Artemisinin Attenuates Post-Infarct Myocardial Remodeling by Down-Regulating the NF- κ B Pathway

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Myocardial infarction (MI) leads to progressive left ventricular (LV) dilatation and is associated with interstitial fibrosis in the non-infarcted myocardium. The NF- κ B signaling pathway plays an important role in ventricular remodeling after MI. Recent studies have indicated that the anti-malarial agent artemisinin can inhibit NF- κ B activation, which may attenuate post-infarct myocardial remodeling. In this study, we investigated the effect of artemisinin on post-infarct myocardial remodeling using a rat model of MI. Adult male Sprague Dawley rats were divided into a sham group ($n = 10$) and MI groups that were treated either with oral gavage of artemisinin (75 mg/kg/day, $n = 20$) or vehicle (0.5% carboxymethyl cellulose, $n = 20$) three times a day for 4 weeks. Each treatment was started at 24 hours after ligation of the left anterior descending coronary artery. Four weeks after MI, the artemisinin-treated group showed a significantly improved survival rate compared with that of the vehicle-treated group (65% vs. 40%, $P < 0.05$). Although infarct size was similar in both groups, echocardiography showed significant improvements in cardiac function and left ventricular dimensions in the artemisinin-treated group. Moreover, the degree of myocardial fibrosis and elevated levels of fibrosis-related factors [transforming growth factor- β 1, collagen type I, matrix metalloproteinase (MMP)-2 and MMP-9] in the non-infarcted myocardium were remarkably ameliorated by artemisinin (all $P < 0.05$). Importantly, artemisinin inhibited the NF- κ B pathway by blocking I κ B α phosphorylation. In conclusion, artemisinin may attenuate post-infarct myocardial remodeling by down-regulating the NF- κ B pathway.

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Myocardial infarction (MI) leads to progressive left ventricular (LV) dilatation and is associated with interstitial fibrosis in the noninfarcted myocardium. Previous studies have shown that nuclear factor-kappaB (NF- κ B) plays an important role in this pathological process (Onai et al. 2007; Timmers et al. 2009). The NF- κ B signaling pathway has been shown to be activated after myocardial ischemia (Li et al. 1999). Activation of NF- κ B induces the activation of genetic programs that lead to the transcription of cytokines, chemokines, and matrix metalloproteinases (MMPs), promoting inflammatory and fibrotic responses that participate in the progression of ventricular remodeling (Onai et al. 2007; Timmers et al. 2009). However, this pathological remodeling can be attenuated by continuous inhibition of NF- κ B (Trescher et al. 2004).

Artemisinin is a natural product used as an alternative drug in the treatment of severe and multidrug-resistant malaria (Haynes 2001). Some minor gastro-intestinal

adverse effects have been reported, such as nausea, vomiting, diarrhea and abdominal pain in the treated patients, which would disappear quickly after stopping treatment (Ribeiro and Oliaro 1998). In addition to its anti-malarial properties, Aldieri et al. (2003) have reported that artemisinin shares with other sesquiterpene lactones the ability to inhibit the activation of NF- κ B in cytokine-stimulated T67 human astrocytoma cells. Several sesquiterpene lactones are known to impair NF- κ B activity, either by alkylating it (Lyss et al. 1998; Garcia-Pineres et al. 2001) or by preventing the degradation of its inhibitory protein I κ B (Hehner et al. 1998; Wong and Menendez 1999; Kim et al. 2001). Recently, Xiong et al. (2010) have demonstrated that artemisinin can ameliorate myocardial hypertrophy via inhibition of the NF- κ B pathway in response to aortic banding. However, its role in long-term ventricular remodeling after MI remains unclear. Therefore, we designed this study to test the effect of artemisinin on ventricular remodeling after

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MI.

Materials and Methods

Surgical procedure

Adult male Sprague Dawley rats, aged 12 weeks and weighing 180–220 g, were anesthetized with an intraperitoneal injection of 3% pentobarbital sodium (30 mg/kg). A left intercostal thoracotomy was performed to expose the heart, and the left anterior descending artery (LAD) was ligated at the origin as previously described (Wang et al. 2010; Wen et al. 2011). The sham group underwent thoracotomy and pericardiotomy, but not LAD ligation. A successful MI model was confirmed by elevation of the ST segment by more than 0.2 mV in leads I, II and aVL. The chest was then closed, and the animals were allowed to recover in a warm, clean cage. Rats that died within 24 h of the operation were excluded from this study. All experiments were approved by the Institutional Animal Care and Use Committee of Wuhan University and were conducted in accordance with the Guidelines for the Care and Use of Laboratory Animals.

