Attenuating effect of post-treatment with QiShenYiQi Pills on myocardial fibrosis in rat cardiac hypertrophy

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Abstract. QiShenYiQi Pills® (QSYQ) is a compound Chinese medicine used for treatment of cardiovascular diseases. However, the potential of QSYQ to inhibit cardiac fibrosis in left ventricle hypertrophy is not explored to date. We investigated the effects of post-treatment with QSYQ on rat myocardial fibrosis in left ventricle hypertrophy induced by pressure over-load through ascending aortic stenosis. QSYQ was administrated 4 weeks after the surgery, at a dose of 0.8 g/kg/day over the next 4 weeks, while echocardiography was performed 4 and 8 weeks, respectively, after the surgery. Eight weeks after the surgery, myocardial blood flow was determined by Laser-Doppler Perfusion Imager and the ratio of heart weight to body weight (HW/BW) was estimated, in concurrent evaluation of myocardial histology and ultrastructure, as well as collagen content by sirius red staining, and immunohistochemistry staining for CD68 and transforming growth factor beta 1. Post-treatment with QSYQ significantly alleviated left ventricular posterior wall end diastolic thickness and the HW/BW, increased left ventricle ejection fraction and left ventricle fractional shortening. QSYQ also decreased myocardial fibrosis size. The expression of CD68 and transforming growth factor beta 1 were obviously suppressed after QSYQ treatment. The results suggest that post-treatment with QSYQ attenuates pressure over-load-induced cardiac hypertrophy and myocardial fibrosis through interfering in inflammatory process.

Keywords: Pressure overload, cardiac fibrosis, salvia miltiorrhiza, transforming growth factor beta 1

1. Introduction

Cardiac hypertrophy occurs in response to a diversity of stimuli, either extrinsic or intrinsic, such as pressure over-load, ischemic disease, neurohumoral factors, and genetic cardiac defects. Although the cardiac hypertrophy initially represents a compensatory mechanism that maintains normal cardiac output, sustained cardiac hypertrophy is believed a leading cause of heart failure and sudden death in humans, and epidemiologic studies have shown an association between ventricular hypertrophy and increased cardiac morbidity and mortality [9].

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Fibrosis is a complex tissue disease characterized by excessive and abnormal deposition of extracellular matrix components [17, 18]. Myocardial fibrosis is an important pathophysiological process that contributes to the conversion from hypertrophy to heart failure by increasing myocardial stiffness and reducing pumping capacity. Thus, preventing myocardial fibrosis is pivotal for improving the outcome of the patients with cardiac hypertrophy [14].

QiShenYiQi Pills® (QSYQ) is a compound Chinese medicine approved by China State Food and Drug Administration in 2003 for treatment of coronary heart disease, angina pectoris. QSYQ consists of the water-ethanol extracts from *radix astragali* (RA), *salvia miltiorrhiza* (SM), *panax notoginseng* (PN) and rosewood. The ability of QSYQ to improve cardiac function has been documented in rats with acute myocardiac infarct [7]. Interestingly, QSYQ is also reported to inhibit the expression of collagen type I and III in rat liver and attenuate the hepatic fibrosis [29]. Increasing studies have been conducted to explore the pharmacology of the herbs contained in QSYQ. The results revealed that SM, and its ingredient salvianolic acid B, is able to improve coronary microcirculation, inhibit platelet aggregation, protect against heart injury caused by ischemia-reperfusion [26], as well as prevent hepatic fibrosis [10]. RA was reported to attenuate autoimmune myocarditis-induced myocardial inflammation and fibrosis [28]. Rosewood was found to ameliorate the cardiac remodeling of rat after acute heart infarct [20]. Taking together, apart from others, the potential of QSYQ to prevent myocardial fibrosis after cardiac hypertrophy is highly suggested. The present study was designed to prove this assumption and explore the underlying mechanism.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats weighing 95–105 g were purchased from the Animal Center of Peking University Health Science Center (Beijing, certificate no. SCXK 2006-0001). The animals were fasted for 12 h before the experiment, while allowing free access to water. All animals were handled according to the guidelines of the Peking University Health Science Center Animal Research Committee.

