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ORIGINAL ARTICLE

Resolvin D1 Attenuates Myocardial Infarction in a Rodent Model with the Participation of the HMGB1 Pathway

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Abstract

Purpose Myocardial infarction (MI) is associated with high morbidity and mortality worldwide. This study aimed to explore the roles of resolvin D1 (RvD1), a metabolite of omega-3 polyunsaturated fatty acids, in protection against MI and investigate its influences on high mobility group box 1 protein (HMGB1) and related molecular mechanisms.

Methods Three-month-old male Sprague–Dawley rats were divided into five groups: sham, MI, MI+0.02 μg RvD1, MI+0.1 μg RvD1, and MI+0.3 μg RvD1. Vehicle control or different doses of RvD1 were injected into the left ventricle (LV) cavity 5 min before MI induction. During MI induction, myocardial ischemia lasted for 45 min followed by 180 min of reperfusion. After the reperfusion, blood and LV samples were collected for biochemical examination.

Results The MI group produced a significant increase in myocardial infarct size, serum cardiac biomarkers (LDH and CK-MB), proinflammatory cytokines (TNF-α and IL-6), and MDA levels, and a significant decrease in SOD level compared with the sham group. Moreover, a significant upregulation of gene and protein expressions of HMGB1 and its related TLR4 and NF-κB were observed in the MI group when compared with the sham group. Pretreatment of RvD1 ameliorated the biochemical changes caused by MI.

Conclusions Our results suggested that RvD1 pretreatment exhibited protective effects against MI through downregulation of HMGB1 and its related TLR4 and NF-κB expressions.

Keywords Resolvin D1 · Myocardial infarction · High mobility group box 1 · Inflammation · Oxidative stress

Introduction

Myocardial infarction (MI), caused by occlusion of the coronary artery [1], is a leading cause of mortality and morbidity worldwide despite the development of emergency medical services, pharmacological treatment, and surgical technique [2]. In cases of MI, rapid reperfusion is the most important way to salvage myocardial tissue from necrosis and reduce the size of infarct tissue. However, reperfusion is usually followed by exacerbated tissue injury and remarkable inflammatory response [3, 4]. Previous reports have suggested that the ischemia/reperfusion-induced damage to the myocardium is related to increased reactive oxygen species (ROS) levels, which can lead to cellular membrane injury with consequent alterations in metabolic processes [5, 6], therefore an antioxidative therapy prior to ischemia may promote the survival of the myocardium during MI [7]. Some researches have also indicated that proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), are quickly elevated in the infarcted myocardium [8, 9], but the exact role these proinflammatory cytokines play during MI remains unclear.

According to previous reports, omega-3 polyunsaturated fatty acid (PUFA)-rich fish oil has multiple effects on the cardiovascular system, including antiarrhythmic, antithrombotic, antiatherosclerotic, and blood pressure-lowering [10, 11]. Resolvin D1 (RvD1) comes from omega-3 PUFA docosahexaenoic acid (DHA) metabolites [12] and was reported to reduce myocardial damage during infarction due to its anti-inflammatory properties and promotion of resolution of inflammation in different models [13–15].

High-mobility group box-1 (HMGB1) has been recognized as a cytokine which can be passively released by cells

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undergoing necrotic cell death. HMGB1 triggers inflammatory responses through its ability to bind the receptor to activate nuclear factor kappa B (NF-κB) [16, 17]. Toll-like receptor 4 (TLR4) has been recognized as a mediator of inflammation and organ injury in different models [18, 19] and was also shown to be activated by HMGB1 [20]. Many studies demonstrated that HMGB1 has a role in numerous cardiovascular diseases, such as atherosclerosis, myocardial I/R injury, MI, and heart failure [21, 22].

In light of these evidences, this study has been designed to evaluate the effect of RvD1 on attenuating MI and investigate the underlying mechanisms associated with HMGB1 expression in the LAD ligation-induced experimental MI rat model.

Methods and Materials

Rat Model of Myocardial Infarction

The study was approved by the Institutional Review Board of Liaocheng People's Hospital. Three-month-old male Sprague–Dawley rats (weight, 250–300 g) were housed under constant conditions with a humidity of 40–50% and a temperature of 21–22 °C, including a 12-h light-dark cycle beginning at 8:00 a.m. Rats were supplied with free access to water and standard rodent chow pellets.

