

Original Article

Mechanisms of renal sympathetic denervation on improving ventricular arrhythmias after acute myocardial infarction in rats

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Abstract: Background: More than 50% of acute myocardial infarction (MI) survivors died from malignant ventricular arrhythmias (VA). Renal sympathetic denervation (RSD) has been demonstrated to exert remarkable effects on VA, but the mechanism remains unclear. Methods: Thirty Sprague Dawley rats were divided into three groups randomly, that is Sham, MI (ligation of left anterior descending artery) and MI+RSD (ethanol ablation). Six hours after modeling, electrocardiogram was recorded. Four weeks later, the left ventricular function indexes were obtained through echocardiography, and cardiac tissues were stained by Masson trichrome for fibrotic analysis. Whole-cell patch-clamp recordings were performed to record the transient outward K⁺ current (I_{to}) and the protein expression of Kv4.2 and Kv4.3 in the left ventricle were detected using Western blot. Results: Compared to that in MI group, RSD group showed reduced incidence of premature ventricular contractions and ventricular tachycardia, increased left ventricular ejection fraction and fractional shortening, and decreased left ventricular end diastolic diameter and left ventricular end systolic diameter. RSD attenuated collagen deposition in the cardiac tissue. RSD group alleviated prolonged action potential duration ($p < 0.05$) especially APD₂₀. The I_{to} current density was significantly decreased in the MI group compared to the sham group, and was reversed by RSD. MI-induced a decreased cardiac protein expression of Kv4.2, but not that of Kv4.3, and it was restored by RSD. Conclusions: RSD reduced the incidence of VA after MI in rats. This may be due to the improvement of left ventricular function, the recovery of cardiac I_{to} density and Kv4.2 protein expression.

Keywords: Renal sympathetic denervation, ventricular arrhythmias, myocardial infarction, left ventricular function, I_{to} current, Kv4.2

Introduction

Ventricular arrhythmia (VA) is the most common complication of acute myocardial infarction (AMI), and it is also an important factor affecting prognosis [1]. Malignant ventricular arrhythmias, such as persistent ventricular tachycardia or ventricular fibrillation, are the main causes of sudden death in AMI patients [2]. The mechanism of ventricular arrhythmias mainly involves reentry and triggering [3, 4], but the VA treatment including antiarrhythmic drugs and catheter ablation are both unsatisfactory at present [5]. More than 50% of AMI survivors

died from malignant ventricular arrhythmias [6]. In recent years, the role of the plant nerve system in the occurrence of arrhythmia is becoming more and more important. The relationship between the autonomic nervous system and ventricular arrhythmia is one of the emphases in the research field of cardiac electrophysiology [7]. Substantial evidence has shown that excessive activation of the sympathetic nervous system could increase the susceptibility to ventricular arrhythmias [8]. The renal sympathetic afferent nerve is the origin of excessive activation of the central sympathetic nerve, and the central nervous system trans-

mits activation signals to the kidney, meanwhile taking signals to the heart or other highly sympathetic dominating organs [9-11]. Tsai provided the direct evidence that RSD could reduce the cardiac sympathetic nerve activity, which prompts that RSD has a potential role in reducing the incidence rate of ventricular arrhythmias. Krum [12] first proposed RSD as a new therapeutic measure for refractory hypertension, and follow-up studies found that RSD also had a therapeutic effect on ventricular arrhythmia. Ukena [13] first reported that two patients with chronic heart failure complicated with refractory ventricular arrhythmias were successfully treated by RSD. Boris [14] also reported that a patient with ventricular arrhythmias after acute ST-segment elevation myocardial infarction was effectively controlled by RSD. Armaganijan [15] took 10 patients with refractory arrhythmia and implanted them with ICD, and the results showed that the average times of the VT/VF, antitachycardia and electrical cardioversion before RSD were 28.5 (1~106), 20.5 (0~52), 8 (0~88), but they were all reduced after RSD operation 6 months later, respectively times were 0 (0~9), 0 (0~7), 0 (0~3). Evranos [16] made a similar clinical trial to Armaganijan and the results also showed that RSD could reduce the average times of the VT/VF, antitachycardia and electrical cardioversion, which suggested that RSD was an effective adjuvant therapy in the treatment of refractory arrhythmia. Linz [17] found that RSD was capable of inhibiting the occurrence of ventricular arrhythmias after acute myocardial ischemia in pigs. Conclusively, a growing body of evidence [18, 19] has confirmed that RSD could reduce the incidence of ventricular arrhythmias, but the mechanism is still unclear. In the research work of this paper, we work to reveal the mechanism of RSD on improving VA after acute myocardial infarction, by studying the relationship between RSD and multiple physiological features of the rat heart, based on the rat model of AMI-induced arrhythmias.

