Effect of ischemic postconditioning on cell apoptosis and expression of relevant genes in non-culprit coronary arteries

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ABSTRACT

This study was performed to determine the effect of ischemic postconditioning on cell apoptosis and angiotensin II receptor type 1 (AT1), connexin 43 (Cx43), and β-tubulin mRNA expression in non-culprit arteries. Non-culprit arterial tissues were isolated from a rabbit myocardial ischemia-reperfusion model and randomly divided into sham, ischemia-reperfusion, and ischemic postconditioning groups. Cell apoptosis was detected by terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) staining. Expression of angiotensin II, AT1, Cx43, and β-tubulin mRNA was evaluated by quantitative real-time polymerase chain reaction (qRT-PCR). TUNEL analysis indicated significantly higher ratios of apoptotic cells in the ischemia-reperfusion group than in the sham group. However, significantly fewer apoptotic cells were observed in the ischemic postconditioning group than in the ischemia-reperfusion group. The qRT-PCR results indicated significantly higher expression of AT1, Cx43, and β-tubulin mRNA in the ischemia-reperfusion group than in the sham group. However, expression of AT1, Cx43, and β-tubulin was lower in the ischemic postconditioning group than in the ischemia-reperfusion group. The ratios of apoptotic cells and mRNA expression of AT1, Cx43, and β-tubulin in non-culprit arteries were increased after ischemia-reperfusion. Ischemic postconditioning may decrease these features and inhibit the progression of non-culprit arteries.

INTRODUCTION

The fundamental treatment strategy of ST-segment elevation myocardial infarction (STEMI) is the earliest possible restoration of myocardial perfusion. Primary percutaneous coronary intervention (PCI) is the most effective treatment for STEMI. PCI has good success rates in restoring blood flow and low rates of infarction or recurrent ischemia, which significantly improves patients’ quality of life and prevents further myocardial necrosis. However, approximately 40%–65% of patients with STEMI present with three-vessel lesions. Additionally, recent clinical studies have shown that PCI can lead to the progression of non-culprit lesions, which might be the most significant factor influencing the prognosis after PCI. The molecular mechanisms of myocardial ischemia-reperfusion (IR) involve myocyte apoptosis, increased

Significance of this study

What is already known about this subject?

- Primary percutaneous coronary intervention can lead to the progression of non-culprit lesions in patients with ST-segment elevation myocardial infarction, which might be the most significant factor influencing the prognosis after primary percutaneous coronary intervention.
- Non-culprit lesion progression can be affected by many factors, such as increased levels of catecholamines and activation of the angiotensin II/mitogen-activated protein kinase/connexin 43 (AgII/MAPK/Cx43) pathway.
- Ischemic postconditioning may inhibit the AgII/MAPK/Cx43 pathway and non-culprit lesion progression. However, the mechanism by which ischemic postconditioning affects the progression of non-culprit lesions has not been examined.

What are the new findings?

- The ratios of apoptotic cells and mRNA expression of AgII receptor type 1 (AT1), Cx43, and β-tubulin in non-culprit arteries were increased after ischemia-reperfusion.
- Ischemic postconditioning may decrease these features and inhibit the progression of non-culprit lesions.

How might these results change the focus of research or clinical practice?

- Apoptosis and mRNA expression of AT1, Cx43, and β-tubulin in non-culprit coronary arteries were increased after ischemia-reperfusion.
- Ischemic postconditioning may decrease apoptosis and the expression of these factors in non-culprit coronary arteries, thus inhibiting their pathological progression.
- In clinical practice, ischemic postconditioning may be used to inhibit non-culprit lesion progression.
catecholamine levels, and activation of the angiotensin II/mitogen-activated protein kinase/connexin 43 (AgII/MAPK/Cx43) pathway. The reason for the progression of non-culprit lesions in patients with STEMI after PCI is not clear, but chronic inflammation and sustained stress may be involved in the progression of non-culprit lesions. Our recent experimental study showed that non-culprit lesion progression can be affected by many factors, such as increased levels of catecholamines and activation of the AgII/MAPK/Cx43 pathway. In addition, Sun et al. found that ischemic postconditioning (IP) may inhibit the AgII/MAPK/Cx43 pathway. Our recent clinical study showed that IP may inhibit non-culprit lesion progression. However, the mechanism by which IP affects the progression of non-culprit lesions has not been examined. We herein report the effect of IP on cell apoptosis and the expression of angiotensin II receptor type 1 (AT1), Cx43, and β-tubulin mRNA in non-culprit coronary arteries of rabbits.