Reagents

Artemisinin (chemical structure shown in Fig. 1) was purchased from Guilin Pharmaceutical Factory (Guilin, Guangxi, P.R. China). The drug was dissolved in 0.5% CMC (carboxymethyl cellulose) immediately before use. The drug safety of artemisinin (75 mg/kg/day) in rats up to 28 days old has been presented in a previous study (Xiong et al. 2010). The 0.5% CMC carrier vehicle was used as a control.

Treatment protocol

Rats surviving 24 h after the operation were assigned randomly to three treatment groups, as follows: artemisinin (75 mg/kg/day) by oral gavage three times a day for 4 weeks (MI + artemisinin group, $n = 20$); the same volume of 0.5% CMC liquid vehicle by oral gavage three times a day for 4 weeks after MI (MI + vehicle group, $n = 20$); and the same treatment as MI + vehicle group was used for the sham-operation group (thoracotomy with LAD isolation but without ligation, $n = 10$) 4 weeks after operation.

Echocardiography and hemodynamic measurements

Echocardiographic studies were performed 4 weeks after myocardial infarction. Before the test, each rat was anesthetized by intra-

peritoneal injection of pentobarbital sodium. The hearts were imaged in two-dimensional mode using short-axis views at the level of the papillary muscles to measure the LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), LV end-diastolic area (LVEDA), and the ratio of fractional shortening (%FS). Ejection fraction (%EF) was calculated using the area-length method. For hemodynamic measurements, a catheter was inserted into the right carotid artery and then advanced into the LV for the recording of LV end-systolic pressure (LVESP), LV end-diastolic pressure (LVEDP), and LV maximum rates of pressure development (dp/dt_{max}).

Infarct size and myocardial histopathology

At 4 weeks after surgery, the heart was excised and fixed with a 10% solution of formalin in PBS. The heart was embedded in paraffin and cut serially from the apex to the base. The infarct size was expressed as a percentage of the total LV wall circumference from each of the 3 LV sections.

To determine the myocyte hypertrophy, the cardiomyocyte cross-sectional area was evaluated, sections were stained with hematoxylin and eosin (HE). Individual myocytes were measured with quantitative digital image analysis software (Image Pro-Plus 4.5). The outlines of 100 myocytes were traced in each section. To assess the degree of fibrosis in non-infarcted areas, the sections were stained using the Mallory-Azan method. In each section, high-power fields of view at a magnification of 400 were scanned with computer-assisted video densitometry, and the images from at least 10 fields from each heart were analyzed as described previously (Takeishi et al. 1999).

Western blot analysis

The peri-infarcted zone of the left ventricle and the same zone of the left ventricle in the sham group were used for western blot analysis. Equal amounts of protein were loaded and separated by SDS-PAGE, transferred to a nitrocellulose membrane, and incubated with monoclonal antibodies to phospho-IKB α , IKB α (Cell Signaling, USA), TGF- β 1, collagen type I, MMP-2, MMP-9 and β -actin (Santa Cruz Biotechnology, Santa Cruz, CA, USA). The membranes were incubated with secondary antibodies (Cell Signaling, USA) and developed with an enhanced chemiluminescence reagent (Santa Cruz Biotechnology, Santa Cruz, CA, USA). Finally, the blots were visualized using an ECL kit (Beyotime Inc., China), and the signals were analyzed using a Bio-Rad image system (Hercules, CA).

Statistical analysis

All values are expressed as the mean $\pm$ standard deviation (s.d.). An independent samples t test was used to compare variables between the two groups. Survival curves after myocardial infarction were created by the Kaplan-Meier method and compared by the log-rank test. Statistical significance was defined as $P < 0.05$.

Results

Survival Rates and Infarct Size

The survival rate of the sham-operated rats was higher compared with the MI rats; 1 of the 10 rats that underwent the sham operation died 24 hours after surgery, but 9 survived (90%) until the time of sacrifice. A successful MI model was confirmed by elevation of the ST segment in leads I, II and aVL (Fig. 2A). A total of 50 rats underwent

Fig. 1. The chemical structure of artemisinin.

Fig. 2. The change of electrocardiography (ECG) after LAD ligation and the survival curves in the different groups 4 weeks after MI.