Materials and methods

Animals and model preparation

The Male Sprague-Dawley rats (200-250 g) were purchased from Animal Center (Wushi, Fuzhou, China) and were housed in a 12 h

dark/light cycle. The temperature was 22~25°C, and the relative humidity was 55%~60%. Thirty experimental rats were divided into three groups randomly, that is sham group (n=10), MI group (n=10) and MI+RSD group (n=10).

In the MI and MI+RSD groups, the rats were anesthetized by intraperitoneal injection of 10% chloral hydrate (3.5 mL/kg), and were ventilated at 75 breaths/min, 5.5 mL tidal volume (Rodent Ventilator, ALC-V8S, Shanghai, China). The heart was exposed and pericardium was incised. The model was produced by ligation of the left anterior descending coronary artery with 6-0 polypropylene suture approximately 3-4 mm distal from its origin. The chest was closed and lungs were reinflated using positive end-expiratory pressure. In the MI+RSD group, the bilateral renal artery and vein was exposed immediately after MI operation and the sympathetic innervation was surgically denervated by cutting all visible nerves, and then the vascular wall was daubed with absolute ethanol for 10 minutes. The rats in the sham group, the surgical procedure was performed without coronary artery ligation and RSD was performed.

TTC staining

Infarct size was assessed using TTC staining as described previously [20]. Briefly, the rat hearts were harvested and frozen at -80°C for 5 min, and then rapidly cut into 6 slices approximately 1 mm thick each. The slices were incubated with 1% triphenyl-tetrazolium chloride (TTC, Solarbio, Beijing, China) for 20 min at 37°C and then fixed in 4% formaldehyde for another 30 min. The viable perfused myocardium was colored in red and the infarcted area in white. The ratio of infarcted area to total area was calculated by computerized planimetry with ImageJ software (NIH, USA). The results were expressed in average of percentage of infarcted area on total area in the 6 slices.

H&E staining

To evaluate the effectiveness of the RSD, the renal artery sections were stained with hematoxylin and eosin (HE, Jiancheng, Nanjing, China) to label sympathetic nerves.

ECG assessment

A standard II lead of electrocardiogram (ECG) was recorded after modeling for 6 hours by using Multichannel physiological signal acquisition system (RM6240CD type, Chengdu, China). Ventricular arrhythmias observed in the ECG were classified as premature ventricular contractions (PVCs), ventricular tachycardia (VT) and ventricular fibrillation (VF) according to the Lambeth standard.

Echocardiographic assessment of left ventricular function

The echocardiogram was performed with high-resolution ultrasound (20 MHz) imaging system (Vevo 2100, Visual Sonics, Ontario, Canada). The left ventricular ejection fraction (LVEF), fractional shortening (FS), left ventricular end diastolic dimension (LVEDD) and left ventricular end systolic dimension (LVESD) were measured before the surgery and after 28 days of left anterior descending coronary artery ligation. The LVEF were defined by the formula $LVEF = (LVEDD - LVESD) / LVEDD \times 100\%$. All echocardiograms were measured in triplicate by the same sonographer, and the averages were taken for analysis.

Masson's staining

The rats were sacrificed by an overdose of chloral hydrate, and then the left ventricles were rapidly harvested and fixed in 4% neutral buffered formalin for 18 hours and embedded in optimal cutting temperature compound (OCT). Longitudinal sections (6 μ m) of hearts were prepared using a microtome. The sections were stained with Masson's trichrome (Maixing, Fuzhou, China) for measurement of fibrosis. The collagen volume fraction in the peri-infarcted areas of left ventricular was calculated by measuring the optical density of fibrotic area using ImageJ software (NIH, USA).

Cardiomyocyte isolation and whole-cell patch-clamp recording

Ventricular cardiomyocytes were isolated by enzymatic dissociation using a method previously reported [21]. Briefly, the rats were anesthetized by intraperitoneal injection of 10% chloral hydrate (3.5 mL/kg). Hearts were rap-

idly excised and the infarct border zones were harvested. Myocardial tissue was first decomposed by Ca^{2+} -free Tyrode's solution containing II type collagenase (0.5 g/L), bovine serum albumin (1 g/L) and XIV type protease (0.1 g/L) for 50 min, followed by decomposition with the similar solution containing II type collagenase (0.5 g/L) and bovine serum albumin (1 g/L) for 40 min. The whole process was carried out in constant oxygen perfusion at 37°C. The freshly isolated myocytes were centrifuged at 1000 rpm for 3 min and resuspended in KB solution, followed by resting for 3 hours and then preserved at 4°C before electrophysiological recording. The rod-shaped cells with clear cross-striation and without spontaneous contraction were selected for patch recording.

