Original Article
Sevoflurane postconditioning improves myocardial mitochondrial respiratory function and reduces myocardial ischemia-reperfusion injury by up-regulating HIF-1

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Abstract: Background: Sevoflurane postconditioning (SPostC) can exert myocardial protective effects similar to ischemic preconditioning. However, the exact myocardial protection mechanism by SPostC is unclear. Studies indicate that hypoxia-inducible factor-1 (HIF-1) maintains cellular respiration homeostasis by regulating mitochondrial respiratory chain enzyme activity under hypoxic conditions. This study investigated whether SPostC could regulate the expression of myocardial HIF-1α and to improve mitochondrial respiratory function, thereby relieving myocardial ischemia-reperfusion injury in rats. Methods: The myocardial ischemia-reperfusion rat model was established using the Langendorff isolated heart perfusion apparatus. Additionally, postconditioning was performed using sevoflurane alone or in combination with the HIF-1α inhibitor 2-methoxyestradiol (2ME2). The changes in hemodynamic parameters, HIF-1α protein expression levels, mitochondrial respiratory function and enzyme activity, mitochondrial reactive oxygen species (ROS) production rates, and mitochondrial ultrastructure were measured or observed. Results: Compared to the ischemia-reperfusion (I/R) group, HIF-1α expression in the SPostC group was significantly up-regulated. Additionally, cardiac function indicators, mitochondrial state 3 respiratory rate, respiratory control ratio (RCR), cytochrome C oxidase (Cco), NADH oxidase (NADHO), and succinate oxidase (SUCO) activities, mitochondrial ROS production rate, and mitochondrial ultrastructure were significantly better than those in the I/R group. However, these advantages were completely reversed by the HIF-1α specific inhibitor 2ME2 (P<0.05). Conclusion: The myocardial protective function of SPostC might be associated with the improvement of mitochondrial respiratory function after up-regulation of HIF-1α expression.

Keywords: Sevoflurane postconditioning, myocardial protective effect, hypoxia-inducible factor-1, mitochondrial respiratory function, respiratory enzyme activity

Introduction

Ischemic heart disease is a major cause of mortality due to human cardiovascular diseases [1]. Restoration of the blood supply to the ischemic myocardia (i.e., reperfusion treatment) is considered the most effective treatment for myocardial ischemia. However, myocardial reperfusion can aggravate or even cause an irreversible injury [2]. Therefore, development of methods that effectively reduce perioperative myocardial reperfusion injury is a current research topic.

A large number of studies have indicated that inhalational anesthetics such as sevoflurane and isoflurane can relieve ischemia-reperfusion injury [3, 4]. Sevoflurane has been applied extensively in clinical practice and basic research due to its stable induction and rapid recovery pharmacological properties. Sevoflurane postconditioning (SPostC) can produce myocardial protective functions similar to ischemic preconditioning and is a promising treatment against post-ischemic reperfusion injury during perioperative period [5]. Currently, the anti-reperfusion injury effect of SPostC is
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thought to be achieved through protection of mitochondrial functions [6]; however, the exact mechanism has not been elucidated. As an important site for ATP production via oxidative phosphorylation, mitochondria play important roles in myocardial ischemia and reperfusion injury [7-9]. The structural integrity and normal functions of mitochondria are the bases for the maintenance of the physiological activities of the heart. Mitochondrial respiratory function and respiratory enzyme activity are the major components that reflect the oxidative phosphorylation process and structural integrity of the mitochondria.

Hypoxia-inducible factor-1 (HIF-1) regulates the expression of a series of hypoxia-sensitive genes under hypoxic conditions to maintain the survival of tissues and cells. Studies have confirmed that HIF-1 is central to cardioprotection against ischemia-reperfusion injury [10]. Recent studies showed that HIF-1 maintained normal cellular respiration by regulating mitochondrial respiratory chain activity. Furthermore, HIF-1 can reduce the production of mitochondrial ROS to avoid cell injury [11]. Thus, we investigated whether the SpostC myocardial protective function was associated with the regulation of myocardial mitochondrial respiratory function.

We used an in vitro rat myocardial ischemia-reperfusion injury model and studied the mechanism underlying the association between anti-myocardial ischemia-perfusion by SPostC and HIF-1 by investigating mitochondrial respiratory function.

