to food and water ad libitum. Since the day of MI surgery or sham operation, the OVX mice were treated with QLQX at a dose of 0.5 g/kg/d or with the same volume of vehicle by oral gavage, with or without intraperitoneal injection of a PPARγ activator or inhibitor at a dose of 1 mg/kg/d for 21 days.

**Serum estradiol assay**

Venous blood was collected in serum tubes and after centrifugation (4°C at 3000 g for 10 min), the supernatant was transferred to RNase/DNase-free tubes. Serum estradiol concentrations were measured by an estradiol radioimmunoassay kit (Northern institute of biological technology, Beijing, China) in accordance with the manufacturer’s instructions. The sensitivity of the assay was ≤ 2pg/ml and the linear range of the standard was 5-400 pg/ml. The intra- and inter-assay coefficients of variation (CV) were 10% and 15%, respectively.

**Evans blue and tetrazolium chloride (TTC) staining**

The infarction degree of the heart was measured by Evans blue and TTC staining as previously described [26]. Briefly, 1% Evans blue stain (Sigma, St.Louis, MO, USA) was first injected to the heart through the carotid artery. The heart were then excised and frozen at ~20°C and cut in semi frozen state into five equally thick sections. Slices were then incubated in 2% TTC solution (Sigma, St.Louis, MO, USA) for 15 min at 37°C and fixed in 10% formalin. The infarcted area appeared pale-white while area at risk was red and blue indicated normal myocardium. Each piece was observed under microscopy and measured using Image J software (NIH).

**Echocardiographic evaluations**

The systolic heart function of the mice was measured by echocardiography. Mice were anesthetized with 2% isoflurane, maintained in the decubitus position and were allowed to breathe spontaneously during the procedure. Echocardiography was performed with a 35-MHz phased-array ultrasound system Vevo 2100 (Visual Sonics Inc, Toronto, Ontario, Canada). M-mode tracings of the left ventricles (LVs) were recorded at the papillary muscle level and then analyzed by a professional investigator blinded to the grouping. The average of at least three times measurements was used for each mouse.

**Masson’s Trichrome staining**

The myocardial fibrosis was examined by Masson’s Trichrome staining. In brief, the mouse hearts were excised and fixed in 4% paraformaldehyde, embedded in paraffin and cut into 5-μm thick serial sections. Masson’s trichrome staining was performed to each section as previously described [19]. Images were captured by a Nikon Eclipse microscope with NIS Elements software and the fibrotic area was dyed blue. The ImageJ software (NIH) was used to measure the fibrotic area. At least 20 fields (400×) were analyzed on each section. The fibrotic fraction was calculated as a percentage of the fibrotic area to the total myocardial area.

**Western blotting**

Total extracted protein lysates from peri-infarct part of the heart tissues were performed using RIPA buffer (Beyotime, Nantong, Jiangsu, China), and protein lysate concentrations were determined using a BCA protein assay kit (Beyotime, Nantong, Jiangsu, China). Equal amounts of tissue protein were loaded in 10% or 12% SDS-PAGE, transferred onto polyvinylidene difluoride (PVDF) membranes, and then incubated with the primary antibodies overnight at 4°C. The primary antibodies were as follows: transforming growth factor-β1 (TGF-β1) (1:1000 dilution; Cell Signaling Technology, Boston, Massachusetts, USA), Bax (1:1000 dilution; Cell Signaling Technology, Boston, Massachusetts, USA), Bcl2 (1:1000 dilution; Cell Signaling Technology, Boston, Massachusetts, USA), PPARγ (1:500 dilution; Abcam, Cambridge, UK), p-Akt (Ser473, 1:1000 dilution; Cell Signaling Technology, Boston, Massachusetts, USA), Akt (1:1000 dilution; Cell Signaling Technology, Boston, Massachusetts, USA), P38 (1:1000 dilution; Cell Signaling Technology, Boston, Massachusetts, USA), p-P38 (Thr180/Tyr182, 1:1000 dilution; Cell Signaling Technology, Boston, Massachusetts, USA), P38 (1:1000 dilution; Cell Signaling Technology,
Quantitative real-time PCR