RvD1 (17(S)-RvD1) was obtained from Cayman Chemical (Ann Arbor, MI, USA) and dissolved in NaCl 0.9%. According to previous reports [15, 23], the plasma level of RvD1 after a 0.1-μg injection is similar to the level obtained with a high omega-3 PUFA diet, and showed a cardioprotective effect. Different doses of RvD1 (0.02 μg, 0.1 μg, or 0.3 μg) were selected in this study to evaluate the dose-dependent effect of RvD1 on MI. The rats were randomly assigned to five groups: sham, MI, MI+0.02 μg RvD1, MI+0.1 μg RvD1, and MI+0.3 μg RvD1. Vehicle (NaCl 0.9%) or different doses of RvD1 were injected directly into the left ventricle (LV) cavity 5 min before MI induction. The MI rat model was established as described previously [23]. In brief, anesthesia was induced by intraperitoneal injection of 60 mg/kg ketamine and 10 mg/kg xylazine, separately. Electrocardiograms and heart rate of rats were monitored throughout the surgical procedure. Left thoracotomy at the 5th intercostal space enabled occlusion of the left anterior descending coronary artery (LAD) with 4–0 silk suture and plastic snare. After 40 min of ischemia, with confirmation by ST segment alterations and the presence of ventricular cyanosis, the suture was removed and reperfusion was permitted for 180 min. The sham operation group rats received surgery without LAD ligation. At the end of the reperfusion period, rats were sacrificed under anesthesia through blood and tissue collection.

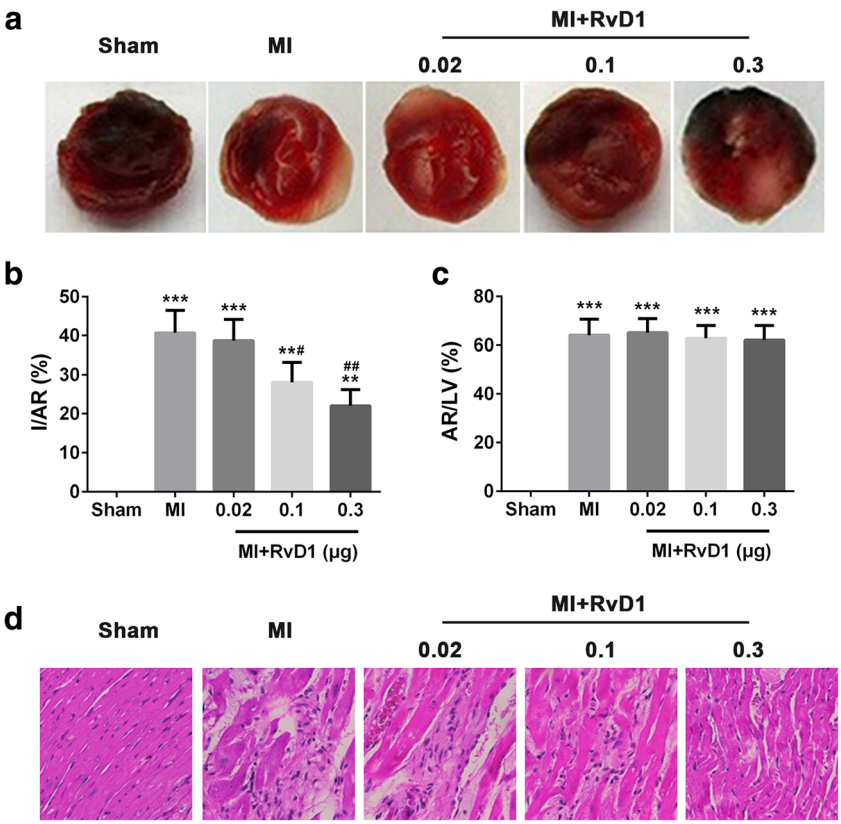

Fig. 1 RvD1 reduces myocardial infarction size and protects cardiomyocyte in MI rats. Rat myocardial slice stained by Evans Blue and TTC (**a**). The MI size was expressed as a percentage of the AR: area at risk (I/AR) (**b**), and AR was expressed as a percentage of the left ventricle (LV) (AR/LV) (**c**). Rat myocardial slice stained by HE (**d**). Data are presented as mean ± SD, $n = 10$ per group, $^{**}p < 0.01$, $^{***}p < 0.001$ compared to the sham group. $\#p < 0.05$, $\#\#p < 0.01$ compared to the MI group. Scale bar = 50 μm