Materials and methods

Animals and experimental groupings

A total of 88 healthy adult male Sprague-Dawley (SD) rats with a body weight of 250-300 g were provided by the experimental animal center of the Third Military Medical University (permission number SCXK2012-0005). All SD rats were raised according to the Guide for the Care and Use of Laboratory Animals released by the National Institute of Health of the USA (1996 revision).

These rats were randomly divided into 4 groups (n=22 rats/group) as follows: normal control (C) group, ischemia-reperfusion (I/R) group, SPostC group, and HIF-1α inhibitor (2-methoxyestradiol, 2ME2) + SPostC (MSP) group. The C group received persistent perfusion of Krebs-Henseleit (K-H) solution for 180 min. The I/R group was equilibrated for 20 min, followed by perfusion of 4°C St. Thomas cardioplegia; afterwards, the rats were perfused with K-H solution for 120 min, and then, whole heart ischemia was performed at 32°C for 40 min. The SPostC group was equilibrated for 20 min, followed by perfusion of 1.0 MAC (minimum alveolar concentration) of sevoflurane-saturated K-H solution for 15 min, and then, whole heart ischemia was per-

Figure 1. The schematic diagram of the isolated rat heart experimental procedures. With the exception of the C group, all hearts were equilibrated for 20 min, followed by whole heart ischemia for 40 min and reperfusion for 120 min. The SpostC received 1.0 MAC sevoflurane treatment for 15 min, followed by reperfusion for 105 min. T1: the end of equilibration; T2: the end of reperfusion.
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formed for 40 min at 32°C, followed by continuous perfusion of K-H solution for 105 min. The MSP group was perfused with 2ME2 (2 µM) + 1.0 MAC of sevoflurane-saturated K-H solution for 15 min after 40 min of whole heart ischemia followed by continuous perfusion of K-H solution for 105 min (Figure 1). The preparation of 1.0 MAC of sevoflurane-saturated K-H was previously described [12, 13]. The sevoflurane concentration was monitored using a ULT-Svi-22-07 gas detector (Division, Finland) and an infrared gas analyzer (Datex-Ohmeda, GE Healthcare) to ensure that the sevoflurane concentration in the K-H solution was maintained at 1.0 MAC.

Establishment of the Langendorff model [14]

The rats were intraperitoneally injected with sodium pentobarbital (40 mg/kg) and heparin (250 U/kg). After anesthetization, the heart was rapidly removed (3-4 mm of the aorta was retained) and placed in K-H buffer pre-cooled to 4°C to discharge all blood in the heart cavities. The K-H buffer solution (mmol/L) was prepared with NaCl (118), KCl (4.7), MgSO\(_4\)•7H\(_2\)O (1.2), KH\(_2\)PO\(_4\) (1.2), NaHCO\(_3\) (25), glucose (11), and CaCl\(_2\) (2.5) at pH 7.45. The heart was immobilized with a Langendorff perfusion needle using a No. 4 surgical thread. Retrograde perfusion of the aorta was performed at 37°C using K-H solution equilibrated in 95% O\(_2\)-5% CO\(_2\) mixed gas under 5.8 kPa perfusion pressure. The pulmonary artery and left atrial appendage were cut open; then, a pressure measuring tube with a rubber balloon was inserted into the left ventricle through the mitral valve opening and connected with a biological function experimental pressure transducer system. The perfusion pressure was maintained at approximately 60-70 mmHg. The size and position of the balloon was adjusted to maintain the left ventricular end-diastolic pressure (LVEDP) at 0-10 mmHg. The above steps were completed within 2 min. The inclusion criteria were a heart rate (HR) >250 beats/min and a left ventricular developed pressure (LVDP) >80 mmHg after the isolated heart was equilibrated for 20 min.

Monitoring of hemodynamics

The heart rate (HR, beats/min), LVDP (mmHg), LVEDP (mmHg), and maximum rate of increase of LV pressure (+dp/dtmax, mmHg/s) at the end of equilibration (T1) and the end of reperfu-

sion (T2) were collected using the Powerlab/8SP data collection system.