2.2. Drug

QSYQ (Batch number: 20090122) was obtained from Tasly Pharmaceutical Co., Ltd. (Tianjin, China), which was prepared from water-ethanol extracts of RA, SM, PN and rosewood under the guidelines of Good Manufacturing Practice and Good Laboratory Practice verified by the Chinese Government agency. QSYQ was dissolved in saline to a concentration of 0.2 g/mL for experiment use.

2.3. Animal model and drug administration

Rats were anesthetized with composite anesthetic (3 mL/kg), including Chloral Hydrate, Salamarum, Embutal, Dehydrated alcohol, Propylene Glycol and distilled water, by intraperitoneal injection. After tracheotomy, the animals were ventilated with a positive pressure respirator (ALC-V8, Shanghai, China). The thorax was opened and ascending aortic stenosis (AAS) was implemented by placing a silver clip (0.9-mm inside diameter) on the ascending aorta. Sham-operated animals underwent an identical procedure but without the clip [4].
Table 1
The number of animals examined in different experimental groups and for various parameters after 8 weeks of AAS

<table>
<thead>
<tr>
<th>Group</th>
<th>Myocardial blood flow, HW/BW, Histology and immunohistochemistry, Myocardium collagen stain examination</th>
<th>Ultrastructure examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham + NS</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Sham + QSYQ</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>AAS + NS</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>AAS + QSYQ</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

After 4 weeks of surgery, 31 animals in the AAS group were revealed by echocardiographic analysis to have left ventricular wall thickness 20% thicker than that in sham group, which were identified as succeeded in the modeling and randomly divided into AAS + NS group (n = 16) and AAS + QSYQ (n = 15) group, while the animals in sham group were randomly divided into Sham + NS (n = 10) group and Sham+QSYQ (n = 10) group.

In AAS + NS and Sham + NS group, saline was given everyday through intragastric administration for the succedent 4 weeks at a dose of 4 mL/kg/day. Over the same period of time, in AAS + QSYQ and Sham + QSYQ group, QSYQ dissolved in saline was given through intragastric administration at the dose of 0.8 g/kg/day, 9.9-fold higher than that for human in clinic. During this period of 4 weeks, a number of animals in AAS + NS group as well as in AAS + QSYQ group died of acute heart failure. Eight weeks after AAS, nine animals were randomly selected from the survival rats in each group for analysis of other parameters. The number of animals examined in different experimental groups and for various parameters is detailed in Table 1.

2.4. Survival

The number of survival animals in each group was scored daily from 4 weeks to 8 weeks after AAS.

2.5. Echocardiographic analysis

The left ventricle function was evaluated 4 and 8 weeks after AAS, respectively, using a Vevo 770 High-Resolution Imaging Systems (Visual Sonics Inc, Toronto, ON, Canada) with a 17.5 MHz linear array transducer (model 716) [1]. Briefly, rats were anaesthetized with 1.5–2.0% isoflurane by mask, the chest was shaved, the animal situated in the supine position on a warming pad, and electrocardiogram limb electrodes were placed. Two-dimensional cine loops and guided M-mode frames were recorded from the parasternal short and long axis. All data were analyzed off-line at the end of the study with software resident on the ultrasound system.

The following parameters were measured as indicators of function and remodeling: left ventricular internal diameter (diastole, LVIDd), left ventricular posterior wall (diastole, LVPWd), left ventricular internal diameter (systole, LVIDs), left ventricle ejection fraction (%EF), and left ventricle fractional shortening (%FS).
2.6. HW/BW

Rats were killed 8 weeks after AAS, and the hearts were removed and washed with normal saline. Both body weight (BW) and heart weight (HW) were determined, and ratio of HW to BW (HW/BW) was calculated to evaluate the hypertrophic response to pressure over-load.

2.7. Myocardial blood flow

After left thoracotomy under anesthesia, myocardial blood flow (MBF) was measured by using Laser-Doppler Perfusion Imager (PeriScan PIM3, Perimed, Sweden) equipped with a computer 8 weeks after AAS surgery. All images were evaluated with the software LDPIwin 3.1 (Perimed, Sweden) [27].