The Whole-cell patch-clamp techniques were performed by an Axopatch 200B amplifier (Axon instrument, USA). Recording pipettes with a tip resistance of 3-5 M Ω when filled with the internal pipette solution were used. For I_{to} recordings, the pipette solution contained in mM: 20 KCl, 110 K-Aspartate, 1 MgCl₂·6H₂O, 5 Na₂-Phosphocreatine, 10 HEPES, 5 K₂-EGTA, 0.1 GTP and 5 Mg₂-ATP (pH adjusted to 7.2 with KOH). 0.2 μ M BaCl₂ was used to block I_{Ca} and I_{K1} , respectively. I_{to} was elicited by a 300 ms depolarizing current stepped from -30 mV to 60 mV with 10 mV increments from a holding potential of -80 mV. The data were acquired with pCLAMP system and analyzed by Origin 7.5 software.

Western blot

The ventricle samples of infarct border zone were lysed, and total protein was extracted using RIPA Lysis Buffer. Before the experiment, the BCA method was used to determine the protein concentration. The 2 mg/mL BSA standard sample was diluted into 8 groups of 0-2000 μ g/mL gradient concentrations using deionized water, and the absorbance value corresponding to 562 nm was used as the ordinate to draw the standard concentration curve of the protein sample, and then the protein concentration of the sample to be tested was calculated according to the standard curve. The protein samples were separated on 8% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinyl-

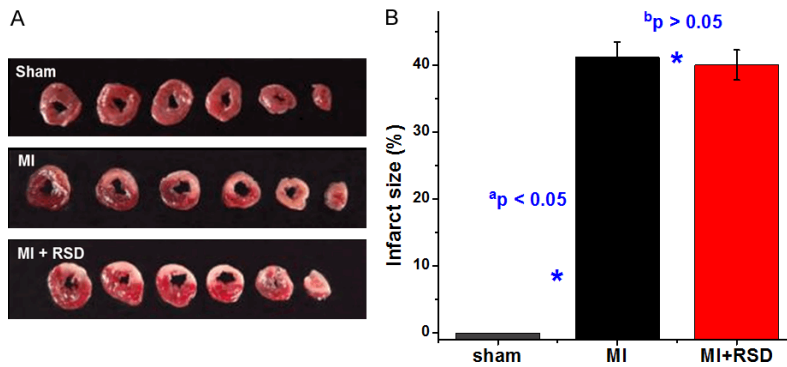


Figure 1. TTC staining was performed to measure the infarct size in rat hearts. A. Photos showed the myocardium infarction region was stained white, whereas the non-infarct area remained red. B. Infarct sizes were presented as a percentage of the infarct area to the total left ventricular area. Values are presented as the mean \pm SD. ^a $p < 0.05$ versus the sham group; ^b $p > 0.05$ versus the MI group.

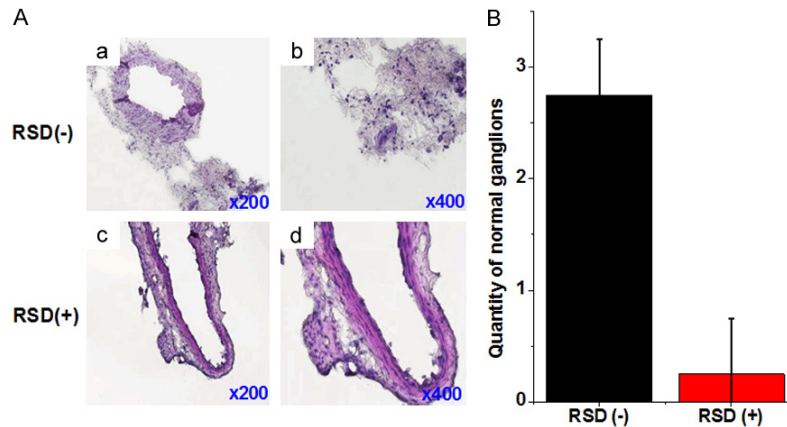


Figure 2. H&E (hematoxylin and eosin) staining of the renal artery and surrounding nerves with or without RSD (renal sympathetic denervation). Aa. Renal artery and ganglions without RSD ($\times 200$). Ab. Magnified view showing a healthy ganglion from image A ($\times 400$). Ac. Renal artery and ganglions with RSD ($\times 200$). Ad. Magnified view of a damaged ganglion from image C ($\times 400$). The ganglionic cells have lost histological details after RSD. B. Sympathetic nerves in RSD group were significantly decreased in comparison with sham group. ^a $p < 0.05$.