METHODS

Animal model of hyperlipidemia

The requirement for informed consent in this study was exempted by the board. As shown in figure 1, 40 healthy male rabbits were randomly divided into a hyperlipidemia group (n=30) and control group (n=10). The rabbits in the hyperlipidemia group were fed a high-fat diet for 80 days, while the rabbits in the control group were fed a normal diet for 80 days. Auricular vein blood samples were taken on the 81st day after a 12 hours fast. The serum was separated after centrifugation to measure the serum level of total cholesterol. Rabbits with a serum total cholesterol level of three times higher than the control group (1–2 mmol/L) were selected from the hyperlipidemia group and used for myocardial IR modeling.

Animal model of myocardial IR

An animal model of acute myocardial ischemia was prepared according to the following operation. Because of the long and steady maintenance of anesthesia, all rabbits were administered intraperitoneal anesthesia using urethane sodium at a dosage of 1 g/kg. In addition, all rabbits were administered 1 mg/kg of lidocaine to prevent ventricular fibrillation. In the control group, thoracotomy was performed on 10 hyperlipidemic rabbits without coronary artery ligation. Another 10 hyperlipidemic rabbits underwent thoracotomy alone. After exposing the pericardium and heart, the left anterior descending coronary artery (LAD) was clamped with 5/0 string and maintained for 30 min. An electrocardiographic monitor was connected subcutaneously (25 mm/s, 10 mm/mV). The model was defined as successfully prepared and thereafter maintained for 30 min under the following conditions: (1) ST elevation or necrotic Q wave observed in corresponding lead on the ECG and (2) dark purple myocardium in the corresponding region. After reperfusion was performed by releasing the clamp, the abdominal incisions were closed. All rabbits were fed a normal diet 1 week after the operation.

Experimental animal groups were as follows: sham group (n=10, thoracotomy without coronary artery ligation), IR group (n=10, thoracotomy, LAD ligation for 30 min, and reperfusion for 1 week), and IP group (n=10, thoracotomy, LAD ligation for 30 min, six cycles of 10 s reperfusion and 10 s ischemia, and reperfusion for 1 week).

H&E staining and observation

Coronary arterial tissues were harvested for H&E staining and observation. The tissues were embedded in paraffin, discontinuously and serially sectioned, stained with H&E, and observed under a light microscope. The thickness of each section was 4 µm. All sections were analyzed with a medical imaging analysis system to measure the thickness of the plaques.

Ratios of apoptotic cells in non-culprit coronary arterial tissues

An animal model of acute myocardial ischemia was prepared according to the following operation. Because of the long and steady maintenance of anesthesia, all rabbits were administered intraperitoneal anesthesia using urethane sodium at a dosage of 1 g/kg. In addition, all rabbits were administered 1 mg/kg of lidocaine to prevent ventricular fibrillation. In the control group, thoracotomy was performed on 10 hyperlipidemic rabbits without coronary artery ligation. Another 10 hyperlipidemic rabbits underwent thoracotomy alone. After exposing the pericardium and heart, the left anterior descending coronary artery (LAD) was clamped with 5/0 string and maintained for 30 min. An electrocardiographic monitor was connected subcutaneously (25 mm/s, 10 mm/mV). The model was defined as successfully prepared and thereafter maintained for 30 min under the following conditions: (1) ST elevation or necrotic Q wave observed in corresponding lead on the ECG and (2) dark purple myocardium in the corresponding region. After reperfusion was performed by releasing the clamp, the abdominal incisions were closed. All rabbits were fed a normal diet 1 week after the operation.

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nitrates. The slices were then washed with 1× phosphate-buffered saline (137 mM NaCl, 2.7 mM KCl, 4.3 mM NaHPO₄, and 1.4 mM KH₂PO₄; pH 7.4). Next, the slides were drained and blocked with goat serum for 30 min and then washed with 1× phosphate-buffered saline for 30 min. The terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) reaction solution was prepared by mixing an end-labeling enzyme and labeling the liquid at a ratio of 1:9. The slices were covered with the TUNEL reaction solution and incubated for 60 min in a moist chamber at 37°C. Negative controls were incubated with labeling liquid without an end-labeling enzyme instead of the TUNEL reaction solution. Positive controls were incubated with DNase I at a concentration of 5.1 U/mL for 10 min at room temperature before adding the TUNEL reaction solution. The samples were blocked with glycerol and observed using a fluorescence microscope (Olympus IX71; Olympus, Tokyo, Japan). Normal nuclei were labeled with blue fluorescence by 4′,6-diamidino-2-phenylindole (DAPI) dye, whereas apoptotic nuclei were labeled with red fluorescence by the TUNEL reagent. Each sample was counted in at least three fields (200× magnification). Apoptosis was determined by the number of positive nuclei per muscle cell. The ratio of apoptotic cells was obtained as the ratio of TUNEL-positive to DAPI-positive cells.