2.8. Histological and immunohistochemistry evaluation of myocardial tissues

Hearts were removed 8 weeks after AAS, fixed in 4% formaldehyde, and further prepared for paraffin sectioning [27]. The paraffin sections (5 μm) were rehydrated, and either stained with hematoxylin and eosin (HE) or incubated with antibody against CD68 (Abcam, UK) or transforming growth factor beta 1 (TGF-β1, Santa Cruz, USA) after being blocked with bovine serum albumin. The samples were then incubated with a biotinylated secondary antibody followed by avidin-biotin-peroxidase complex. Positive staining was visualized with diaminobenzidine. The images were captured by a digital camera connected to a microscope (BX512DP70, Olympus, Japan). Five fields were selected for each animal; the number of CD68-positive cells and the mean optical density of TGF-β1 were determined using Image-Pro Plus 5.0 software (Media Cybernetics, USA).

2.9. Myocardial collagen stain

Myocardial collagen content was determined using the sirius red staining technique. Briefly, hearts were perfusion-fixed 8 weeks after AAS, processed for paraffin section and stained with picrosirius red. The percent area of extracellular picrosirius red staining was computed from five fields randomly selected from the mid-myocardium in order to exclude large cardiac arteries and/or veins, as well as any cutting and/or compression artifacts. The collagen content in myocardial tissue was evaluated in terms of two variables: the collagen volume fraction (CVF) and the volume ratio of perivascular collagen to myocardial vessel lumen (VRPM). Three to five fields were randomly selected and measured in each sample, and the mean was calculated [22, 24].

2.10. Myocardial ultrastructure

Fresh myocardial tissues (1 mm³) were excised from the left ventricle 8 weeks after AAS. Tissues were fixed with 3% glutaraldehyde and post-fixed with 1% osmium tetroxide. The specimens were processed for ultrathin sections. The sections were stained with uranium acetate and lead citrate, and the ultrastructures of myocardial tissue were then examined by a transmission electron microscope (JEM-1230, Tokyo, Japan) [27].
2.1. Statistics

All parameters were expressed as mean ± S.E. Statistical analysis was performed using one-way ANOVA followed by Tukey test for multiple comparisons. A probability of less than 0.05 was considered to be statistically significant.

3. Results

3.1. Survival

Figure 1 shows the number of the survival rats at different time points after QSYQ treatment in the 4 groups. All rats in the sham group survived 4 weeks of observation, while 7 of 16 animals in AAS + NS group died of acute heart failure within the first week, and only 9 rats left by the end of observation, representing a survival rate of 56%. Post-treatment with QSYQ significantly restored the survival rate of animals, reaching to 93% at the end of experiment with only one rat died of acute heart failure.

3.2. Echocardiogram

M-mode echocardiograms of the rat hearts in various conditions were acquired 4 weeks and 8 weeks after AAS, respectively, and the representative images are presented in Fig. 2. Note that compared to sham group (Fig. 2, A1), the pressure over-loaded heart exhibits marked hypertrophy after 4 weeks of AAS with normal chamber dimensions and significantly increased LVPWd (Fig. 2, A2). After 8 weeks of AAS, a prominent ventricular dilation is noted accompanied by systolic dysfunction (Fig. 2, B3) in comparison with sham group (Fig. 2, B1). These alterations were ameliorated by administration of QSYQ (Fig. 2, B4). The beneficial action of QSYQ for rat cardiac insults induced by pressure over-load was confirmed by quantitative analysis of the echocardiograms, as shown in Table 2, wherein 8 weeks of AAS brought about significant increase in LVPWd, development of systolic dysfunction, as suggested by reduction in FS, and dilative remodeling, as suggested by marked increase in LVIDs, while administration of QSYQ attenuated these impairments significantly.
3.3. Changes in MBF

Figure 3A shows the color images acquired by Laser-Doppler Perfusion Imager in four groups after 8 weeks of AAS, where the different magnitude of MBF is indicated by distinct color with the red color representing the highest MBF. No obvious difference in MBF was noted between Sham + NS group (A1) and Sham + QSYQ group (A2). As expected, however, manipulation of AAS gave rise to an apparent decrease in MBF (A3) compared to the sham group (A1), which was attenuated apparently by treatment with QSYQ (A4). This result was verified by quantitative evaluation of coronary blood flow, as shown in Fig. 3B, which was carried out 8 weeks after AAS and presented as percentage of baseline.