Measurement of mitochondrial respiratory function

Myocardial mitochondria were extracted, and mitochondrial proteins were quantitated. Mitochondrial respiratory function was measured using a Clark oxygen electrode [15, 16]. The total volume of the reaction solution was 1 mL, and the temperature was 37°C. First, 900 µL of the mitochondrial respiration measurement medium was added; after equilibration for 15 min, 50 µL of the mitochondrial suspension at a final concentration of 1 mg/mL was added, and the 20-30 sec oxygen consumption curve was recorded. After the curve was stabilized, 10 µL of succinic acid (final concentration 5 mM) and 1 µL of rotenone (final concentration 2 µM) were added. After state 4 respiration was entered, the results was recorded for 1 min. Next, 9 µL of ADP (final concentration 100 µM) was added to induce state 3 respiration. The changes in the oxygen consumption curve were recorded; when all of the ADP was completely phosphorylated to ATP, the mitochondria entered state 4 respiration. Mitochondrial respiratory control rate (RCR) = the oxygen consumption rate in state 3 respiration/the oxygen consumption rate in state 4 respiration.

Measurement of mitochondrial respiratory enzyme activity [15, 17]

Extracted and quantitated mitochondria were repeatedly frozen and thawed at -80°C and 20°C to prepare the mitochondrial subunits. The mitochondrial respiratory chain enzyme activities, including that of cytochrome C oxidase (CcO), NADH oxidase (NADHO), and succinate oxidase (SUCO), were measured. The total volume of the reaction solution was 1 mL, and the temperature was 37°C. The CcO measurement medium, NADHO measurement medium, and SUCO measurement medium were added (900 µL each) and equilibrated for 15 min. The mitochondrial subunit suspension preparation (50 µL) was added, and the 5-10 min oxygen consumption curves were recorded.

Measurement of the mitochondrial ROS production rate

The myocardial mitochondrial ROS production rate was measured using fluorescence spec-
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trometry [18]. The basic principle is that dichlorodihydrofluorescein diacetate (DCFH-DA) can diffuse through the mitochondrial membrane and form reduced dichlorodihydrofluorescein (DCFH), which does not exhibit fluorescence activity because of hydrolysis by esterases in the mitochondria. DCFH is rapidly oxidized by ROS into the highly fluorescent active substance dichlorofluorescein (DCF). The speed of the oxidization of DCFH into DCF positively correlates with the ROS production rate. In this experiment, we used the 3 mL cuvette reaction system with 2.9 mL of mitochondrial ROS measurement medium and 0.5 mg of mitochondria; we also included one cuvette that did not contain mitochondria. Succinic acid at a final concentration of 3.3 mmol/L was added and used as the substrate; then, 3 μL of DCFH-DA at a final concentration of 5 mmol/L was added and incubated at 37°C for 15 min. The fluorescence intensity of the substrate without mitochondria (F1) and the fluorescence intensity of the sample with mitochondria (F) were measured. The ROS production rate was the result of subtracting F1 from F.

Myocardial ultrastructure

After reperfusion, myocardial tissues with sizes of 1 mm×1 mm×1 mm were collected from each group. The ultrastructure of the myocardial mitochondria were observed using a trans-

Figure 2. The cardiac function indicators at the end of equilibration (T1) and the end of reperfusion (T2). A: HR; B: LVEDP; C: LVEDP; D: +dp/dt_{max}. Data are presented as the mean ± SEM (n=22). *P<0.05 vs T1; T2 time point: ^P<0.05 vs C, *P<0.05 vs I/R, &P<0.05 vs SPostC.

Figure 3. The changes in the HIF-1α protein levels at the end of reperfusion. Data are presented as the mean ± SEM (n=6). *P<0.05 vs I/R; #P<0.05 vs SPostC.
mission electron microscope after fixation, washing, dehydration, embedding, sectioning, and staining.

Western blot analysis

After the repeated reperfusion, the left ventricular myocardial tissues were cut (n=6) and immediately placed in liquid nitrogen for storage. Total proteins were extracted from the myocardial tissues and lysed in tissue lysis buffer. Samples containing 30 µg of protein were subjected to SDS-PAGE and then transferred onto a membrane. After the membrane was blocked at 37°C for 2 h, an HIF-1α primary antibody was added at a 1:1000 dilution and incubated at 4°C overnight. The membrane was washed with TBST and then incubated with an HRP-labeled secondary antibody at a 1:5000 dilution at room temperature for 1 h. The images were developed using electrochemiluminescence (ECL). Analysis of the gray density values of the target protein bands was performed using the Quantity One imaging analysis system.