Assessment of Infarct Size

Myocardial infarct size was measured according to a previously reported method [24]. After 180 min of reperfusion, the rat LAD was reoccluded and 0.5% Evans Blue (Sigma-Aldrich, St. Louis, MO) was injected intravenously to identify the area at risk (AR). Then, the rats were sacrificed and their hearts were immediately removed and frozen at − 80 °C for 5 min. The LV was sliced into four transverse 2-mm sections and incubated in 2,3,5-triphenyltetrazolium chloride solution (1% TTC, pH 7.4) (TTC, Shanghai Solarbio Bioscience & Technology Co., LTD) at 37 °C for 20 min to better distinguish the area of infarction (I). The normal myocardium was stained blue, the ischemic myocardium was stained light red, and the infarcted myocardium appeared pale white. MI was expressed as percentage of the AR ((I/AR) %)), and the AR was expressed as percentage of the LV area ((AR/LV) %).

LV Histological Examination

Myocardial tissues of LV were fixed in 4% paraformaldehyde, embedded in paraffin, and subsequently sectioned into 5-mm slices. The paraffin sections were subjected to hematoxylin and eosin (HE) staining and were subsequently analyzed under an optical microscope.

Enzyme-Linked Immunosorbent Assay

Blood samples were collected via cardiac puncture and centrifuged at 4 °C, and the serum obtained was stored at − 80 °C until required. The hearts were harvested and washed with normal saline. LV tissue was homogenized at 0–4 °C and the homogenate was centrifuged, and the supernatant was collected and stored at − 80 °C until required. Commercially available kits (Bio-Source Inc.) were used to detect the levels of CK-MB, LDH, SOD, MDA, TNF-α, and IL-6 in serum or LV according to the manufacturer's protocol.

Western Blot Analysis

LV tissues were homogenized in RIPA lysis buffer, and total protein was quantified. Extracted protein from studied groups was separated by SDS-PAGE and electroblotted onto PVDF membranes. After incubation in 5% nonfat dry milk, Tris-HCl, 0.1% Tween 20 for 1 h, primary antibodies, TLR4, HMGB1, and NF-κB (Santa Cruz, Dallas, TX, USA) were added and incubated at 4 °C overnight. Appropriate secondary antibodies were incubated for 2 h at room temperature. Protein bands were analyzed using the ChemiDoc imaging system (Bio-Rad, CA, USA).

Real-Time Quantitative PCR

Real-time quantitative PCR (qPCR) was performed as previously described [25]. Briefly, total RNA from LV tissue was isolated and analyzed for quantity and quality. For quantitative expressions of TLR4, HMGB1, and NF-κB, the total RNA from each group was used for reverse transcription by using High-Capacity cDNA Reverse Transcriptase kit (Applied Biosystems, Waltham, MA, USA). After that, the cDNA was amplified with the SYBR Green PCR Master Mix Kit (Applied Biosystems). The primer sequences used were as follows: TLR4 (forward primer: 5′-CGGAAAGTTATTGTGGTGGTGT-3′, reverse primer: 5′-GGACAATGAAGATGATGCCAGA-3′), HMGB1 (forward primer: 5′-CCGGATGCTTCTGT CAACTT-3′ reverse primer: 5′-TTGATTTTTGGGCG GTACTC-3′), NF-κB (forward primer: 5′-AGAG CAACCGAAACAGAGAGG-3′, reverse 5′-TTTG