dene fluoride (PVDF) membrane. The membranes were blocked with 5% nonfat milk for 1 hour at room temperature, and were incubated overnight at 4°C with the primary antibodies (rat anti-Kv4.2 and anti-Kv4.3, monoclonal antibody, Abcam, Cambridge, UK) and the primary anti-Kv4.2 and Kv4.3 protein antibodies were diluted with TBST solution at a ratio of 1:1000 according to the instructions, followed by incubation for 1 hour at room temperature with secondary antibody (Goat anti-Mouse, Multi Sciences, Zhejiang, China), this concentration is also diluted according to the product instructions. The membranes were visualized by an enhanced chemiluminescence detec-

tion system (Image Station 4000R, Kodak, USA). Autoradiography images were analyzed by Carestream Molecular Imaging analysis software.

Statistical analysis

Experimental data were obtained from the statistical average of multiple samples in the same group of subjects and all values were presented as the mean \pm standard deviation. Statistical analysis was performed with SPSS 20.0 software. First, the experimental values were statistically analyzed, and the experimental values collected from each sample of sham, MI and MI+RSD group were consistent with normal distribution and odd variance. And then one-way analysis of variance was applied to compare mean differences among the sham, MI and MI+RSD groups. Furthermore, LSD method was used for multiple comparisons, and sham, MI, MI+RSD groups were compared in pairs to analyze whether there were significant differences between them. The statistical method of t test was used for significance test and the p -value

of less than 0.05 was considered to be statistically significant.

Results

MI induced by ligating left anterior descending coronary artery

TTC staining was performed to confirm whether the rat model of MI was successfully established. The result showed that the myocardium infarction region was stained white, while the non-infarct area remained red (**Figure 1A**). There was no significant difference in infarct size between MI group and MI+RSD group

