Original Article
Renal sympathetic denervation improves cardiac function through attenuating myocardial apoptosis after myocardial infarction in rats

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Abstract: Objective: This study aims to investigate whether renal sympathetic denervation (RSD) can reduce myocardial apoptosis after myocardial infarction (MI) and explore the potential mechanisms. Methods: Six-four male Sprague-Dawley rats were randomly assigned to sham, RSD, sham+MI and RSD+MI group. Three days after sham or RSD operation, MI was induced. Plasma angiotensin II, aldosterone and noradrenaline, left ventricular (LV) function, myocardial apoptosis rate, the mRNA and protein expression levels of apoptotic factors (including bax, bcl-2 and caspase3), and transforming growth factor \(\beta_1\) (TGF-\(\beta_1\)) in LV were evaluated 4 weeks post-MI. Results: Rats in the sham+MI group showed significantly deterioration in LV function and hemodynamics, which were improved when RSD performed before MI. The myocardial apoptosis rate, along with the mRNA and protein levels of bax, cleaved caspase-3, in the RSD+MI group were significantly lower when compared with sham+MI group, while the levels of bcl-2 were significantly higher. The mRNA and protein levels of TGF-\(\beta_1\) in LV and plasma angiotensin II, aldosterone and noradrenaline levels significantly were increased after MI, while the levels decreased following RSD treatment. Conclusions: The positive effects of RSD on cardiac dysfunction post-MI may be partly regulated via attenuating myocardial apoptosis through downregulation of TGF-\(\beta_1\).

Keywords: Renal sympathetic denervation, myocardial apoptosis, myocardial infarction, transforming growth factor \(\beta_1\)

Introduction
Cardiac remodeling post myocardial infarction (MI) leads to ventricular dysfunction and the subsequent development of heart failure, which might result in a poor outcome and high cardiovascular mortality rate [1, 2]. Accumulating evidences indicate that myocardial apoptosis plays a key role in the development of myocardial infarction disease [3, 4]. Cardiomyocyte death due to apoptosis is closely interrelated with the progression of left ventricular (LV) remodeling and dysfunction during ischemia-reperfusion and myocardial infarction (MI) [5-7].

It was reported that RSD has improved sodium and water retention and inhibited overactivation of the SNS and RAAS. The effects of surgical RSD intervention on heart failure (HF) post-MI was studied, which demonstrated that RSD has preventive and therapeutic effects on LV remodeling [8]. However, whether the effect of improving cardiac remodeling of RSD includes reducing myocardial apoptosis, and what is the role of RSD in the inhibition of apoptosis in MI are yet to be elucidated.

In the present study, it was hypothesized that RSD might act against the progression of LV remodeling after MI through attenuating myocardial apoptosis. Therefore, we employed the rat model of acute myocardial infarction to explore the impact of RSD on myocardial apoptosis and observe the potential mechanisms.
RSD attenuates myocardial apoptosis post-MI in rats

Material and methods

Ethics statement

All procedures involving animals conformed with the “Guide for the Care and Use of Laboratory Animals” published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). The animal study protocol was approved by the Institutional Animal Care Committee at Wuhan University.

Animals and Group setting

Total number of six-four male Sprague-Dawley rats (SPF level, 180-200 g) were used, purchased from BEIJING HFK BIOSCIENCE CO., LTD (Beijing, China). These rats were housed in plastic cages with Tek-Fresh bedding at a constant 21°C temperature with a 12 h light-dark cycle and had free access to commercial, species-specific food pellets and clean tap water during the whole experiment. The animals were acclimatized to laboratory conditions for one week prior to all experiments. The rats were randomly divided into four groups: sham group (sham, n=16), RSD group (renal sympathetic denervation, n=16), sham+MI group (MI 3 days after sham denervation, n=16), RSD+MI (MI three days after renal sympathetic denervation, n=16).