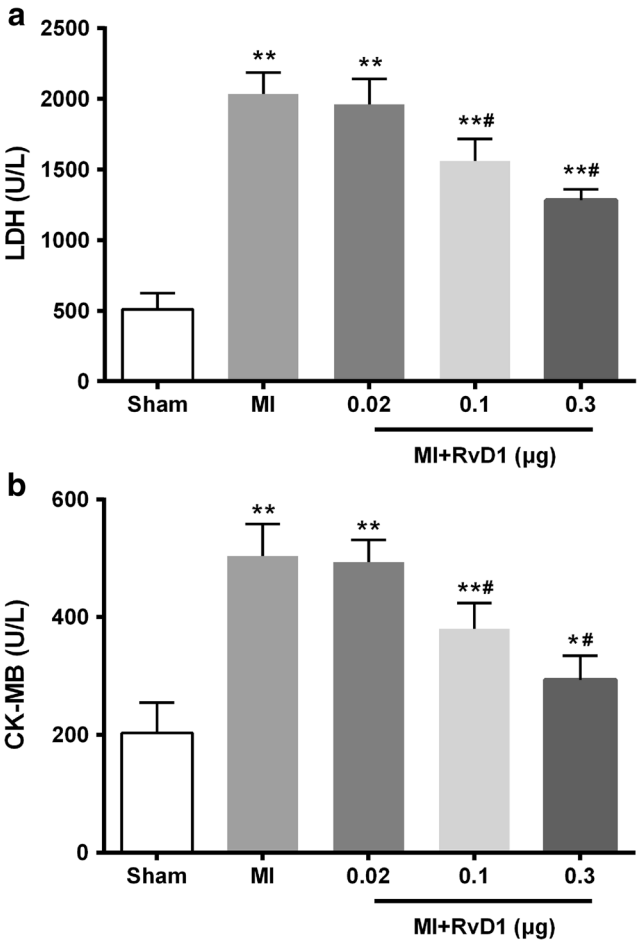

Fig. 2 Effects of RvD1 on cardiac biomarker levels in serum. Lactate dehydrogenase (LDH) (**a**) and creatine kinase-MB (CK-MB) (**b**) levels were detected. Data are presented as mean ± SD, $n = 10$ per group, $^{*}p < 0.05$, $^{**}p < 0.01$ compared to the sham group. $\#p < 0.05$ compared to the MI group

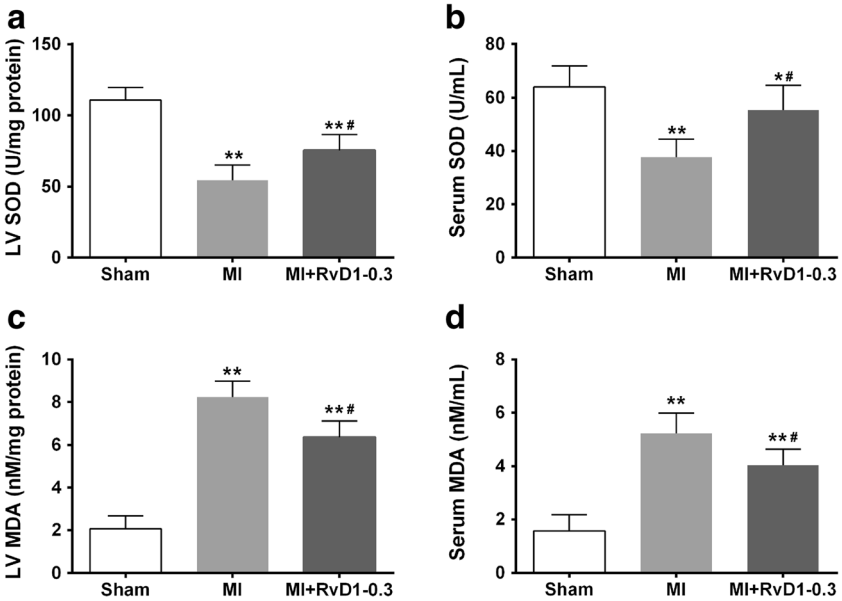

Fig. 3 Effects of RvD1 on SOD and MDA levels in LV tissues and serum of MI rats. The levels of SOD (**a**, **b**) and MDA (**c**, **d**) from LV and serum were determined by ELISA. Data are presented as mean ± SD. $n = 10$ per group. $^{*}p < 0.05$, $^{**}p < 0.01$ compared to the sham group. $\#p < 0.05$ compared to the MI group

CAGGCCCCACATAGTT-3′), and GAPDH (forward primer: 5′-CCCCTTCATTGACCTCAACTACATGG-3′ reverse primer: 5′-GCCTGCTTCACCACCTTCTT GATGTC-3′). Changes in the expressions were analyzed.