Total RNA was extracted from the peri-infarct part of the heart tissues using miRNeasy Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer’s protocol. Total RNA was reverse transcribed into cDNA using SuperScript Reverse Transcriptase (BioRad, Hercules, CA, USA). Quantitative real-time PCR (qRT-PCR) was performed with an ABI 7900HT Fast Real Time PCR System using SYBR green Supermix Kit (BioRad, Hercules, CA, USA). The mRNA level was calculated using the $2^{-∆∆C_t}$ method. GAPDH was used as the internal control. Primer sequences used in this study are as follows (forward and reverse primers): α-SMA: GTC CCA GAC ATC AGG GAG TAA and TCG GAT ACT TCA GCG TCA GGA; Collagen I: TCT AGA CAT GTT CAG TTT GTT GGA and TCT GTA CGC AGG TGA TTG GTG; Cd36: TGT GTT TGG AGG CAT TCT CA; Fatp: GCG TTT CGA TGG TTA TGT and TTG AGT TAG GGT CCA ACTG; Pdk4: CCG CTG TCC ATG AAGCA and GCA GAA AAG CAA AGG ACGTT; Glut4: ACT CTT GCC ACA CAG GCTCT and CCT TGC CCT GTC AGG TATGT; Acadm: TAA TCG TGT AGG GAG GAGGT and GGC AGC AGA AAT GAA ACTCC; Acadl: GCT TCA GCC TCC ACT CAGAT and GGC TAT GGC ACC GAT ACCT; Acadvl: TAT CTC TGG CCA GCG ACTTT and TGG GTA TGG GAA CAC CTGAT; Cpt1a: CTC CGC CTG AGC CAT GAAG and CAC CAG TGA TGA TGC CATTCT; Cpt1b: GGA TGT TCG AGA TGC ACAGC and GGA AGC TGT AGA GTA CCG GCCG; Cpt2: GGC CAC CAA CCT GAC GTGTTT and GAA GGA ACA AAG CGG ATGAG; Ucp2: TCA TCA AAG ATA CTC TCC TCA AAGC and TGA CCG TGG TGC AGA AGC; Ucp3: TGA TCA GAT GAG CTA CGA and CCA AAG GCA GAG ACA AAG TGA; GAPDH: CCT TCC GTG TTC CTA CCC and GCC CAA GAT GCC CTT CAGT.

Statistical analysis

Data were expressed as the mean ± SE. Multiple comparisons between groups were examined using one-way analysis of variance (ANOVA) followed by Bonferroni’s post-hoc test and $P$ values less than 0.05 were considered to be statistically significant. All analyses were performed using GraphPad Prism 6.

Results

**QLQX preserves cardiac function after MI in OVX female mice**

The 8-week-old female mice were randomized into four groups seven days after OVX: i) OVX/Sham + vehicle, ii) OVX/MI + vehicle, iii) OVX/Sham + QLQX, and iv) OVX/MI + QLQX. There was a significant reduction in serum estradiol level seven days after OVX (Fig. 1A). TTC and Evans Blue staining was used to evaluate area at risk (AAR) and infarct size induced by LAD ligation 3 days after operation. The results showed that percentage of AAR/infarct weight was about 40% and percentage of infarct size/AAR was about 30%, and there was no difference between groups receiving vehicle or QLQX 3 days post-MI, indicating that QLQX did not take effects in the acute phase of MI (Fig. 2). Echocardiography was used to examine heart function 21 days after MI or sham operation. We found that the EF and FS were significantly decreased 21 days after MI, which could be reversed by QLQX, and QLQX did not affect EF or FS in OVX/Sham mice (Fig. 1B and 1C).

**QLQX attenuates myocardial fibrosis and apoptosis of the OVX/MI mice**

Masson’s trichrome staining revealed that the fibrotic area was significantly reduced with treatment of QLQX compared to MI mice receiving vehicle (Fig. 3A), which was consistent with the decrease in collagen deposition that had manifested as lower expression
Fig. 1. QLQX improves the heart function of OVX female mice post MI. (A) seven days after the bilateral ovariectomy operation, serum estradiol level was measured by radioimmunoassay. The serum estradiol level was reduced significantly. ***, P < 0.001; n = 30 per group. (B) 21 days after MI, heart function was measured by echocardiography and M-mode pictures of the left ventricles (LVs) were recorded at the papillary muscle level. (C) The M-mode pictures were analyzed. Ejection fraction (EF) and fractional shortening (FS) were decreased 21 days after MI and were improved by QLQX treatment. **, P < 0.01; ***, P < 0.001; n = 6 per group. QLQX, qiliqiangxin; OVX, ovariectomized; MI, myocardial infarction.

Fig. 2. Three days after MI, Evans blue and tetrazolium chloride staining was performed to detect the area at risk and the infarction area of the heart in acute stage after MI. QLQX does not affect the area at risk and the infarction area of the heart in acute stage compared to the vehicle treated group. n=5 per group. QLQX, qiliqiangxin; MI, myocardial infarction.

levels of collagen I, collagen III and α-SMA in the QLQX treatment group (Fig. 3B). TGF-β, a well-recognized marker of fibrosis, was detected by western blot and showed a significant increase in MI mice compared to the sham group, which was reversed by QLQX treatment (Fig. 3C). In addition, myocardial apoptosis was detected by western blotting analysis of the pro-apoptotic protein Bax and the anti-apoptosis protein Bcl2. The expression of Bax was
significantly decreased while Bcl2 expression was significantly increased in QLQX-treated MI mice, leading to an increased Bcl2/Bax ratio compared to the vehicle-treated MI group (Fig. 3D). At the same time, we found that QLQX did not affect mRNA level of Collagen I, Collagen III and α-SMA, Bcl2 and Bax expression, or TGF-β level in OVX mice without MI operation (Fig. 4).