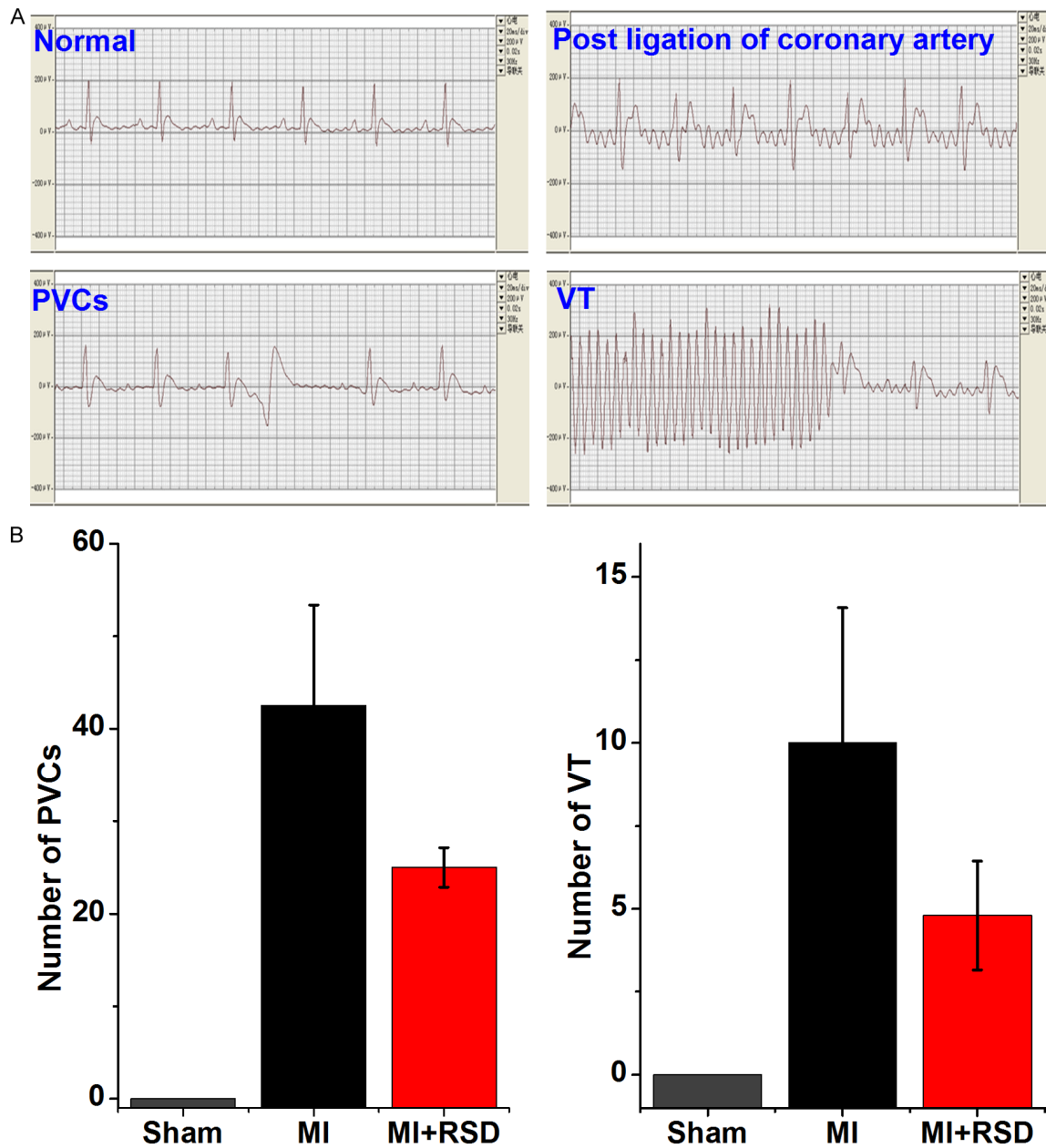


Figure 3. A. The standard II lead of electrocardiogram (ECG) manifestations of normal, post ligation of coronary artery, PVCs and VT in rats. B. Ventricular arrhythmias could be induced by myocardial infarction. RSD (renal sympathetic denervation) treatment reduced the incidence of PVCs and VT. ^a $p < 0.05$ versus the sham group; ^b $p < 0.05$ versus the MI group.

(41.22 ± 2.23 vs 40.06 ± 2.22 , $p > 0.05$) (Figure 1B).

Histology of the renal artery and nerves

The renal artery and surrounding nerves were stained with H&E (Figure 2A). The results showed that sympathetic nerves in RSD group were significantly decreased in comparison with sham group (0.25 ± 0.50 vs 2.75 ± 0.50 ,

$p < 0.05$) (Figure 2B). Some nerves lost histological details after RSD. In contrast, these alterations were not observed in rats without ablation.

Effect of RSD on occurrence of AMI-induced arrhythmias

The ECG manifestations in rats were showed in Figure 3A and ST-segment elevation was

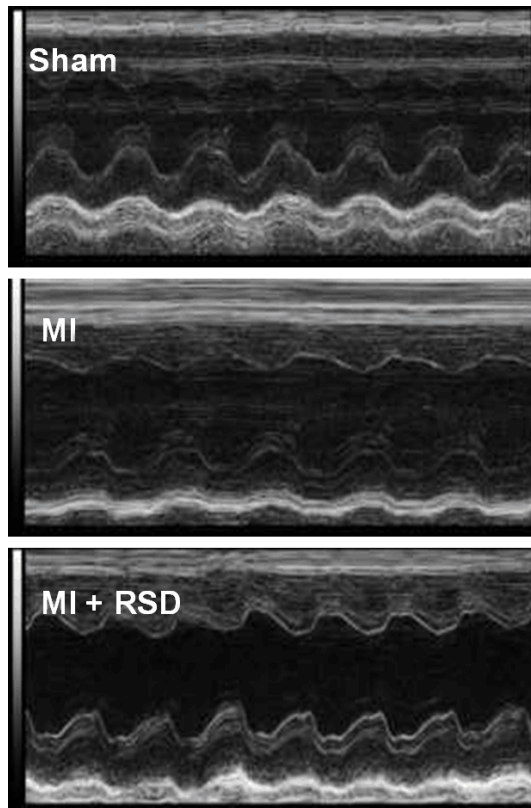


Figure 4. Echocardiographic images of rat hearts in three groups.

clearly observed after coronary artery ligation. Ventricular arrhythmias could be significantly induced by MI. Compared with MI group, MI+RSD group has a lower incidence of PVCs (25.00 ± 2.16 vs 42.50 ± 10.88 , $p < 0.05$) and VT (4.80 ± 1.64 vs 10.00 ± 4.08 , $p < 0.05$) (**Figure 3B**).

Effect of RSD on cardiac function after MI

The echocardiographic images were showed in **Figure 4**. There were no significant differences in pre-operative echocardiogram parameters among the three groups. The MI group had significantly decreased LVEF (32.39 ± 10.64 vs $75.28 \pm 8.72\%$, $p < 0.05$) and FS (16.13 ± 5.68 vs $45.49 \pm 7.53\%$, $p < 0.05$), and increased LVEDD (8.26 ± 0.79 vs 5.70 ± 0.33 mm, $p < 0.05$) and LVESD (7.01 ± 0.91 vs 3.37 ± 0.71 mm, $p < 0.05$) at 4 weeks after coronary artery ligation compared to that of the sham group. The decline of LVEF (32.39 ± 10.64 vs $51.49 \pm 8.91\%$, $p < 0.05$) and FS (16.13 ± 5.68 vs $27.07 \pm 5.42\%$, $p < 0.05$) was significantly attenuated by the

MI+RSD group, and the elevation of LVEDD (8.26 ± 0.79 vs 6.63 ± 0.28 mm, $p < 0.05$) and LVESD (7.01 ± 0.91 vs 4.85 ± 0.73 mm, $p < 0.05$) was also attenuated by the MI+RSD group (**Table 1**).