Renal sympathetic denervation

Under general anesthesia with 2% pentobarbital sodium (40 mg/kg ip), bilateral renal denervation or sham operation was performed in the four groups. Both kidneys were surgically denervated by carefully stripping and cutting all visible nerves along the renal arteries and veins from the aorta to the hilum at about 2-4 mm of the kidney. Then the area was moistened with a 10% phenol/ethanol solution for 10-15 minutes. Before and after surgery, we evaluated the effects of RSD by electrically stimulating the renal sympathetic nerves for 20-30 seconds (Grass S48 nerve stimulator, 0.2 ms, 15 V, 10 Hz). For normal rats, it was observed that electrical stimulation could cause the heart rate to increase 8-15 bpm, the blood pressure to increase 5-10 mmHg, and the kidney to become paler. For animals after RSD, the above changes in blood pressure, heart rate, or kidney color were absent. For sham denervation, the surgery was the same, but the renal artery and vein were not isolated and the nerves were left intact. The rats were placed in 26°C environment, after they were awoken. Pethidine 40 mg and penicillin 400,000 U was given by intramuscular injection daily for 3 days to relieve the pain and prevent infection.

Model of myocardial infarction

MI was induced by surgical ligation of proximal left anterior descending coronary under intraperitoneal anesthesia (2% pentobarbital sodium (40 mg/kg)). After fixed in supine position, endotracheal intubation was adopted for mechanical ventilation. A left thoracotomy was performed to expose the heart and left anterior descending coronary artery. A 7-0 silk suture was used to ligate the left anterior descending coronary artery approximately 2-3 mm from its origin. Successful ligation leads to the heart beat decreased and the white surface of the heart. An infarct area was assessed four weeks post-MI and a total area of 30% to 40% of the LV was judged as a successful MI rat model. Then, The thorax was closed layer by layer with 6-0 silk suture, and rats were placed in 26°C environment after operation. After rats were awoken, penicillin 400,000 U and pethidine 40 mg was given by intramuscular injection daily for 3 days to prevent infection and relieve the pain.

Echocardiography

About 4 weeks after MI induction, under intraperitoneal anesthesia (2% pentobarbital sodium (40 mg/kg)), transthoracic echocardiography was performed on all animals. Heart function was estimated using an echocardiography system equipped with a 15-MHz phased-array transducer (SONOS 5500, Hewlett-Packard, Andover, MA). Two-dimensional M-mode imaging was taken in the left ventricular (LV) long and short axis views, LV internal dimensions in systole and diastole were measured. LV ejection fraction (EF) was determined in the papillary muscle level short axis view, and fractional shortening (FS) was automatically calculated, using Chart 5 software for analysis.

Hemodynamic study

LV hemodynamics were measured with a Millar Microtip catheter (SPR-407, Millar Institute,
RSD attenuates myocardial apoptosis post-MI in rats

Houston, TX, USA) inserted into the right carotid artery and advanced into the LV. The peak systolic pressure (LVSP), LV end-diastolic pressure (LVEDP), positive/negative change in pressure over time (dP/dt\text{max}, and dP/dt\text{min}) were obtained from the signal processing computer system of the multichannel electrophysiology instrument.

Neurohormonal analysis

After echocardiographic examination at the end of experiment, blood samples were drawn from the superior vena cava, centrifuged at 3000 rpm for 10 min, plasma was isolated and placed in microtubes and then stored at -80°C for further analysis. ELISA kits were adopted to measure plasma aldosterone (ALD), angiotensin II (Ang II) and noradrenaline (NE) levels.

Histopathological analysis

Four weeks post-MI, the surviving rats were sacrificed with excessive pentobarbital sodium anesthesia according to the experimental design. Both the left and right renal arteries and veins, along with surrounding fascia tissue were removed, rinsed four times in physiological saline and then put in 4% formalin solution for histopathological detection. The renal vessels and the surrounding connective tissue (including the proximal, the middle and the distal) were plastic embedded and stained with haematoxylin eosin staining and analyzed as described by Gal-Or O et al [9]. Each section was examined under a microscope (Olympus BX60, Olympus Companies, Japan) in order to observe the removal level of renal nerves.

TUNEL assay

After sacrificed, part of the rat heart infarct tissue was fixed in paraformaldehyde, then was paraffin embedded and sectioned to be prepared for pathological examination. According to manufacturer's instructions (Cell death detection assay; Roche), TUNEL assays were carried out with the prepared sections. Positive cells were stained brown. The index of apoptotic cardiomyocytes was calculated as the percentage of apoptotic nuclei/total number of nuclei with 5 field sunder high magnification.