Statistical Analysis

One-way ANOVA analysis followed by the Bonferroni post hoc test was used for determining significant differences between groups. Statistical analyses were carried out via SPSS software 11.0. Statistical difference was considered significant at $p < 0.05$.

Results

RvD1 Pretreatment Alleviated the Infarct Size and Showed Cardioprotective Effects

MI size (I) was expressed as percentage of the area at risk (AR) and was significantly different between groups. As shown in Fig. 1a, no area at risk (AR) and infarct size (I) was observed in the sham group. LAD ligation-induced MI in the control group showed the I/AR ratio of 40.83% ± 7.19% (Fig. 1b). However, the I/AR ratio was reduced in the RvD1 0.1 and 0.3-μg groups (26.69% ± 7.05% and 23.01% ± 5.32%) compared with that in the control group ($p < 0.05$ or

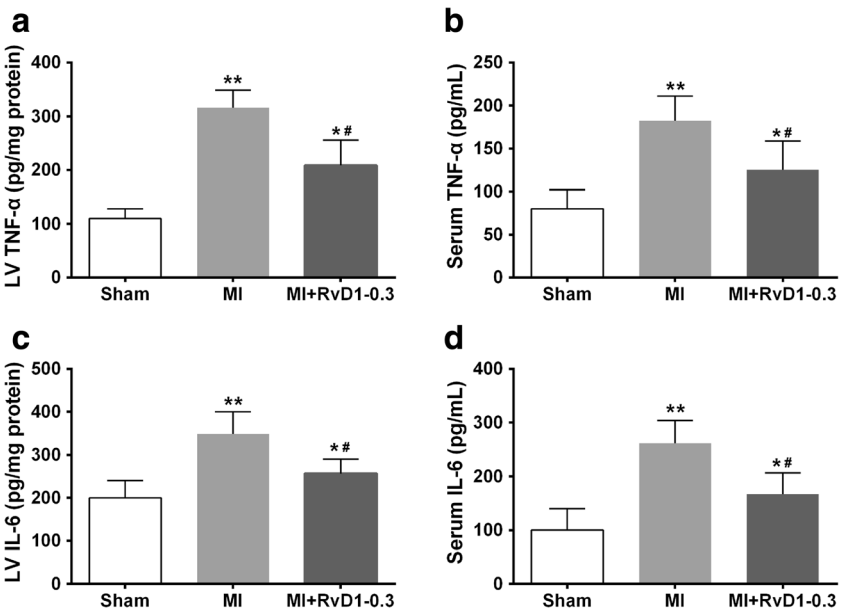

Fig. 4 Effects of RvD1 on the proinflammatory cytokine levels in LV tissues and serum of MI rats. The levels of TNF-α (**a**, **b**) and IL-6 (**c**, **d**) from LV and serum were determined by ELISA. Data are presented as mean ± SD. $n = 10$ per group. $^{*}p < 0.05$, $^{**}p < 0.01$ compared to the sham group. $\#p < 0.05$ compared to the MI group

$p < 0.01$), while there was no significantly statistical difference for the RvD1 0.02-μg group. The AR, expressed as percentage of the LV, was similar between groups except for the sham group, representing about 60% of the LV (Fig. 1c).

Inflammatory cell infiltration and cellular morphology were detected by HE staining (Fig. 1d). The LV myocardium was arranged in a regular pattern, which was well preserved in the sham group, while large necrotic areas with fragmentation, pyknosis, and karyorrhexis were observed in the LV myocardium of the MI group. Inflammatory cell infiltration could be seen, and the surviving cardiomyocytes formed an irregular pattern in the MI group as well. With high RvD1 dose treatment (0.3 μg), pyknosis, karyorrhexis, and inflammatory cell infiltration were markedly decreased, while the cardiomyocyte damage was partially improved. The improvement in the 0.02-μg RvD1 group was not obvious.

Effects of RvD1 on Myocardial Enzymes

The activity of myocardial enzymes (LDH and CK-MB) in serum is shown in Fig. 2a and b. The levels of LDH and CK-MB were significantly ($p < 0.01$) elevated in the serum of the LAD ligation-induced MI group compared with the sham group. Effects of RvD1 on myocardial enzymes were similar to infarct size; they were both dose-dependent. Myocardial enzymes in groups pretreated with 0.1 μg and 0.3 μg of RvD1 were significantly ($p < 0.05$) reduced compared to the LAD ligation-induced MI group, but no significantly statistical difference for the RvD1 0.02-μg group.