Quantitative real-time polymerase chain reaction for expression of AT1, Cx43, and β-tubulin mRNA in non-culprit coronary arterial tissues

TRIzol and chloroform reagents were used to extract total RNA from vascular smooth muscle cells according to the manufacturer’s instructions. Briefly, after the addition of 2 mL of TRIzol reagent to lyse vascular smooth muscle cells for 20 min, the sample was transferred to a 2 mL Eppendorf tube. Next, 400 µL of chloroform was added. The tube was shaken vigorously for 30 s and allowed to stand for 15 min. Next, the sample was centrifuged at 13,000 × g for 15 min at 4°C. The supernatant from the final extraction step was transferred to a clean 2 mL Eppendorf tube, in which RNA was precipitated with 500 µL of isopropanol at −20°C for 2 h. Precipitated RNA was collected by centrifugation at 13,000 × g for 15 min at 4°C, and the pellet was washed with 1 mL of 75% ice-cold ethanol. The RNA pellet was resuspended in 20 µL of nuclease-free water, and the two duplicate tubes were combined. The RNA concentration was measured using a spectrophotometer (Biolab ND-1000; Thermofisher Scientific, Waltham, MA, USA) at 260 nm. RNA purity was assessed by determining the A260/A280 ratio.

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Table 1  Primer sequences for RT-PCR

| Gene name | GenBank accession no. | Forward primer 5′–3′ | Reverse primer 5′–3′ |
|-----------|----------------------|----------------------|----------------------|
| AT1       | NM_030985.4          | TCTGACATCGTGACGACTGC | CGTAGACAGGGCTTGAGTGG |
| Cx43      | NM_012567.2          | GACTGCTTCACTCGACTGCC | CGCGATCCTTAACGCCTTG |
| β-tubulin | NM_139254.2          | CTGCTCATACGCAAATGCG  | TGGGGAAGCAAGATGCGTAG |

Statistical analysis

Statistical analysis was performed using SPSS 20.0 statistical software (IBM, Armonk, New York, USA). Descriptive statistical data are expressed as mean ± SD. Statistical significance was determined using one-way analysis of variance and the least significant difference test. P < 0.05 was considered statistically significant.

RESULTS

H&E staining of non-culprit arterial tissues

H&E staining indicated that the structures of non-culprit artery tissues were clear and that the alignment of vascular smooth muscle fibers was regular in each group. However,
significant atherosclerotic plaques were present in the IR and IP groups compared with the sham group (figure 2).

**Ratios of apoptotic cells in non-culprit coronary arterial tissues**

As shown in figure 3, a higher ratio of apoptotic cells was observed in non-culprit coronary arterial tissues of the IR group than sham group (46.11±5.92 vs 3.77±6.31, p<0.001). However, a lower ratio of apoptotic cells was observed in non-culprit coronary arterial tissues in the IP group than IR group (28.36±9.41 vs 46.11±5.92, p<0.001).

**AT1, Cx43, and β-tubulin mRNA expression in non-culprit coronary arterial tissues**

Expression of AT1 (30.576±1.760 vs 1.002±0.068, p<0.01), Cx43 (15.171±1.736 vs 1.009±0.133, p<0.01), and β-tubulin (1.361±0.042 vs 1.003±0.083, p<0.01) mRNA in the IR group was significantly higher than that in the sham group. However, expression of AT1 (4.697±0.227 vs 30.576±1.760, p<0.01), Cx43 (2.267±0.312 vs 15.171±1.736, p<0.01), and β-tubulin (1.083±0.098 vs 1.361±0.042, p<0.01) mRNA was significantly lower in the IP than IR group (figure 4).

Expression of Cx43 protein was significantly higher in the IR than sham group (1.69±0.21 vs 1.05±0.11, p<0.0001). However, expression of Cx43 protein was significantly lower in the IP than IR group (0.81±0.15 vs 1.69±0.21, p<0.0001) (table 2, figure 5).