RT-PCR analysis

Four weeks post-MI, the rats were sacrificed, then the mRNA expression levels of bax, bcl-2, caspase3, and TGF-β in the LV infarct areas were evaluated using real-time PCR system. Total RNA was extracted from tissues using RN easy Fibrous Tissue Mini Kit (Qiagen, Valencia, CA, USA) according to manufacturers protocol. The cDNA synthesis was performed according to the manufacturer’s instructions (Qiagen, Valencia, CA, USA). We used cDNA synthesized from 1 μg RNA to create a standard curve for relative quantification. Primer sequences were as followed: Bax: F, CAGGCGAATTGGC-GATG-AAC, R, CCCAGTTGAGTTGCCGCTT. Bcl-2: F, CTGGCATC-TTCTC-CTTCCAG, R, CGGTAGCGAC-GAGAGAAGTC. Caspase3: F, TGGACTCGC-GGT-ATTAGACA, R, GCGAAATGACTGGAGGAA. TGF-β: F, CACTC-CGTTGGCTCTAGTG, R, GGA-CTGCGAGCCTTAGTT. All PCR products stained with 0.5 μg/mL ethidium bromide were run on 1.5% agarose gels, and the housekeeping gene β-actin was used as an internal control. PT2 Profiler PCR Array Analysis software, version 3.4 (Qiagen, Valencia, CA, USA) was used to quantified the data from the densities of the bands.

Western blot analysis

The total protein samples were extracted according to manufacturer’s instructions in the Western blot kit. Fifty mg proteins were separated by SDS-polyacrylamide gel and transferred to Pure Nitrocellulose Blotting membranes. The membranes were blocked using 5% non-fat milk, then incubated overnight with primary antibodies against bax, bcl-2 (bax, bcl-2: 1:1000; CST, USA), cleaved caspase3 (cleaved caspase3; 1:1000; Proteintech Group, China), and TGF-β1 (1:600; Bioworld, China). β-actin was used as loading control. The corre-

Table 1. Infarct size and body weight four weeks post-MI

<table>
<thead>
<tr>
<th></th>
<th>sham</th>
<th>RSD</th>
<th>sham+MI</th>
<th>RSD+MI</th>
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<tr>
<td>n</td>
<td>16</td>
<td>16</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Infarct size (%)</td>
<td>--</td>
<td>--</td>
<td>38.3 ± 2.1</td>
<td>36.9 ± 1.8</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>388 ± 9.9</td>
<td>380 ± 8.7</td>
<td>362 ± 9.5</td>
<td>366 ± 10.1</td>
</tr>
</tbody>
</table>

Values are means ± SD. RSD, renal sympathetic denervation; sham, sham operation of RSD; sham+MI, rats treated with MI 3 days after sham operation of RSD; RSD+MI, rats treated with MI 3 days post-RSD. *P<0.05 vs. sham group or RSD group; **P<0.05 vs. sham+MI group.
RSD attenuates myocardial apoptosis post-MI in rats

Corresponding horseradish peroxidase conjugated secondary antibody (goat anti-rabbit immunoglobulin G, Proteintech Group, China) was added and incubated at 37°C for 3 h. Band intensities were visualized and quantified using photo documentation system.

Statistical analysis

Data were shown as means ± SEMs. Comparisons between groups were determined by one-way ANOVA with Student's t-test. Results were considered statistical significance when P<0.05.

Results

Mortality

1.5% (1/67) rats died due to anesthesia accident, 3.0% (2/67) rats died resulted from loss of blood after RSD, 4.5% (3/67) rats died because of heart failure post-MI in sham+MI group and 3.0% (2/67) in RSD+MI group. There was no obvious difference in the weight and the area of MI among all the four groups at the end of the experiment (Table 1).

Echocardiographic changes after RSD

Four weeks after MI surgery, the rats showed a significantly increase in LVEDD and decrease in LVEF and LVFS (Figure 1, P<0.01), compared to the sham group or RSD group. Treatment of RSD 3 days before MI clearly decreased LVEDD and significantly improved LVEF and LVFS compared to the sham+MI group (Figure 1, P<0.01).

Haemodynamics

Compared to the sham animals, 4 weeks post-MI rats showed remarkably decreased LVSP, dP/dt_max and dP/dt_min, increased LVEDP (P<0.05). However, the decrease in LVSP, dP/dt_max and dP/dt_min was significantly attenuated in the rats with RSD treatment 3 days before MI, and a significant increase was shown in LVSP (P<0.05) (Table 2).