3.4. HW/BW

To evaluate the hypertrophic response to 8 weeks of AAS, we measured ratio of HW to BW in different groups, and the results are presented as graphics in Fig. 4. As noticed, no obvious difference in HW/BW
Table 2  

<table>
<thead>
<tr>
<th>Group</th>
<th>4 weeks</th>
<th>8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LVIDd (mm)</td>
<td>LVPWd (mm)</td>
</tr>
<tr>
<td>Sham (n = 10)</td>
<td>5.89 ± 0.46</td>
<td>1.76 ± 0.18</td>
</tr>
<tr>
<td>AAS (n = 31)</td>
<td>6.51 ± 0.15</td>
<td>2.96 ± 0.10*</td>
</tr>
<tr>
<td>Sham + NS (n = 10)</td>
<td>6.95 ± 0.16</td>
<td>2.24 ± 0.11</td>
</tr>
<tr>
<td>AAS + NS (n = 9)</td>
<td>6.88 ± 0.31</td>
<td>3.55 ± 0.13*</td>
</tr>
<tr>
<td>AAS + QSYQ (n = 14)</td>
<td>6.96 ± 0.31</td>
<td>2.96 ± 0.06*</td>
</tr>
</tbody>
</table>

The parameters were determined 4 and 8 weeks after AAS, respectively. LVIDd, left ventricular internal diameter (diastole); LVPWd, left ventricular posterior wall (diastole); LVIDs, left ventricular internal diameter (systole); EF, LV ejection fraction; FS, LV fractional shortening. Values are means ± S.E. from 6 animals. *p < 0.05 vs. Sham + NS, #p < 0.05 vs. AAS + NS.

Fig. 3. The effect of QSYQ on CBF of rats. A: The CBF images acquired by Laser-Doppler Perfusion Imager in Sham + NS group (A1), Sham + QSYQ group (A2), AAS + NS group (A3) and AAS + QSYQ group (A4). Flux is represented on color scale from dark blue (low flux) to red (high flux). B: The statistical results of CBF determined 8 weeks after AAS in different groups. Values are means ± S.E. from 6 animals. *p < 0.05 vs. Sham + NS, #p < 0.05 vs. AAS + NS.

between Sham + NS group and Sham + QSYQ group was observed. The HW/BW of AAS + NS group increased to more than 2 fold higher than that of sham group, which was significantly attenuated by post-treatment with QSYQ.
Fig. 4. The effect of QSYQ on rat HW/BW. The HW to BW ratio was estimated 8 weeks after AAS in different experimental conditions. Values are means ± S.E. from 6 animals. *p < 0.05 vs. Sham + NS, #p < 0.05 vs. AAS + NS.

Fig. 5. Effect of post-treatment with QSYQ on histology of myocardial tissue of rats. The tissue was taken 8 weeks after AAS from animals in different conditions and stained by hematoxylin and eosin. A: the locations of the samples for HE stain; B: histology of myocardial tissue at higher magnification. 1: Sham + NS group; 2: Sham + QSYQ group; 3: AAS + NS group; 4: AAS + QSYQ group. E: Edema; MF: muscle fiber. Bar = 50 μm.

3.5. Histology

Figure 5 illustrates the results of histological examination of the left ventricle myocardial tissues in different groups. Compared with the Sham+NS group (B1), distinct alterations occurred in myocardial tissues from the AAS + NS group (B3), including tissue edema and muscle fiber thickening. Of notice, all the pressure over-load-induced alterations were ameliorated by post-treatment with QSYQ (B4).
Fig. 6. Effect of post-treatment with QSYQ on expression of CD68 in myocardium. A: representative photomicrographs of immunohistochemistry staining for CD68 labeled macrophages in rat myocardium in Sham + NS group (A1 and A5), Sham + QSYQ group (A2 and A6), AAS + NS group (A3 and A7) and AAS + QSYQ group (A4 and A8). M indicates macrophage. Bar = 50 μm. B: the quantitative analysis of the number of CD68 labeled macrophages. Bar = 10 μm. Values are means ± S.E. from 6 animals. *p < 0.05 vs. Sham + NS, #p < 0.05 vs. AAS + NS.