Statistical analysis

SPSS 17.0 statistical software was used for the data analysis. Measurement data are presented as the mean ± standard error of the mean (SEM). The within group comparisons were performed using the analysis of variance of repeated measurement design. The comparison between groups was performed using univariate analysis of variance. P<0.05 indicated that the difference had statistical significance.

Results

Cardiac function indicators

No significant differences were detected in the HR, LVDP, LVEDP, and +dp/dt max between groups at the end of equilibration (P>0.05). The HR, LVDP, and +dp/dt max in all groups were significantly decreased at the end of reperfusion compared to the end of equilibration, whereas LVEDP was significantly increased (P<0.05) (Figure 2A-D). The comparison of all groups at the end of reperfusion showed that LVEDP was significantly decreased and HR, LVDP, and +dp/dt max were significantly increased in the SPostC group compared to the I/R group (P<0.05). However, none of the cardiac function indicators between the SPostC and I/R groups were significantly different after the application of the HIF-1α inhibitor (P>0.05) (Figure 2A-D).

Expression of the HIF-1α protein

Compared to the I/R group, myocardial HIF-1α expression in the SPostC group at the end of reperfusion was significantly up-regulated. Compared to the SPostC group, HIF-1α protein expression in the MSP group at the end of reperfusion was significantly down-regulated (P<0.05); however, no significant difference was detected in HIF-1α protein expression between the MSP and I/R groups (P>0.05) (Figure 3).

Mitochondrial respiratory function

The mitochondrial state 3 respiration and RCR at the end of equilibration (T1) and at the end of reperfusion (T2). Data are presented as the mean ± SEM (n=6)

<table>
<thead>
<tr>
<th></th>
<th>State 3</th>
<th>RCR</th>
<th>State 3</th>
<th>RCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>147.31±5.42</td>
<td>2.43±0.09</td>
<td>145.23±7.59</td>
<td>2.24±0.14*</td>
</tr>
<tr>
<td>I/R</td>
<td>145.05±8.33</td>
<td>2.35±0.17</td>
<td>70.16±5.99</td>
<td>1.11±0.09**</td>
</tr>
<tr>
<td>SpostC</td>
<td>146.46±5.11</td>
<td>2.34±0.19</td>
<td>121.94±6.24</td>
<td></td>
</tr>
<tr>
<td>MSP</td>
<td>147.47±7.91</td>
<td>2.36±0.14</td>
<td>71.02±5.29</td>
<td>1.14±0.08**</td>
</tr>
</tbody>
</table>

*P<0.05 vs T1; T2 time point: *P<0.05 vs C, *P<0.05 vs I/R, *P<0.05 vs SPostC.

Mitochondrial respiratory enzyme activity

The CcO, NADHO, and SUCCO activities at the end of equilibration did not significantly differ at the end of equilibration among all groups (P>0.05). The mitochondrial state 3 respiration and RCR at the end of reperfusion were significantly decreased in all groups compared to the end of equilibration (P<0.05). The comparison of all groups at the end of reperfusion showed that the mitochondrial state 3 respiration and RCR in the SPostC group were significantly increased compared to those in the I/R group (P<0.05); no significant difference in respiration function was observed between the MSP and I/R groups (P>0.05) (Table 1).
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Table 2. The changes in mitochondrial CcO, NADHO, and SUCO activities at the end of equilibration (T1) and at the end of reperfusion (T2). Data are presented as the mean ± SEM (n=6)

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
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<tbody>
<tr>
<td></td>
<td>NADHO</td>
<td>CcO</td>
</tr>
<tr>
<td>C</td>
<td>316.56±13.93</td>
<td>97.39±5.75</td>
</tr>
<tr>
<td>I/R</td>
<td>313.20±12.62</td>
<td>94.27±4.31</td>
</tr>
<tr>
<td>SpostC</td>
<td>311.07±14.12</td>
<td>97.18±6.66</td>
</tr>
<tr>
<td>MSP</td>
<td>310.60±11.35</td>
<td>96.85±5.44</td>
</tr>
</tbody>
</table>

*P<0.05 vs T1; T2 time point: ^P<0.05 vs C, #P<0.05 vs I/R, &P<0.05 vs SPostC.