Effects of RSD on plasma levels of NE, Ang II and ALD

As shown in Figure 2, compared with the values in the sham group or the RSD group, the plasma levels of NE, Ang II and ALD increased in
RSD attenuates myocardial apoptosis post-MI in rats

Histopathological analysis of the removal level of renal nerves

Histopathologically, almost all the normal renal sympathetic nerves distributed around the renal arteries (Figure 3A-F). No evidence of integrated renal sympathetic nerves was found at the end of the experiment, and the surrounding tissues around the renal arteries after RSD showed necrotic, while the walls of the renal arteries were undamaged (Figure 3G-I).

RSD reduced myocardial apoptosis in the hearts 4 weeks post-MI

The index of apoptosis by TUNEL assay

Positive cells were stained brown. Just a few apoptotic cells were detected in the sham group or RSD group. Compared with the sham group or RSD group, MI significantly increased the apoptosis rate. However, the level of apoptosis in the RSD+MI group was significantly lower when compared with that in the sham+MI group (Figure 4A-D, P<0.01).

The mRNA expression levels of bax, caspase-3 and bcl-2

Table 2. Haemodynamics parameters obtained at four weeks post-MI

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sham</th>
<th>RSD</th>
<th>sham+MI</th>
<th>RSD+MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVSP (mmHg)</td>
<td>121.6 ± 7.0</td>
<td>125.0 ± 6.2</td>
<td>92.3 ± 4.5</td>
<td>106.3 ± 6.5</td>
</tr>
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<td>LVEDP (mmHg)</td>
<td>4.4 ± 1.5</td>
<td>3.2 ± 0.7</td>
<td>20.6 ± 4.0</td>
<td>9.3 ± 2.4</td>
</tr>
<tr>
<td>dP/dt_{max} (× 10^3 mmHg s^{-1})</td>
<td>9.7 ± 1.1</td>
<td>9.4 ± 1.2</td>
<td>4.9 ± 0.6</td>
<td>8.0 ± 1.0</td>
</tr>
<tr>
<td>dP/dt_{min} (× 10^3 mmHg s^{-1})</td>
<td>4.9 ± 0.6</td>
<td>5.1 ± 0.8</td>
<td>3.3 ± 0.4</td>
<td>4.4 ± 0.5</td>
</tr>
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</table>

Values are means ± SD. Abbreviations: LVSP, left ventricular systolic pressure; LVEDP, LV end-diastolic pressure; dP/dt max and dP/dt min maximal and minimal values of rate of change in LV pressure; RSD, renal sympathetic denervation; Sham, sham operation of RSD; sham+MI, rats treated with MI 3 days after sham operation of RSD; RSD+MI, rats treated with MI 3 days post-RSD. *P<0.05, **P<0.01 vs. sham group or RSD group, respectively; ***P<0.05 vs. sham+MI group.

Figure 2. Plasma levels of noradrenaline, angiotensin II and aldosterone at four weeks post-MI. RSD, renal sympathetic denervation; sham, sham operation of RSD; sham+MI, rats treated with MI 3 days after sham operation of RSD; RSD+MI, rats treated with MI 3 days post-RSD. **P<0.01 vs. sham group or RSD group; ##P<0.01 vs. sham+MI group.
RSD attenuates myocardial apoptosis post-MI in rats

The changes of three proteins expression were concordant with mRNA levels. Bcl-2 expression levels in the sham+MI group were significantly lower than that in the sham group or RSD group (P<0.01), while Bcl-2 expression level was significantly increased in the RSD+MI group compared with the sham+MI group (P<0.01). However, bax and cleaved caspase-3 (activated caspase-3) proteins expression levels showed inverse expression compared with Bcl-2. Both bax and cleaved caspase-3 expression levels in the sham+MI group were significantly higher than that in the sham group or RSD group (P<0.01), which were evidently lower in the RSD+MI group than that in the sham+MI group (P<0.01) (Figure 6).

RSD lowered the expressions of TGF-β1 in the hearts 4 weeks after MI

In isolated cardiomyocytes of adult rat, TGF-β1 has been shown to induce apoptotic cell death [10]. It was demonstrated that both the mRNA and protein expression levels of TGF-β1 in the LV was significantly upregulated post-MI. However, the overexpression of TGF-β1 post-MI was enormously abolished following RSD treatment. (Figure 7A, P<0.05, Figure 7B, P<0.01).