(A) A successful MI model was confirmed by elevation of the ST segment in leads I, II and aVL. Arrows indicate the ST segment (panel a) and the elevated ST segment after LAD ligation (panel b). (B) Survival curves, created by the Kaplan-Meier method. The survival rates were compared by the log-rank test between the MI+artemisinin group and the MI+vehicle group. Animals were followed up for 28 days after MI. The survival rates were significantly higher in the MI+artemisinin group than the MI+ vehicle group from the 14th day until the 28th day (65% versus 40%, $P < 0.05$).

Fig. 3. Detection of the infarct area 4 weeks after MI.

(A) Mallory-Azan-stained LV transverse sections 4 weeks after MI. Blue coloration indicates the infarct area. (B) Infarct area was determined as percentage of total LV area. There was no significant difference in the circumferential infarct size between groups. The data are expressed as the mean $\pm$ s.d.

LAD ligation, and 10 (20%) died after 24 hours. The remaining 40 rats were randomly allocated either to the MI+ artemisinin group ($n = 20$) or the MI + vehicle group ($n = 20$). The survival rate up to 4 weeks after MI was significantly higher in the artemisinin-treated MI group than in the vehicle-treated MI group (Fig. 2B) (65% versus 40%, $P < 0.05$). Thirteen rats in the artemisinin-treated MI group and 8 rats in the vehicle-treated MI group survived up to 28 days. However, the mean infarct size at 4 weeks after MI was similar between the artemisinin-treated and the vehicle-treated MI groups (Fig. 3) ($38.38\% \pm 4.36\%$ and $41.00\% \pm 4.40\%$, respectively, $P > 0.05$).

Echocardiographic Measurements and Hemodynamics

Cardiac function was evaluated 4 weeks after MI using echocardiography and left heart catheterization, revealing significant differences in cardiac morphology and function among the sham, vehicle-treated and artemisinin-treated groups (Table 1). LVEDP, LVESD and LVEDD were significantly higher, while FS and $dP/dt_{\max}$ were significantly lower in both the vehicle-treated group and the artemisinin-treated group than in the sham group, suggesting that the MI model was well established in the present study. However, artemisinin administration significantly inhibited ventricular remodeling and improved cardiac function, as

Table 1. Echocardiographic assessment and Hemodynamic data.

	sham	MI + vehicle	MI + artemisinin
N	9	8	13
LVEDD (mm)	3.12 ± 0.19	$5.39 \pm 0.59^{\#}$	$4.54 \pm 0.43^{\# \&}$
LVESD (mm)	2.93 ± 0.20	$4.25 \pm 0.33^{\#}$	$3.67 \pm 0.41^{\# \&}$
FS (%)	28.8 ± 2.4	$14.87 \pm 1.95^{\#}$	$20.3 \pm 2.5^{\# \&}$
EF (%)	88.25 ± 4.26	$55.75 \pm 6.25^{\#}$	$72.0 \pm 7.2^{\# \&}$
Heart rates (beats/min)	404 ± 13	406 ± 16	399 ± 12
LVESP (mmHg)	106.22 ± 7.61	$78.75 \pm 4.23^{\#}$	$83.15 \pm 5.82^{\#}$
LVEDP (mmHg)	7.53 ± 0.78	$18.21 \pm 0.90^{\#}$	$12.70 \pm 1.90^{\# \&}$
dP/dt _{max} (mmHg/s)	$5,702 \pm 385$	$3,551 \pm 482^{\#}$	$4,308 \pm 343^{\# \&}$

Data are expressed as the mean $\pm$ s.d. $^{\#}$, $P < 0.05$ vs sham group; $\&$, $P < 0.05$ vs MI + vehicle group.

Fig. 4. M-mode echocardiograms obtained from two groups. Representative M-mode traces in the MI + vehicle group (A) and the MI + artemisinin group (B) measured at 4 weeks after MI. EDD indicates end-diastolic diameter; ESD indicates end-systolic diameter.

shown by significant increases ($P < 0.05$) in FS, EF and dP/dt_{max}, and significantly decreased LVEDP, LVESD and LVEDD compared to the vehicle-treated group (Fig. 3). These results suggest that LV dysfunction after MI was significantly ameliorated by artemisinin. The infarct size was evaluated after hemodynamic evaluation in each rat. Because the infarct size did not differ between the vehicle-treated group and the artemisinin-treated group, the differences in cardiac function were not attributable to the infarct size variation.