Effects of RvD1 on SOD and MDA

Since 0.3 μg of the RvD1 pretreated group showed the greatest effect on the infarct size and myocardial enzymes compared with the RvD1 0.02 and 0.1-μg groups, only the RvD1 0.3-μg group was used to test the effects of RvD1 on SOD and MDA levels in LV tissues and serum. SOD levels were significantly lower, and MDA levels were significantly higher in the LAD ligation-induced MI group compared with the sham group (Fig. 3a, b, $p < 0.01$). With the treatment of 0.3 μg of RvD1, the LAD ligation-induced increase in MDA and reduction in SOD levels were significantly inhibited (Fig. 3c, d, $p < 0.05$ vs. the MI group).

Effects of RvD1 on TNF-α and IL-6

ELISA analysis revealed TNF-α and IL-6 levels in LV tissues and serum. TNF-α and IL-6 levels were significantly higher in both LV tissues and serum in the LAD ligation-induced MI group compared with the sham group (Fig. 4a–d, $p < 0.01$). With the treatment of 0.3 μg of RvD1, the LAD ligation promoted an increase in TNF-α and IL-6 levels were significantly inhibited (Fig. 4, $p < 0.05$) compared with the MI group.

Effects of RvD1 on HMGB1

Compared with the sham group, HMGB1 protein and mRNA expressions in LV tissues were significantly upregulated by 2.6-fold and 3.3-fold, respectively, in the MI group (Fig. 5a–c $p < 0.01$). With the pretreatment of 0.3 μg of RvD1, HMGB1 protein and mRNA levels (1.9-fold and 2.2-fold of the sham group, respectively) were downregulated (Fig. 5, $p < 0.05$) compared with the MI group (2.6-fold and 3.3-fold of sham group).

Effects of RvD1 on TLR4 and NF-κB

The protein and mRNA expressions of TLR4 (1.7-fold and 2.0-fold, respectively, Fig. 6a–c) and NF-κB (2.3-fold and

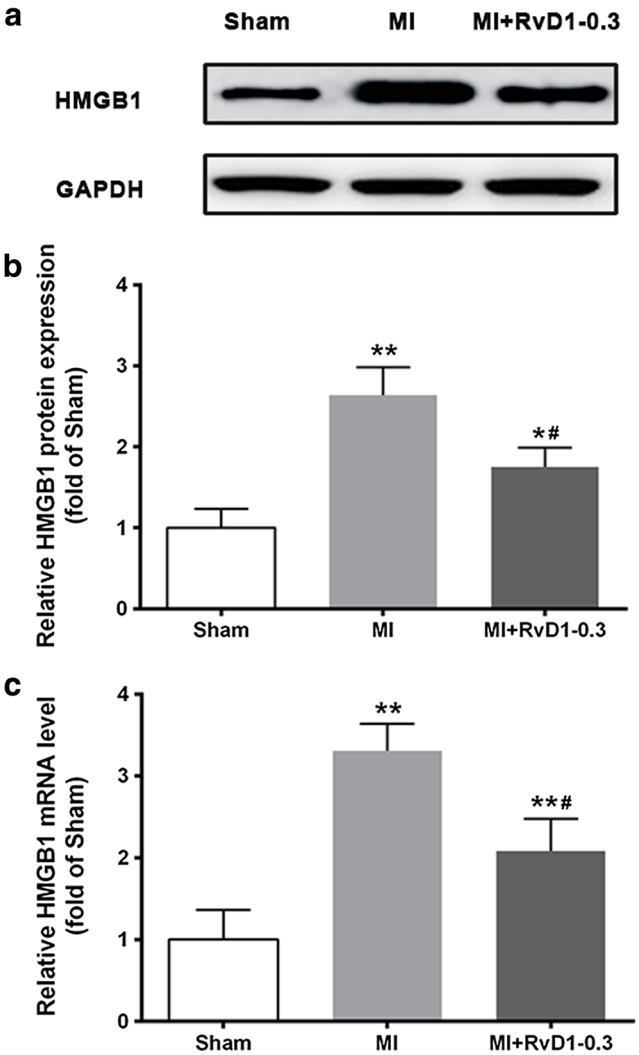

Fig. 5 Effects of RvD1 on HMGB1 protein and mRNA levels in LV tissues of MI rats. Protein expression of HMGB1 (**a**) was detected by western blot, and relative levels of HMGB1 protein (**b**) from western blot and mRNA (**c**) from qRT-PCR were analyzed. Data are presented as mean ± SD. $n = 10$ per group. $^{*}p < 0.05$, $^{**}p < 0.01$ compared to the sham group. $\#p < 0.05$ compared to the MI group