Discussion

Cardiac dysfunction can be caused by myocardial remodeling after myocardial infarction. One of the major determinants of myocardial remod-
RSD attenuates myocardial apoptosis post-MI in rats

Figure 4. Myocardial apoptosis analysis by TUNEL assay. Positive cells were stained brown. A-C. TUNEL staining of apoptosis post-MI in LV (Arrows show positive cells); D. Statistical analysis of apoptosis. RSD, renal sympathetic denervation; sham, sham operation of RSD; sham+MI, rats treated with MI 3 days after sham operation of RSD; RSD+MI, rats treated with MI 3 days post-RSD. **P<0.01 vs. sham group or RSD group; ##P<0.01 vs. sham+MI group.

Figure 5. The mRNA expression levels of bax, caspase-3 and bcl-2. A. Relative expressions of bax, bcl-2 and caspase-3 detected in LV by RT-PCR analysis. B. Statistical analysis of the mRNA expression levels of bax, bcl-2 and caspase-3. RSD, renal sympathetic denervation; sham, sham operation of RSD; sham+MI, rats treated with MI 3 days after sham operation of RSD; RSD+MI, rats treated with MI 3 days post-RSD. **P<0.01 vs. sham group or RSD group; ##P<0.01 vs. sham+MI group.
RSD attenuates myocardial apoptosis post-MI in rats

eling post-MI is the extent of cardiomyocyte death which can occur due to necrosis and apoptosis in the ischemic zone. It is reported that cardiomyocyte apoptosis occurred continuously over an extended period of time in a rat MI model [11]. Bcl-2, Bax, and Caspase-3 have been at the center of research attention, among many factors and mechanisms associated with

Figure 6. The protein expression levels of bax, cleaved caspase-3 and bcl-2. A. Results for the protein expression of bax, bcl-2 and cleaved caspase-3 by Western blot analysis; B. Statistical analysis of protein expression of bax, bcl-2 and cleaved caspase-3. RSD, renal sympathetic denervation; sham, sham operation of RSD; sham+MI, rats treated with MI 3 days after sham operation of RSD; RSD+MI, rats treated with MI 3 days post-RSD. **P<0.01 vs. sham group or RSD group; ##P<0.01 vs. sham+MI group.

Figure 7. The mRNA and protein expression levels of TGF-β1. TGF-β1 mRNA (A) and TGF-β1 protein (B). RSD, renal sympathetic denervation; sham, sham operation of RSD; sham+MI, rats treated with MI 3 days after sham operation of RSD; RSD+MI, rats treated with MI 3 days post-RSD. *P<0.05, **P<0.01 vs. sham group or RSD group, respectively; #P<0.05, ##P<0.01 vs. Sham+MI group, respectively.
RSD attenuates myocardial apoptosis post-MI in rats

myocardial apoptosis [12]. In the present study, it was demonstrated that MI significantly increased the apoptosis rate when compared with sham group or RSD groups. Meanwhile, we observed the mRNA and protein levels of the three apoptotic factors in the hearts 4 weeks post-MI, and found that the mRNA and protein levels of bax increased significantly in the sham+MI group than that either in the sham group or RSD group. The expression levels of caspase-3 Mrna and activated caspase-3 protein displayed similar tendency as that of the Bax. However, the mRNA and protein levels of the anti-apoptoticbcl-2 showed inverse changes compared with the expression of bax, which were lower in the Sham+MI group compared with that in the RSD group. All the results indicated that apoptosis played an important role in the process of myocardial apoptosis post-MI.

Previous experimental studies have found that RSD treatment has a great deal of beneficial effects on HF, including reduced sodium retention, lower incidence of atrial and ventricular fibrillation, and increased renal blood flow [8, 13, 14]. In the current study, it demonstrated that RSD performed 3 days before MI, can lessen the LV dysfunction and LV dilatation post-MI. LVEF, LVSP, dP/dt\(_{\text{max}}\) and dP/dt\(_{\text{min}}\) increased significantly and LVEDP, LVESD, LVEDD decreased marked ly RSD treated rats, compared with that of MI rats (Figure 1; Table 2). The results confirmed that RSD actually improved heart function post-MI.