Effect of RSD on myocardial fibrosis

Masson staining showed that the cardiac myocytes were dyed red and the collagen fibers were dyed blue under light microscope (**Figure 5A**). The area of the collagen fraction was significantly increased in MI group compared with sham group (24.84 ± 6.07 vs 1.23 ± 0.15 , $p < 0.05$). The extent of collagen deposition was attenuated in MI+RSD group compared to MI group (9.75 ± 1.22 vs 24.84 ± 6.07 , $p < 0.05$) (**Figure 5B**).

Effect of RSD on APD in rat hearts

Action potentials were recorded in current clamp mode (**Figure 6A**). The result showed that MI group had prolonged action potential duration (APD, 137.5 ± 6.81 vs 115.9 ± 6.36 , $p < 0.05$) and APD of 50% repolarization (APD₅₀, 58.45 ± 1.44 vs 43.32 ± 2.39 , $p < 0.05$). Compared with MI group, prolonged APD and APD₅₀ have been shortened in the MI+RSD group (**Figure 6B**).

Effect of RSD on I_{to} in rat hearts

To detect the effect of RSD on I_{to} in MI rats, we examined I_{to} under whole-cell voltage-clamp mode. At the test potential of +60 mV, the current density of I_{to} was significantly decreased in MI group than that in sham group (11.30 ± 5.81 vs 22.10 ± 10.55 , $p < 0.05$), while RSD treatment could obviously increase the suppressed I_{to} current density (15.82 ± 7.80 vs 11.30 ± 5.81 , $p < 0.05$). The current-voltage (I-V) curves demonstrating the changes of I_{to} in different groups were plotted in **Figure 7B**.

Effect of RSD on protein expression of Kv4.2 and Kv4.3

Western immunoblots indicated that the protein expression levels of myocardial Kv4.2 and Kv4.3 were significantly decreased in the MI group compared with sham group (0.79 ± 0.04 vs 1.00 ± 0.00 , $p < 0.05$ and 0.86 ± 0.06

Table 1. Changes of echocardiographic parameters in the three groups

Group	n	LVEF (%)	FS (%)	LVEDD (mm)	LVESD (mm)
Sham	10	75.28±8.72	45.49±7.53	5.70±0.33	3.37±0.71
MI	8	32.39±10.64 ^a	16.13±5.68 ^a	8.26±0.79 ^a	7.01±0.91 ^a
MI+RSD	6	51.49±8.91 ^{a,b}	27.07±5.42 ^{a,b}	6.63±0.28 ^{a,b}	4.85±0.73 ^{a,b}

Note: LVEF (left ventricular ejection fraction), FS (fractional shortening), LVEDD (left ventricular end diastolic dimension), LVESD (left ventricular end systolic dimension), MI (myocardial infarction), RSD (renal sympathetic denervation). Values are presented as the mean ± SD. ^a*p* < 0.05 versus the sham group; ^b*p* < 0.05 versus the MI group.