QLQX increases the expression level of PPARγ in OVX/MI mice

We detected the expression of AKT, MAPK pathway and PPARγ in the mouse hearts of three groups (OVX/sham+vehicle, OVX/MI+vehicle, OVX/MI+QLQX) by western blotting, and the expression level of PPARγ was significantly decreased in the OVX/MI mice compared to the sham group, while QLQX dramatically increased the expression level of PPARγ in OVX/MI mice. However, there were no significant changes in the expression of phosphorylation-AKT (Ser473), phosphorylation-ERK (Thr202/Tyr204), or phosphorylation-P38 (Thr180/Tyr182) between the MI mice treated with vehicle and QLQX (Fig. 5).
PPARγ activation is required for the therapeutic effect of QLQX in attenuating adverse cardiac remodeling

Since QLQX could attenuate post-MI cardiac remodeling in OVX female mice and PPARγ was elevated by QLQX, we further explored whether PPARγ was necessary for the therapeutic effect of QLQX. A PPARγ activator (Rosiglitazone, 1 mg/kg/d) or PPARγ inhibitor (T0070907, 1 mg/kg/d) was intraperitoneally injected into the OVX mice in combination with QLQX after MI. The PPARγ expression level in the hearts of mice from three groups (OVX/MI+QLQX, OVX/MI+QLQX+Rosiglitazone, OVX/MI+QLQX+T0070907) was detected to determine the intervention effect, revealing that PPARγ level in the OVX/MI+QLQX+T0070907 group was significantly reduced compared to the OVX/MI+QLQX group, while the PPARγ expression in the OVX/MI+QLQX+Rosiglitazone group was parallel to that in the OVX/MI+QLQX group (Fig. 6A).

Echocardiography was applied again to examine cardiac function at the end of the animal protocol, showing that the treatment benefit of QLQX on EF and FS post MI was abolished by T0070907, while it was not further enhanced by Rosiglitazone (Fig. 6B and Fig. 6C).

T0070907 also interrupted the treatment effect of QLQX on myocardial fibrosis and apoptosis after MI in OVX female mice. The detection of collagen I, collagen III and α-SMA by real-time PCR showed that the collagen deposition in hearts from QLQX/T0070907 treated mice was much heavier than those from the group treated with QLQX alone (Fig. 7A). TGF-β, Bax and Bcl2 expression was also detected in all four groups by western blot. The increased
Fig. 5. Twenty-one days after MI, protein expression of PPARγ, p-AKT, AKT, p-ERK, ERK, p-P38, P38 was detected by western blotting. The protein level of PPARγ was down-regulated in the OVX/MI mice compared to the OVX/Sham group, which was reversed by QLQX treatment. While QLQX does not affect the ratio of p-AKT/AKT, p-ERK/ERK and p-P38/P38. *, P < 0.05; ***, P < 0.001; n = 6 per group. QLQX, qiliqiangxin; OVX, ovariectomized; MI, myocardial infarction.

Fig. 6. T0070907 abolishes the effect of QLQX on preserving heart function of the OVX/MI mice during the adverse remodeling stage while Rosiglitazone does not further promote the protective effect of QLQX. (A) Western blotting analysis showed the protein level of PPARγ was down-regulated by T0070907 while not further enhanced by Rosiglitazone as compared with the group treated by QLQX alone. ***, P < 0.01; n = 6 per group. (B&C) 21 days after MI surgery, echocardiography was performed to examine the heart function and M-mode pictures were analyzed. T0070907 abolished the effect of QLQX on promoting ejection fraction (EF) and fractional shortening (FS) of the post-MI OVX mice. **, P < 0.01; n = 6 per group. QLQX, qiliqiangxin; OVX, ovariectomized; MI, myocardial infarction.
level of TGF-β and Bax, as well as the decreased level of Bcl2 and the Bcl2/Bax ratio induced by T0070907 (Fig. 7B), indicated again that the PPARγ inhibitor could prevent the anti-fibrosis and anti-apoptosis effect of QLQX on post-MI hearts in OVX female mice.