It was confirmed that RSD can reduce renin activity and attenuate the adverse effects of angiotensin II and aldosterone on ventricular structure and function, which improves cardiac dysfunction. Whereas, it was hypothesized that the benefit of RSD in heart failure post-MI maybe due to the reduction of myocardial cell apoptosis [15]. Therefore, the role of RSD in post-MI cardiomyocyte apoptosis was the focus of this study. We found that the level of apoptosis in the RSD+MI group was significantly lower when compared with sham+MI group. It was also observed that the mRNA levels of bax and caspase-3, as well as the expression levels of bax and activation caspase-3, decreased significantly in the MI group pre-treated with RSD than in the MI group pre-treated with RSD sham operation. Meanwhile, the mRNA and protein levels of the anti-apoptotic bcl-2 were evidently higher in the RSD+MI group than that in the sham+MI group. These results highly suggested that RSD might improve the LV function post-MI by reducing cardiomyocyte apoptosis.

We further investigated the underlying mechanisms of reduced myocardial apoptosis by RSD treatment. TGF-β1 is one of the most important signaling molecules which is closely related with RAAS. Previous studies have demonstrated that angiotensin II induced TGF-β1 expression in a p38-MAP kinase-dependent way [16]. It also was shown that angiotensin II stimulate the TGF-β1 geneactivation through PKC- and p38 MAPK-dependent pathways [17]. TGF-β1 was markedly induced and rapidly activated in the infracted myocardium, but it could be attenuated by angiotensin receptor blockers or angiotensin-converting enzyme inhibitors, which suggested that angiotensin II played a pivotal role in stimulating TGF-β1 synthesis [18]. TGF-β1 promotes apoptosis via SMAD-signaling in cardiomyocytes, which contributes to cardiomyocytes loss after myocardial infarction. In another study, it was indicated that inhibiting the expressions of TGF-β1 and its downstream apoptosis-related molecules, such as Bax and Caspase-3, could protect cardiac fibroblasts against hypoxia-induced apoptosis [19]. It was also confirmed that reduction of TGF-β1 levels may have contributed to reduced apoptosis after myocardial infarction [20]. RSD could significantly decrease the level of plasma angiotensin II [21], which increases the TGF-β1 expression in adult ventricular cardiomyocytes [22]. Therefore, in this study, we aimed to investigate the change of TGF-β1 level in hearts post-MI after RSD treated rats. We found that both mRNA and protein expressions of TGF-β1 in the LV were significantly lower in the MI group pre-treated with RSD than in the MI group pre-treated with RSD sham operation, suggesting that TGF-β1 may be an important mediator involving in the processing of RSD induced cardiomyocyte apoptosis reduction.

It was observed in the current study that RSD prevented the increase trend of circulating NE, Ang II and ALD in rats post-MI (Figure 2). It is consistent with a previous report, which was related to RSD induced reduction in RAAS activity inhibition and local norepinephrine spillover through blocking of afferent and efferent renal
sympathetic nerves [23]. Ang II has been shown to be a positive feedback factor for peripheral and central SNS, which also activates RAAS of many organs, especially the heart [24]. Therefore, it can be explained that RSD can block the RAAS and the sympathetic nervous system effectively and inhibit excessive neurohormonal activation post-MI. This further explains the mechanisms of how RSD influenced the relevance of TGF-β1 and myocardial apoptosis in this study.

Conclusions

It was reported that renal nerves may regenerate three to six weeks after RSD treatment [25]. In this study, no evidence of integrated renal sympathetic nerves was founded at the end of the experiment, while the walls of the renal arteries were undamaged, demonstrating that the current RSD was safe and effective during the observation period.

Our findings showed that RSD might act against the cardiac dysfunction post-MI through attenuating myocardial apoptosis. TGF-β1 signaling pathway might play an indispensable role in the process of RSD induced reduction of cardiomyocyte apoptosis.

Limitations

The levels of local SNS and RAAS activity, such as angiotensin II receptors, was not discussed in the current study, more studies about the issue must be conducted in our future works. Meanwhile, the TGF-β1 signaling pathway is required to further investigation.

Disclosure of conflict of interest

None.

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References


RSD attenuates myocardial apoptosis post-MI in rats