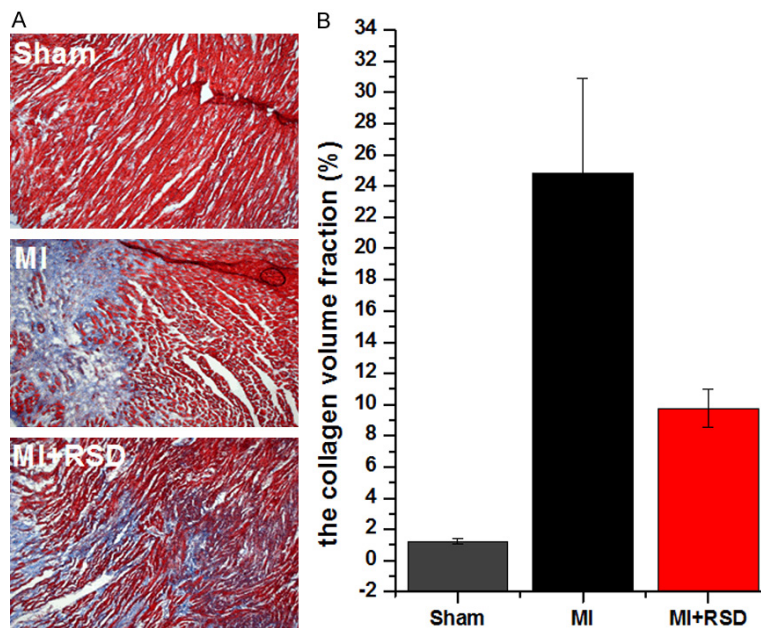


Figure 5. Masson's trichrome staining for assessment of myocardial fibrosis. A. Photos showed that the cardiac myocytes were dyed red and the collagen fibers were dyed blue under light microscope ($\times 100$). B. The area of the collagen fraction was significantly increased in MI groups compared with sham groups. RSD treatment attenuated myocardial fibrosis in MI rats. ^a*p* < 0.05, versus the sham group; ^b*p* > 0.05 versus the MI group.

vs 1.00 ± 0.00 , *p* < 0.05) (Figure 8A). Interestingly, the RSD treatment could significantly increase the Kv4.2 protein expression level (0.90 ± 0.02 vs 0.79 ± 0.04 , *p* < 0.05) while making no difference on Kv4.3 protein level (Figure 8B).

Discussion

In our experiment, we first observed the effect of RSD on the occurrence of VA. Second, we recorded the APD and found the prolonged APD in MI group could be shortened by RSD especially APD₅₀. APD₅₀ mainly reflected repolariza-

tion I phase of the action potential, so we detected I_{to} and its relevant ion channel proteins.

In the rat AMI model, we showed that the I_{to} density and protein expression level of Kv4.2 and Kv4.3 were decreased in the marginal zone of myocardial infarction. Furthermore, we first found that RSD could alleviate the decline of I_{to} density and up regulate Kv4.2 protein expression level. I_{to} is the main current of repolarization I phase of action potentials in cardiac myocytes, and it can affect the action potential morphology and duration. Kv4.2 and Kv4.3 are the major subunits of I_{to} in cardiomyocytes. Previous studies have shown that the protein expression levels of Kv4.2 and Kv4.3 in cardiomyocytes were decreased after MI, and it could decrease I_{to} density and then prolonged action potential duration (APD) [22, 23], which can cause the occurrence of early after depolarization and contribute to ventricular arrhythmias. Moreover, the decrease of I_{to} current density can increase the sensitivity of the myocardium to hypokalemia, ischemia and acidosis, which can increase the sus-

ceptibility to arrhythmias. Some studies have showed that cardiac nerve sprouting or isoproterenol could suppress I_{to} and increased the susceptibility to ventricular fibrillation. Ventricular electrical remodeling is one of the important factors of the occurrence of ventricular arrhythmia after myocardial infarction, and myocardial electrophysiological heterogeneity in different positions of the myocardium increases the risk of ventricular arrhythmias. Here we show that RSD can reduce the incidence of ventricular arrhythmias, and its mechanism is possibly related to attenuation of the decline of I_{to} current density through the up-

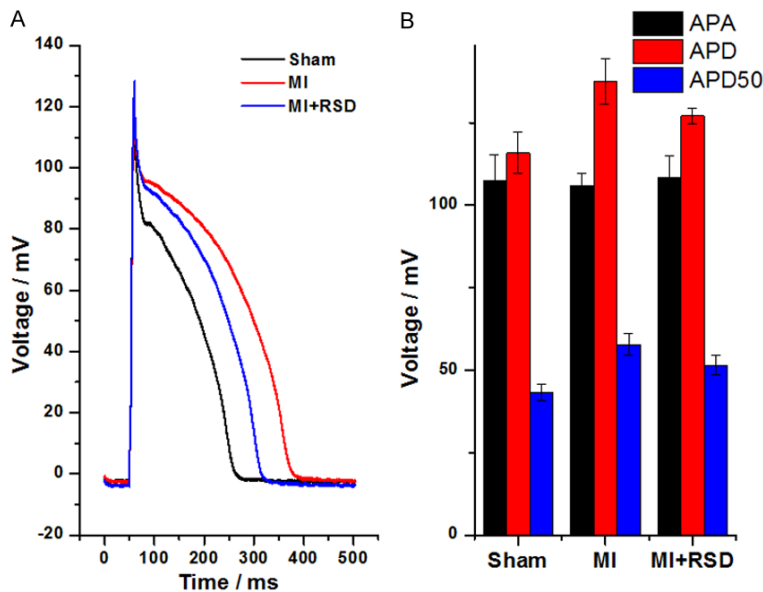


Figure 6. The effect of RSD on APD in MI rat hearts. A. The representative action potential traces in three groups rat hearts. B. ^a*p* < 0.05, versus the sham group; ^b*p* < 0.05 versus the MI group; ^c*p* > 0.05 versus the sham group; ^d*p* > 0.05 versus the MI group.