Table 3. The mitochondrial ROS production rates (RPR) at the end of equilibration (T1) and at the end of reperfusion (T2). Data are presented as the mean ± SEM (n=6)

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RPR (u.s⁻¹.mg⁻¹)</td>
<td>RPR (u.s⁻¹.mg⁻¹)</td>
</tr>
<tr>
<td>Control</td>
<td>1.97±0.13</td>
<td>6.89±0.54*</td>
</tr>
<tr>
<td>I/R</td>
<td>2.01±0.08</td>
<td>12.96±0.82**</td>
</tr>
<tr>
<td>SpostC</td>
<td>1.99±0.11</td>
<td>9.12±0.61**</td>
</tr>
<tr>
<td>MSP</td>
<td>2.00±0.09</td>
<td>13.01±0.69**</td>
</tr>
</tbody>
</table>

*P<0.05 vs T1; T2 time point: ^P<0.05 vs C, *P<0.05 vs I/R, &P<0.05 vs SPostC.

(P<0.05). The comparison of all groups at the end of reperfusion showed that the CcO, NADHO, and SUCO activities in the SPostC group were significantly increased compared to those in the I/R group; however, the CcO, NADHO, and SUCO activities did not significantly differ between the MSP and I/R groups (P>0.05) (Table 2).

Mitochondrial ROS production rates

The mitochondrial ROS production rates in all groups at the end of reperfusion were significantly increased compared to the rates at the end of equilibration. The mitochondrial ROS production rate at the end of reperfusion in the SPostC group was significantly lower than the rate in the I/R group. After the application of the HIF-1α inhibitor, the ROS production rates were not significantly different between the MSP and I/R groups (P>0.05) (Table 3).

Ultrastructure of myocardial mitochondria

In the C group, the myofilaments typically exhibited an ordered arrangement with no obvious dissolution or fractures; the morphology of the mitochondria was intact with a round or oval shape and an orderly arrangement, and the cristae were closely connected. In the I/R group, the myocardial structure was severely damaged, with the myofilaments dissolved or even fractured; the mitochondria were significantly swollen, the crista space was widened and broken, and the sarcoplasmic reticulum was highly expanded. In the SPostC group, the myofilaments exhibited an ordered arrangement; some myofilaments and sarcomere spaces were widened and dissolved, but the majority of the mitochondria had an intact morphology with clear and visible cristae. Conversely, some mitochondria were slightly swollen but did not exhibit dissolutions and ruptures. In the MSP group, the myocardial structure was damaged, the myofilaments were dissolved, and the mitochondria were significantly swollen (Figure 4).

Discussion

Our study showed that SPostC significantly up-regulated HIF-1α protein expression when compared to the I/R group, improved mitochondrial respiratory function and mitochondrial respiratory enzyme activity, and relieved ischemia-reperfusion injury. However, the myocardial protection effect of SPostC completely disappeared after the application of the HIF-1α inhibitor. This suggested that the myocardial protection effect of SPostC might be associated with the improvement of mitochondrial respiratory function after the up-regulation of HIF-1α expression.

As a representative inhalational anesthetic, sevoflurane has been applied extensively in clinical practice. Compared to other volatile anesthetics, sevoflurane not only produces excellent anesthetic effects but also plays important protective roles in the perioperative myocardial ischemia-reperfusion process; therefore, it is considered as the choice of selection when defending the perioperative myocar-
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dial ischemia-reperfusion injury. Our results showed that LVDP, +dp/dt\textsubscript{max}, and HR were significantly increased at the end of reperfusion in the SPostC group compared to the I/R group, which was consistent with the results of Inamura et al [19]. Currently, the function of SPostC in the improvement of cardiac functions in the ischemic heart is thought to be associated with its maintenance of normal mitochondrial structure and function [20, 21].