3.6. CD68 expression in myocardium

To determine the effect of post-treatment with QSYQ on inflammation induced by pressure over-load, immunohistochemistry staining of CD68 was conducted 8 weeks after AAS. Figure 6A shows the images of CD68 staining in the left ventricle myocardium from the various groups. In Sham + NS group (A1) and Sham + QSYQ group (A2), few CD68-positive cells were found in the myocardium (A5, A6). In contrast, a large number of CD68-positive cells were observed in the AAS + NS group (A3, A7). Noticeably, the number of CD68-positive cells in the myocardium of AAS + QSYQ group was decreased apparently (A4, A8). Figure 6B is the statistical results of CD68-positive cells in the left ventricle myocardium from various groups, which is consistent with the qualitative survey.

3.7. TGF-β1 expression in myocardium

Figure 7A shows the representative images of immunohistochemistry staining of TGF-β1 in myocardial tissues in different groups. Positive staining was obvious on cardiac myocytes in the AAS + NS group
3.8. Collagen deposition in myocardium

Sirius red staining was applied to examine the collagen deposition in myocardium in different conditions 8 weeks after AAS, and the result is presented. The collagen deposition was evaluated by determination of collagen volume fraction of myocardial tissue (CVF, A) and the volume ratio of perivascular collagen to myocardial vessel lumen (VRPM, B). As evidenced from the representative images (A and B), as well as from quantitative analysis (C and D), both CVF and VRPM were increased significantly in AAS + NS group, compared with Sham + NS group, and these increases were ameliorated by post-treatment with QSYQ.
Fig. 8. The effect of post-treatment with QSYQ on collagen deposition in rat myocardium. Collagen was stained by sirius red. The sections in different experimental conditions are displayed in A and B to show the collagen deposition in myocardium (A) and perivascular interstice (B), respectively. 1: Sham + NS group; 2: Sham + QSYQ group; 3: AAS + NS group; 4: AAS + QSYQ group. Bar = 50 μm. C and D: Quantification of collagen deposition in myocardium (C) and perivascular interstice (D). CVF: Collagen volume fraction; VRPM: the volume ratio of the perivascular collagen to myocardial vessel lumen. Values are means ± S.E. from 6 animals. *p < 0.05 vs. Sham + NS, #p < 0.05 vs. AAS + NS.

3.9. Myocardial ultrastructure

The ultrastructures of the left ventricular myocardial tissues from different groups were examined. The representative electron micrograms of cardiac muscle cells in each condition were displayed in Fig. 9A. In Sham + NS group, cardiac myofibrils stood regularly arranged with well-preserved myofilaments, and mitochondria occupied the cytoplasm between myofibrils with densely packed cristae (A1). Similar ultrastructure feature of cardiac myocyte was observed in QSYQ alone group (A2). In contrast, AAS elicited a prominent structure alteration in cardiac myocyte, characterized by interruption of myofilaments with numerous dense mitochondria clumped within the empty area (A3). The AAS-induced alteration in cardiac myocyte was attenuated obviously by post-treatment with QSYQ (A4). Figure 9B presents the
Fig. 9. Influence of post-treatment with QSYQ on the ultrastructure of myocardial tissues of rats. A: the representative electron micrographs of myocardial cells of rats from different groups. B: the representative electron micrographs of capillaries in rat myocardium from different groups. 1: Sham + NS group; 2: Sham + QSYQ group; 3: AAS + NS group; 4: AAS + QSYQ group. C: cardiac myofibril; Col: collagen fibrils; E: endothelial cell; M: mitochondrion.

representative electron micrographs of capillaries with surrounding tissues. The endothelium of capillaries in the Sham + NS group as well as in Sham + QSYQ group was preserved well and both the capillary and surrounding tissue displayed normal ultrastructural features (B1 and B2). The pressure over-load led to an apparent increase in the occurrence of collagen fibrils accompanied by fibroblasts in the frequently dilated perivascular interstice (B3), which was relieved by post-treatment with QSYQ (B4).