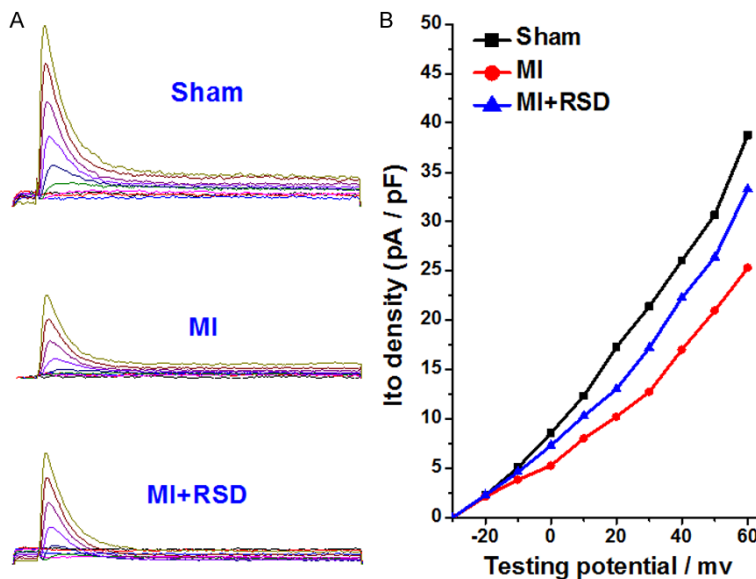


Figure 7. The effect of RSD on I_{to} in MI rat hearts. A. The transient outward K⁺ current (I_{to}) was elicited by a 300 ms depolarizing current stepped from -30 to +60 mV with 10 mV increments from a holding potential of -80 mV. 0.2 μM BaCl₂ was used to block I_{Ca} and I_{K1}. B. The current voltage (I-V) relationships in three groups rat hearts. ^a*p* < 0.05, versus the sham group; ^b*p* > 0.05 versus the MI group.

antiarrhythmic role. In addition, our results demonstrated RSD's effect of improving cardiac function after MI by increasing EF and FS and reducing LVEDD and LVESD. Collagen fiber hyperplasia is an important factor in myocardial fibrosis and cardiac remodeling after MI, the Masson staining showed that RSD can reduce the degree of myocardial fibrosis, which may be an important pathological mechanism of its role improving cardiac function after MI.

Conclusions

Electrical remodeling and structure remodeling play a critical role in the occurrence and maintenance of ventricular arrhythmias after myocardial infarction. Our results indicated that the mechanism of RSD on inhibition of VA after MI was linked to the reverse of I_{to} density through the up-regulation of Kv4.2 protein expression and the improvement of cardiac function.

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regulation of Kv4.2 protein expression level. The recovery of I_{to} current can mitigate electrophysiological heterogeneity and thus play an

Disclosure of conflict of interest

None.

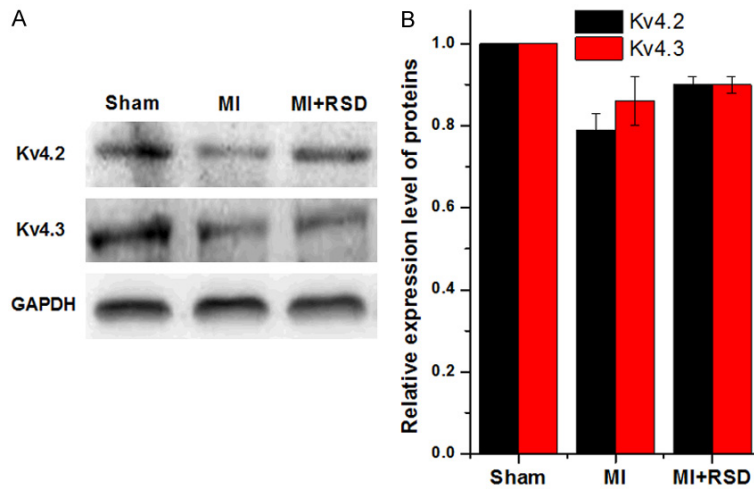


Figure 8. Western blot analysis of Kv4.2 and Kv4.3 protein expression levels in three groups. GAPDH was used as a loading control. A. The protein expression levels of myocardial Kv4.2 and Kv4.3 were significantly decreased in the MI group than that in sham group. B. RSD treatment increased the Kv4.2 level, but not the Kv4.3 level. ^a $p < 0.05$, versus the sham group; ^b $p > 0.05$ versus the MI group.

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