Amelioration of Myocyte Hypertrophy by artemisinin at the Peri-infarcted Zone

Cross-sectional areas of cardiomyocytes in the peri-infarcted zone of the myocardium were evaluated with HE staining (Fig. 5B). As summarized in Fig. 5C, 4 weeks after MI, the cross-sectional area of cardiomyocytes in the peri-infarcted zone of the myocardium was significantly increased both in the MI group and the artemisinin-treated MI group compared with the sham group ($293.00 \pm 18.48 \mu\text{m}^2$ versus $218.50 \pm 12.03 \mu\text{m}^2$ and $258 \pm 18.45 \mu\text{m}^2$ ver-

Fig. 5. Histology analysis of myocardial hypertrophy in the peri-infarcted zone 4 weeks after MI.

(A) The peri-infarcted zone and infarcted zone. (B) HE staining showed (magnification of $\times 400$) in the corresponding zone in the sham group, the peri-infarcted zone in the MI + vehicle group and the MI + artemisinin group. (C) Summarized data of the cross-sectional area of cardiomyocytes in different groups. The values are the mean $\pm$ S.D. # $P < 0.05$ vs. sham group; & $P < 0.05$ vs. MI+vehicle group.

218.50.00 $\pm$ 12.03 μm^2 , respectively, $P < 0.05$). However, myocyte hypertrophy was significantly attenuated in the artemisinin-treated group (293.00 $\pm$ 18.48 μm^2 versus 258 $\pm$ 18.45 μm^2 , $P < 0.05$).

Effects of artemisinin on cardiac fibrosis in the non-infarcted area

Reactive fibrosis in the non-infarcted area adversely affects myocardial stiffness, leading to cardiac dysfunction (Weber and Brilla 1991). We examined myocardial fibrosis 4 weeks after MI induction by a quantitative histological analysis of Mallory-Azan-stained sections and found a significantly higher extent of perivascular and interstitial fibrosis in the non-infarcted area of vehicle group and the artemisinin group compared with that of the sham group. However, the perivascular and interstitial fibrosis in the non-infarcted area was significantly attenuated in the artemisinin-treated group (Fig. 6 and Fig. 7).

Artemisinin inhibits phospho-IkB α protein expression

NF- κ B, a heterodimeric cytosolic protein, is kept inactive in resting cells by binding with a member of the I κ B α inhibitor protein family. Activation of NF- κ B involves the phosphorylation and subsequent proteolytic degradation of the inhibitory protein I κ B α by specific I κ B kinases. The free NF- κ B then passes into the nucleus, where it binds to the kappaB (κ B) site in the promoter or enhancer of several specific genes, including those involved in inflammatory reactions (Li and Verma 2002). Four weeks after MI, we examined the protein levels of phosphorylated-I κ B α (p-I κ B α) and I κ B α in the non-infarcted myocardium using western blot analysis and found that the p-I κ B α /I κ B α ratio in the vehicle group was significantly higher than that of the sham group (1.32 $\pm$ 0.03 versus 0.91 $\pm$ 0.03; $P < 0.05$), while the p-I κ B α /I κ B α ratio in the sham group was almost the same as that in the artemisinin group (0.91 $\pm$ 0.03 versus 0.92 $\pm$ 0.02; $P > 0.05$), indicating that artemisinin may completely block I κ B α phosphorylation. Accordingly, we speculate that artemisinin inhibited NF- κ B activation by

Fig. 6. Histology analysis of myocardial fibrosis in the perivascular area 4 weeks after MI.

(A) Mallory-Azan-stained showed (magnification of $\times 400$) in the perivascular area of corresponding zone in the sham group, the peri-infarcted zone in the MI + vehicle group and the MI + artemisinin group. Arrows indicate the myocardial fibrosis in the perivascular area. (B) Summarized data of the myocardial fibrosis in the perivascular area in different groups. The values are the mean $\pm$ s.d. $^{\#}P < 0.05$ vs. sham group; $^{\&}P < 0.05$ vs. MI + vehicle group.

Fig. 7. Histology analysis of myocardial fibrosis in the interstitial area 4 weeks after MI.

(A) Mallory-Azan-stained showed (magnification of $\times 400$) in the interstitial area of corresponding zone in the sham group, the peri-infarcted zone in the MI + vehicle group and the MI + artemisinin group. (B) Summarized data of the myocardial fibrosis in the interstitial area in different groups. The values are the mean $\pm$ s.d. $^{\#}P < 0.05$ vs. sham group; $^{\&}P < 0.05$ vs. MI+vehicle group.

preventing I κ B α phosphorylation and degradation, consistent with a previous study (Li et al. 2000) (Fig. 8).