3.1-fold, respectively, Fig. 6a, d, e) in LV tissues were upregulated in the MI group compared with the sham group (Fig. 6, $p < 0.01$). With the pretreatment of 0.3 μg of RvD1, the increase in protein and mRNA levels of TLR4 (1.4-fold and 1.6-fold, respectively) and NF-κB (1.7-fold and 1.9-fold, respectively) was significantly inhibited (Fig. 6, $p < 0.05$) compared with the MI group.

Discussion

MI is usually accompanied by the occurrence of post-ischemic arrhythmia, cardiomyocyte death, myocardial stunning, and a no-reflow phenomenon and results in high mortality rates in MI patients [26]. An MI-induced interaction between LV remodeling and renal dysfunction is known as advanced cardiorenal syndrome, which contributes to progressive heart failure and kidney failure [27]. In this case, developing efficient therapies and agents for MI treatment is essential and urgent.

RvD1, a metabolite of omega-3 PUFA, has been used as a new agent in different animal models, such as skin infection, sepsis, peritonitis, and gingivitis models [28, 29], and it was proven that RvD1 can alleviate the injuries, protect the tissues, and increase the survival rate of animals by its anti-inflammatory property [30]. Recently, studies on the protective effect of RvD1 on ischemic injury in the brain, and the heart have just been reported [23, 31].

Pharmacological functions of RvD1 were tested in different MI models, and RvD1 showed its therapeutic utility in cardioprotection, post-MI cardiac healing, and protection from heart failure [32]. RvD1 and other resolvin molecules were confirmed to be present in the infarcted LV compared with no-MI controls [33], which suggested that RvD1 may play an important role in the pathophysiology of heart failure, but the underlying mechanism is still not clear. Gilbert et al. [15] confirmed that myocardium infarct size in the MI rat model was reduced by intraventricular administration of 0.1- or 0.3-μg RvD1 with the involvement of the PI3K/Akt pathway, as the cardioprotective function of RvD1 could be abolished by PI3K/Akt inhibitors. In recent reports, Kain et al. [27, 34] demonstrated that RvD1 promoted the resolution of inflammation initiated by MI by limiting the activation of neutrophils and clearing macrophages in the LV to improve cardiac functions.

CK-MB and LDH are sensitive markers of MI; when MI occurs, the levels of CK-MB and LDH increase and they are thought to be related to the degree of myocardial infarct [35, 36]. Therefore, LDH and CK-MB are often thought as biochemical markers to diagnose and monitor myocardial injury induced by MI. TNF-α and IL-6 are important proinflammatory factors that are over-released during MI which can induce cardiac dysfunction and increase infarct size after MI [37], while RvD1