The mitochondrion is the key organelle that provides energy to the myocardia. During ischemia-reperfusion, mitochondrial structures and mitochondrial respiratory functions are damaged, causing a reduction in ATP synthesis that further aggravates myocardial injury [22, 23]. Previous studies confirmed that HIF-1 plays a critical role in the defense against myocardial ischemia-reperfusion injury [10]. Upon treatment with the HIF-1α-specific inhibitor 2ME2, HIF-1α levels after ischemia-reperfusion in isolated hearts were significantly lower than those in the ischemia-reperfusion only group and were comparable to the levels in the non-ischemic heart group [24]. Under hypoxic conditions, up-regulation of HIF-1α expression not only regulates energy production by the mitochondrial respiratory chain and maintains CcO activities but also reduces ROS production from the mitochondria to avoid myocardial injury [11].

HIF-1 is the most important transcription factor involved in the transcriptional regulation of hypoxic responses. HIF-1 is a heterodimer that is primarily composed of the HIF-1α and HIF-1β subunits. Under normal oxygen conditions, prolyl hydroxylase (PHD) and factor inhibiting HIF (FIH) in normal cells use oxygen as the sub-

Figure 4. The changes in the myocardial ultrastructure in the left ventricle at the end of reperfusion (n=4). The magnification is 10,000×.
strate to hydroxylate the HIF-1α protein in the cytoplasm. Then, the hydroxylated HIF-1α is ubiquitinated by the E3 ubiquitin ligase complex von Hippel-Lindau (VHL) and degraded through the ubiquitin-proteasome degradation pathway. Under hypoxic conditions, PHD and FIH are suppressed and HIF-1α degradation is blocked. A large number of HIF-1α proteins accumulate and are translocated into the nucleus to form heterodimers with HIF-1β to produce active HIF-1. HIF-1 interacts with hypoxia response elements to regulate downstream target gene expression, which is conducive to cell survival under hypoxic conditions [25].

In this study, to confirm whether the myocardial protective function of SPostC was associated with the maintenance of mitochondrial respiratory function after HIF-1 up-regulation, we measured the HIF-1α protein expression level. The results showed that HIF-1α protein expression was significantly increased in the SPostC group and the mitochondrial state 3 respiration, RCR, and mitochondrial respiratory chain enzyme activities (Cco, NADHO, and SUCO) were significantly better than those in the I/R group. Moreover, the mitochondrial ultrastructure in the SPostC was more intact and the ROS production rate was significantly lower than that in the I/R group. To validate the experimental results, we applied the HIF-1α inhibitor 2ME2 and found that the above advantages of SPostC disappeared completely. Therefore, our results suggested that the myocardial protective function of SPostC might be due to the up-regulation of HIF-1α expression by improving mitochondrial respiratory function, thereby relieving myocardial ischemia-reperfusion injury.

The study conducted by Sirvinskas et al also found that the application of sevoflurane during coronary artery bypass grafting surgery protected the myocardial mitochondrial outer membrane from ischemia-reperfusion injury and avoided the loss of CcO [26]. However, the researchers did not identify the pathway used by sevoflurane to protect the integrity of mitochondrial structure and function. In this study, we hypothesized that SPostC could reduce ROS release by the mitochondria to avoid injury to the mitochondrial membrane system through the up-regulation of HIF-1α expression [27, 28] thereby maintaining normal mitochondrial respiratory chain operations to provide energy for the restoration of cardiac function after myocardial ischemia-reperfusion; alternatively, SPostC could increase the nuclear translocation and expression of HIF-1α to promote the binding between HIF-1α and HIF-1β to form active HIF-1, which in turn could promote the expression of downstream target genes, promote mitochondrial respiration, and maintain mitochondrial enzyme activity, thereby relieving myocardial ischemia-reperfusion injury.

Conclusion

Our study showed that SPostC up-regulated HIF-1α expression in the rat myocardia, improved mitochondrial respiratory function during myocardial ischemia-reperfusion, and maintained normal mitochondrial electron transport chain function, thereby relieving myocardial ischemia-reperfusion injury in rats. This study will provide theoretical support for the mechanism underlying the myocardial protection by SPostC.

Acknowledgements

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Disclosure of conflict of interest

None.

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