4. Discussion

In agreement with others [21], the results of present study revealed that pressure over-load by 8 weeks of AAS gave rise to an apparent myocardial hypertrophy in rat, as evidenced by the increased left ventricular wall thickness and HW/BW, the decrease in FS, and the increase in LVIDs, all of which were attenuated significantly by post-treatment with QSYQ. Interestingly, QSYQ post-treatment was also found to prevent the concomitant deposition of collagen in both myocardial tissue and perivascular interstice, indicating the potential of QSYQ to protect hypertrophy myocardium from fibrosis.

The finding that 8 weeks of AAS resulted in a decrease in FS and an increase in LVIDs, indicative of the occurrence of systolic dysfunction and left ventricular dilative remodeling, points to the development of decompensatory hypertrophy. Meanwhile, a reduced MBF was noted after 8 weeks of AAS, suggesting the dysfunction of coronary microcirculation. The impairment of cardiac microcirculation during the development of cardiac hypertrophy has been widely recognized [12], and can be ascribed to a variety of
factors, such as reduced capillary density, vascular remodeling, extravascular compressive forces imposed by elevated left ventricular cavity pressure [8, 19].

It is proposed that a crosstalk between microcirculation dysfunction and myocardial hypertrophy exists that interplay to aggravate the pathological process [3, 13]. Therefore, a management capable of improving microcirculation may be expected to attenuate cardiac hypertrophy. In this regard, SM and PN, the ingredients of QSYQ, have been demonstrated in animal models to ameliorate the microcirculatory disturbance in mesentery [6, 23], brain [16, 25], as well as in heart [20, 28]. It is likely that this potential of QSYQ is, at least partly, responsible for its beneficial effect on cardiac hypertrophy observed in present study.

One of the mechanisms underlying the attenuation of QSYQ on cardiac hypertrophy may reside in the antioxidant property observed for SM contained in this compound. Increased myocardial and vascular xanthine oxidase activity has been reported in human heart failure [2]. The enhanced reactive oxygen species (ROS) production in the progress of pressure over-load cardiac hypertrophy is well recognized, which is implicated in the development of cellular hypertrophy and remodeling, through at least in part, activation of redox-sensitive protein kinases such as the mitogen-activated protein kinase superfamily. In addition, the transition from compensated cardiac hypertrophy to heart failure is found to associate with increased oxidative stress, which may promote myocyte apoptosis and necrosis [15]. Another consequence of increased ROS production in heart failure is a loss of endothelial nitric oxide synthase-derived nitric oxide, leading to formation of the toxic peroxynitrite, and may contribute to impaired peripheral vascular function and coronary perfusion [5, 11]. Thus, as an antioxidant, QSYQ may exert attenuation effect on cardiac hypertrophy by acting either on the cardiac myocyte directly, or on the coronary microcirculation indirectly, or both. Nonetheless, this argument needs verification by further works.

The potential of QSYQ for preventing myocardium fibrosis following cardiac hypertrophy has been suggested by the observation that SM is able to prevent hepatic fibrosis [10], and RA able to attenuate myocarditis-induced myocardial fibrosis [28]. The present study confirms this notion by the evidence from both immunohistochemistry and electron microscopy. The rationale behind this effect of QSYQ is at present unknown. However, it may be accounted for, at least in part, by the ability of QSYQ to ameliorate progress of cardiac hypertrophy. In addition, the finding that QSYQ depressed the expression of CD68 and TGF-β1 induced by pressure over-load provides further clue for understanding this issue. As is reported, pressure over-load triggers a transient inflammatory response in the myocardium associated with increased macrophage density and expression of pro-inflammatory cytokines, such as TNF-α and IL-1β [22]. The pro-inflammatory cytokines regulate the fibrotic process through several distinct pathways, and, among others, may stimulate expression of TGF-β1 that promotes matrix deposition. Taken together, we propose that QSYQ prevent the myocardium fibrosis following cardiac hypertrophy by interfering in the inflammatory process triggered by pressure over-load. More works are required for getting into the detail of the mechanism.

In summary, post-treatment with QSYQ inhibited cardiac hypertrophy and myocardium fibrosis induced by pressure over-load, probably due to its inherent antioxidant potential and via interfering in inflammatory process.

References


[23] Y.-C. Li et al. / Chinese medicine and myocardial fibrosis