QLQX improved cardiac energy metabolism in OVX/MI mice

Since it is known that menopausal might induce metabolism disorder in women and PPARγ plays an important role in regulating glucose and fat metabolism, we explored whether OVX or QLQX affects glucose and fatty acid metabolism in mice. A total of 13 genes associated with fatty acid uptake/esterification (Lpl, Cd36 and Fatp), glucose oxidation (Pdk4 and Glut4), mitochondria/peroxisomal β-oxidation (Acadm, Acadl, Acadvl, Cpt1a, Cpt1b, and Cpt2) and uncoupling (Ucp2 and Ucp3) were detected by PCR in OVX female mice or QLQX-treated OVX/MI mice. We showed that 9 genes (Lpl, Cd36, Pdk4, Acadvl, Cpt1a,
Cpt1b, Cpt2, Ucp2 and Ucp3) were significantly down-regulated by OVX (Fig. 8A), implying that OVX impeded glucose and fatty acid consumption in the heart. Moreover, in the post-MI remodeling hearts of the OVX mice, the mRNA level of 8 genes (Fatp, Glut4, Acadm, Acadl, Acadvl, Cpt1a, Cpt1b and Cpt2) was decreased as compared with the sham operated OVX mice (Fig. 8B), indicating that cardiac energy metabolism was further impeded after MI. Interestingly, QLQX upregulated 9 of the 13 genes (Cd36, Fatp, Pdk4, Acadm, Acadl, Acadvl, Cpt1a, Cpt1b and Cpt2) (Fig. 8B), facilitating energy metabolism in the chronic ischemic mice heart, especially fatty acid oxidation. It is worth mentioning that among the 9 genes up-regulated by QLQX, 5 genes (Acadm, Acadl, Cpt1a, Cpt1b, Cpt2) were the downstream targets of PPARγ, revealing that QLQX not only upregulated PPARγ expression, but also activated its downstream targets.

Discussion

It is recognized that estrogen deficiency produces a series of cardiovascular risk factors such as glucose- and lipoprotein-metabolism disorder, leading to insulin resistance, metabolic syndrome, finally inducing an increased incidence and mortality of coronary heart disease in postmenopausal women [11]. In our study, we also found that OVX impeded glucose and fatty acid consumption in the mice heart. It seems that hormone replacement therapy (HRT) should be instrumental in producing cardiovascular protection [27]; however, based on 19 studies including 40410 participants, there was no strong evidence that oral HRT was associated with lower rates of cardiovascular mortality in postmenopausal population, and instead, previous evidence indicated that HRT was associated with higher rates of venous thromboembolism [16]. In this study, we provide QLQX as a promising alternative to HRT in the treatment of postmenopausal women suffering from MI. QLQX alleviated myocardial fibrosis and apoptosis, thus reducing loss of heart function during adverse cardiac remodeling after MI in OVX mice. Moreover, PPARγ inhibitors abolished the cardiac protective function
of QLQX, supporting the fact that PPARγ activation is required for the cardiac protective effects of QLQX in MI in OVX mice.

Here, we also revealed that QLQX not only upregulated PPARγ expression, but also upregulated its downstream targets named Acadm, Acadl, Cpt1a, Cpt1b and Cpt2. These 5 genes mediate mitochondrial β-oxidation or peroxisomal oxidation in the heart [28-31]. Along with these, QLQX also up-regulated expressions of Cd36 and Fatp, which mediate fatty acid esterification [32, 33], and Pdk4, which mediates glucose oxidation [34, 35]. The above results reveal that QLQX improves energy metabolism in the OVX/MI heart via facilitating both of fatty acid β-oxidation and glucose oxidation, and this effect is mediated by PPARγ to a large extent.

Previous studies have demonstrated the therapeutic effects of PPARγ activators on ischemia injury and pathological remodeling of the heart [36-39]. Our study further indicated that PPARγ activation was beneficial for post-MI pathological remodeling in estrogen-deficient mice. These findings indicate that PPARγ is a promising therapeutic target in post-MI treatment, however, the most common PPARγ agonist thiazolidinediones (TZDs) is not recommended for heart failure (HF) patients and patients under risks of HF because it may induce fluid retention and edema, leading to increased mortality of HF. Interestingly, we found that traditional Chinese medication QLQX could not only serve as a PPARγ activator and improve post-MI pathological remodeling, but also avoid fluid retention and edema in HF patients in the clinical trials [17], which might be explained by the synergistic effect of active ingredients in compound Chinese medication.

As a limitation of our study, the expression and function of co-regulatory molecules of PPARγ is unclear in the case of QLQX treatment. It would be interesting to further investigate the QLQX-PPARγ regulation network in the heart in both genders. Moreover, clinical trials are needed to determine whether QLQX has a beneficial effect on postmenopausal women suffering from MI since the mouse model of bilateral ovariectomy is actually slightly different from clinical postmenopausal conditions.

In conclusion, our study indicates that QLQX has a therapeutic effect on the post-MI heart via PPARγ in estrogen-deficient mice, promising to be a novel prescription for the prevention and treatment of menopausal women with coronary heart disease.

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