Effects of artemisinin on expression of TGF- β 1 and collagen type I protein

TGF- β 1 plays an important role in the pathogenesis of

cardiac remodeling and fibrosis after MI. In the infarcted heart, TGF- β 1 expression is upregulated, promoting the trans-differentiation of myofibroblasts and collagen type I protein synthesis through Smad3-dependent pathways (Bujak et al. 2007). To investigate the mechanism of the artemisinin-mediated attenuation of ventricular remodeling

Fig. 8. Western blot analysis of the phospho-IKB α and IKB α proteins after MI. (A) Representative western blots for phospho-IKB α , IKB α proteins. The β -actin level was used as an internal control. (B) Immunoblot signals for phospho-IKB α and IKB α were quantified by densitometry, and the intensities were normalized to that of β -actin. The values are the mean $\pm$ S.D. [#] $P < 0.05$ vs. sham group; [&] $P < 0.05$ vs. MI + vehicle group.

after MI, we examined expression levels of TGF- β 1 and collagen I proteins in the non-infarcted myocardium by western blot analysis. TGF- β 1 and collagen I protein levels were significantly increased in the vehicle group compared with the sham group. In contrast, the increased expression of TGF- β 1 and collagen I was significantly reduced in the artemisinin group compared with the vehicle group. Compared with the sham group, the level of TGF- β 1 protein in the non-infarcted myocardium was significantly higher in the artemisinin-treated group. However, the level of collagen I protein is no significant difference between sham group and artemisinin-treated MI group. These results indicate that artemisinin can reduce TGF- β 1 and collagen I protein expression effectively, helping to prevent ventricular remodeling (Fig. 9).

Effect of artemisinin on MMP-2 and MMP-9 expression

To further investigate the mechanism by which artemisinin ameliorates myocardial remodeling, we analyzed the expression of MMP-2 and MMP-9, which play important roles in the degradation of extracellular matrix (ECM) macromolecules following MI (Ducharme et al. 2000; Hayashidani et al. 2003). The expression levels of MMP-9 and MMP-2 in the non-infarcted myocardium at 4 weeks after MI induction were significantly increased in the vehicle group compared with those in the sham group. These increased expression levels were significantly reduced in the artemisinin group compared with those in the vehicle group. However, compared with the sham group, the level

of MMP-9 protein in the non-infarcted myocardium was significantly higher in the artemisinin-treated group. Importantly, the level of MMP-2 protein was similar between sham group and artemisinin-treated MI group. These results indicate that artemisinin attenuates left ventricular remodeling by restoring the expression of MMP-2 and MMP-9 directly and/or indirectly (Fig. 9).

Discussion

To our knowledge, the present study is the first to demonstrate that artemisinin inhibits ventricular remodeling and improves cardiac function and survival after MI. The cardioprotective effect of artemisinin is made possible by the inhibition of NF- κ B signaling pathways, resulting in the inhibition of inflammation and ventricular remodeling and ultimately preventing cardiac dysfunction. Our findings suggest that artemisinin could be an effective preventive and therapeutic candidate against ventricular remodeling and heart failure after MI.

MI is commonly complicated by maladaptive LV remodeling, which refers to alterations in LV chamber mass, geometry, and function. Remodeling is a chronic process, mediated by progressive structural changes in cardiomyocytes and the extracellular matrix (ECM) and interstitial fibrosis, leading to LV dilatation (Cohn et al. 2000). This adverse LV remodeling causes depressed cardiac performance and is an independent determinant of morbidity and mortality after MI (Mann 1999). In the present study, we created a rat model of MI to exhibit LV enlargement and

Fig. 9. Western blot analysis of the TGF- β 1, collagen type I, MMP-2 and MMP-9 proteins after MI. (A) Representative western blot analysis for TGF- β 1, collagen type I, MMP-2 and MMP-9 in the non-infarcted myocardium at 4 weeks after MI induction. The β -actin level was used as an internal control. (B) Immunoblot signals for TGF- β 1, collagen type I, MMP-2 and MMP-9 were quantified by densitometry, and the intensities were normalized to that of β -actin. The values are the mean $\pm$ s.d. [#] $P < 0.05$ vs. sham group; [&] $P < 0.05$ vs. MI+vehicle group.

its dysfunction, which resulted in high mortality rates up to 4 weeks after MI. Although the infarct size in the LV was similar in the vehicle and the artemisinin groups, LV geometric, structural, and functional remodeling was improved in the artemisinin group with much lower mortality rates and less cardiac dysfunction. Our findings indicate that artemisinin could attenuate ventricular remodeling after MI.