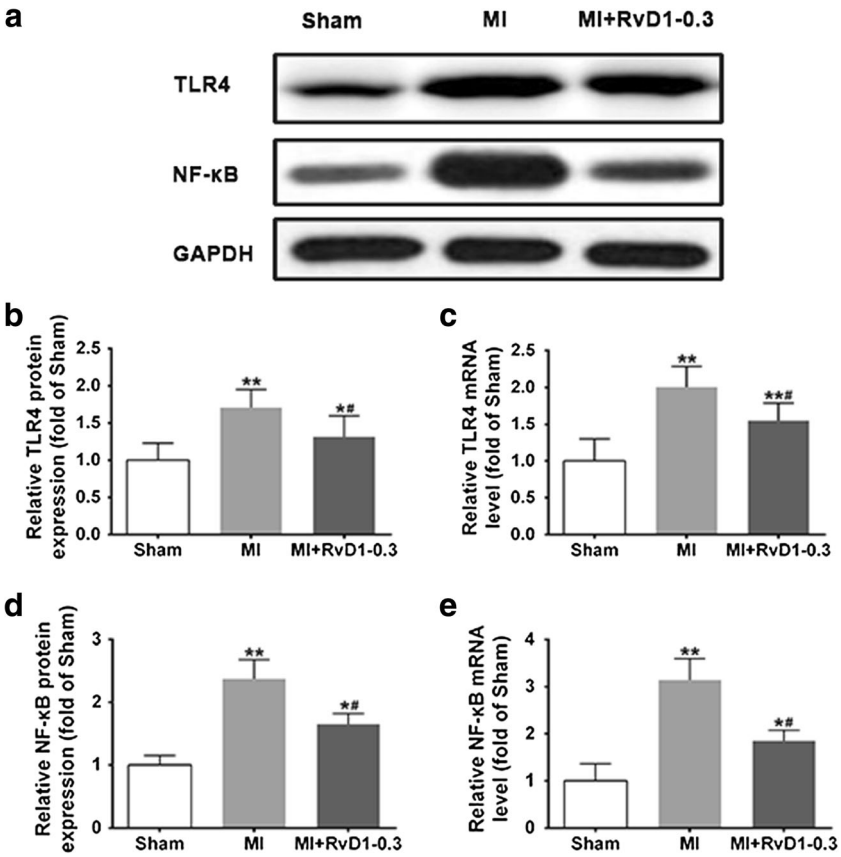

Fig. 6 Effects of RvD1 on protein and mRNA levels of TLR4 and NF-κB in LV tissues of MI rats. Protein expressions of TLR4 and NF-κB (**a**) were detected by western blot, and relative levels of TLR4 and NF-κB protein (**b**, **d**) from western blot and mRNA (**c**, **e**) from qRT-PCR were analyzed. Data are presented as mean ± SD. $n = 10$ per group. $^{*}p < 0.05$, $^{**}p < 0.01$ compared to the sham group. $\#p < 0.05$ compared to the MI group

showed high potential in limiting pro-inflammatory cytokines and modulating the chemokine signaling in peritoneal macrophage and cardiac fibroblast cultures in vitro [38]. When MI occurs, the damage of myocardial tissue due to ischemia is related to the oxidative stress which can lead to cellular membrane injury [5] and antioxidant therapy prior to ischemia may help the myocardium survive during MI. HMGB1 was reported to activate proinflammatory signaling pathways, such as TNF-α and IL-6, by interacting with TLR4 and NF-κB [16–19]. Recently, further evidence is supporting the viewpoint that HMGB1 is an early mediator of tissue injury and inflammation following ischemia-reperfusion of different organs [39, 40].

Our results are also consistent with this viewpoint. In LAD ligation-induced MI rats, HMGB1, TLR4, and NF-κB signaling pathways were all upregulated, proinflammatory cytokines TNF-α and IL-6 were upregulated, and oxidative stress appeared. With the pretreatment of RvD1, these changes caused by MI were suppressed: inflammatory responses were ameliorated, oxidative stress was suppressed, infarct size was significantly reduced, and the increased levels of LDH and CK-MB observed in untreated MI rats were inhibited. Histological examination confirmed the cardioprotective effect of RvD1 in the MI rat model. Both the mRNA and protein expression levels of HMGB1 and its downstream effectors, TLR4 and NF-κB, were downregulated in the RvD1-pretreated group. However, it is worthy to note that NF-κB expression is not necessarily related to increased inflammatory activities.

Our results indicated that RvD1 pretreatment ameliorated myocardial damage following MI, possibly mediated by reducing the expression of the HMGB1 pathway, which might offer a new view on MI therapy in the future. However, further research should be carried to validate this idea.

Conclusion

The present study indicates that pretreatment of RvD1 ameliorates MI by suppressing oxidative stress and inflammatory cytokines, along with downregulating mRNA and protein expressions of HMGB1, TLR4, and NF-κB, which suggests that RvD1 is a promising therapeutic agent for MI, and that the underlying mechanism may involve the HMGB1, TLR4, and NF-κB pathways.

Compliance with Ethical Standards

Conflict of Interest The authors declare that there is no conflict of interest.

Research Involving Human Participants and/or Animals All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Informed Consent Not applicable.

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