Several mechanisms may have contributed to attenuate LV remodeling by artemisinin treatment. First, myocardial hypertrophy of the peri-infarct zone plays an important role in ventricular remodeling. There is evidence suggesting that NF- κ B activation is a causal event in the cardiac hypertrophy response (Purcell et al. 2001; Gupta et al. 2002). Purcell showed that NF- κ B activation is necessary and sufficient to produce a hypertrophic response through G protein binding to isolated cardiocyte receptors (Purcell et al. 2001). Additionally, blocking NF- κ B ameliorates myocardial hypertrophy in response to the chronic infusion of angiotensin (Kawano et al. 2005). Similarly, Xiong et al. (2010) reported that artemisinin attenuates myocardial hypertrophy in response to aortic banding via the inhibition of NF- κ B activation. In the present study, we found that

artemisinin inhibits NF- κ B activity by preventing the degradation of I κ B α , consistent with a previous study (Li et al. 2000). At the same time, myocardial hypertrophy of the peri-infarct zone was significantly ameliorated by artemisinin treatment, indicating that artemisinin attenuates ventricular remodeling at least in part by anti-myocardial hypertrophy in the peri-infarct zone. The possible mechanism is related to the inhibition of NF- κ B activation.

Second, interstitial fibrosis was aggravated by inflammatory factor stimulation, which was also included in the ventricular remodeling. NF- κ B is a key transcription factor that regulates inflammatory processes (Barnes and Karin 1997). Following MI, activation of the NF- κ B signaling pathway induces an inflammatory reaction, increasing TGF- β 1 expression. It is known that TGF- β 1 plays a key role in the development of myocardial fibrosis by modulating fibroblast conversion to myofibroblasts and extracellular matrix production (Border and Noble 1994). In the present study, artemisinin suppressed TGF- β 1 expression and prevented interstitial fibrosis, indicating that artemisinin attenuates ventricular remodeling, possibly by inhibiting TGF- β 1 expression.

Finally, ECM turnover is involved in LV remodeling. Various members of the MMP family have been described to mediate post-MI LV remodeling (Spinale et al. 1998; Mukherjee et al. 2003; Yarbrough et al. 2003). Specifically, MMP-9 and MMP-2 are recognized as major contributors. The targeted deletion of MMP-9 and MMP-2 results in significantly reduced LV enlargement following MI (Ducharme et al. 2000; Hayashidani et al. 2003). In our study, MMP-2 and MMP-9 protein levels were significantly lower in the non-infarcted myocardium of the artemisinin-treated group compared to the vehicle-treated group. This may explain the inhibition of progressive LV enlargement in the artemisinin-treated group. However, the mechanism of artemisinin inhibition of MMP-2 and MMP-9 expression still remains unclear. Previous studies have documented that the induction or stimulation of MMPs at the transcriptional level is mediated by a variety of inflammatory cytokines, hormones, and growth factors, many of which are regulated by NF- κ B (Meikle et al. 1992; Han et al. 2001; Xie et al. 2004; Friehs et al. 2006). Taking all of these into consideration, we speculate that artemisinin inhibits the expression of MMP-9 and MMP-2 through NF- κ B pathway inhibition, acting as one of the mechanisms by which artemisinin attenuates ventricular remodeling after MI.

Several limitations of the present study must be mentioned. First, we cannot exclude the possibility that the administration of artemisinin in advance of or during the hyperacute period of MI may cause myocardial rupture or the progression of LV remodeling via the retardation of wound healing. Although no unfavorable effects of artemisinin were observed in the present study, additional experiments with various treatment timings are desirable. Second, the effects of continuous administration and various dosages of artemisinin should be analyzed to determine the most appropriate timing and dose of artemisinin for the treatment of cardiac remodeling. Third, if there had been an additional experimental group, artemisinin-treated sham group, to elucidate the effects of artemisinin alone on the rat heart, our results would have been more convincing. Fourth, the rats used in the MI model of this study were only 12 weeks old, while MI primarily occurs in aged patients clinically. Finally, if we had compared the effect of artemisinin with that of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) on ventricular remodeling after myocardial infarction, the results of this study may have had a greater impact.

In conclusion, artemisinin can inhibit ventricular remodeling and improve cardiac function following MI. The cardioprotective effect of artemisinin is possibly caused by the interruption of NF- κ B signaling pathways, resulting in the inhibition of inflammation and ventricular remodeling and ultimately preventing cardiac dysfunction.

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Conflict of Interest

The authors declare no conflict of interest.

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