**DISCUSSION**

PPCI in a culprit artery is the preferred strategy for the treatment of patients with acute STEMI. However, approximately 40%–65% of patients with STEMI present with three-vessel lesions. A clinical follow-up study of such patients after successful PPCI suggested that non-culprit lesions may progress, which may be the most important factor influencing the prognosis of patients with acute myocardial infarction after successful PPCI.4

Few studies have examined the progression of non-culprit lesions. Hanratty et al demonstrated exaggeration of non-culprit lesions during acute myocardial infarction and indicated that inflammatory and spastic mechanisms may be involved in non-culprit lesion progression. On follow-up angiography of 117 patients with acute coronary syndrome, Tsiamis et al found that non-culprit lesions may progress and that acute myocardial infarction may be an independent predictive factor for this progression. Our previous study suggested that non-culprit lesion progression may be the most important prognostic factor in patients with STEMI after successful PPCI. This indicates that inflammation and stress might contribute to the progression of non-culprit lesions. In addition, the AgII-MAPK-Cx43 pathway might be involved in the progression of non-culprit lesions according to the findings in a rabbit model of IR.6 Sun et al demonstrated that IP can inhibit the MAPK-Cx43 pathway, indicating that IP may inhibit non-culprit lesion progression.

In the present study, we investigated the effect of IP on cell apoptosis and mRNA expression of AT1, Cx43, β-tubulin, and Cx43 protein in non-culprit coronary arteries of a rabbit IR model. H&E staining of non-culprit arterial tissues showed that the structures of the non-culprit arterial tissues were clear and that the alignment of vascular smooth muscle fibers was regular in each group. There were no significant pathological changes in the IR or IP group compared with the sham group (figure 1).

Quantitative analysis of apoptosis in non-culprit coronary arterial tissues indicated significantly higher ratios of apoptotic cells in the IR than sham group (46.11±5.92 vs 3.77±6.31, p<0.001). Moreover, the ratios of apoptotic cells were significantly lower in the IP than IR group (28.36±9.41 vs 46.11±5.92, p<0.001). These results suggest that IR may increase cell apoptosis in non-culprit coronary arterial tissues and that IP may prevent non-culprit lesion progression by inhibiting this apoptosis.
Quantitative analysis of AT1, Cx43, and β-tubulin mRNA expression in non-culprit coronary arterial tissues indicated higher expression of AT1 and β-tubulin in the IR than sham group. In addition, lower expression of AT1 and β-tubulin mRNA was observed in the IP than IR group. These results indicate that AT1, Cx43, and β-tubulin may participate in the progression of non-culprit lesions and that IP may prevent this progression by inhibiting mRNA expression of AT1, Cx43, and β-tubulin and activation of the AgII-MAPK-Cx43-β-tubulin pathway in non-culprit coronary arterial tissues.\(^{11-14}\)

We observed lower mRNA expression of AT1, Cx43, and β-tubulin, and Cx43 protein in non-culprit coronary arteries in the IP than IR group. However, He et al\(^{15}\) found that IP increased Cx43 expression in the left ventricular myocardial cellular membrane and attenuated reperfusion injury in a rat model of acute myocardial infarction. Although this result was not in conflict with our findings, He et al\(^{15}\) investigated the role of IP on Cx43 expression in the left ventricular myocardial cellular membrane during an early stage (1 and 3 hour after reperfusion), whereas we investigated the role of IP on expression of non-culprit coronary arteries at a later stage (1 week after reperfusion).

Schulz et al\(^{16}\) reported that in contrast to its importance for ischemic or pharmacological preconditioning, Cx43 does not impact the cardioprotection achieved by IP. The results of their study also implied a role for IP on Cx43 expression in the left ventricular myocardial cellular membrane during the early stage, which is not in conflict with our findings.

Cx43 is present in the cell membrane and in mitochondria. Indeed, Cx43 in the inner mitochondrial membrane may participate in functional coordination between subsarcolemmal and interfibrillar mitochondria. Cx43 in the subsarcolemmal mitochondria is involved in regulation of reactive oxygen species production through modulation of potassium permeability and oxidative phosphorylation. Notably, subsarcolemmal mitochondria appear to play a prominent role in superoxide production. In addition, Cx43 in subsarcolemmal mitochondria is involved in calcium uptake from the sarcoplasmic reticulum and antioxidant regeneration. In contrast, interfibrillar mitochondria are important players in energy demand—supply matching, cytosolic calcium buffering, and antioxidant regeneration as a result of their intimate communication with the sarcoplasmic reticulum. In the present study, we aimed to determine the effect of IP on cell apoptosis and mRNA expression of AT1, Cx43, β-tubulin, and Cx43 protein in non-culprit coronary arteries of rabbits. As such, differences in the distribution and function of Cx43 in various cellular locations, as well as the role of individual mitochondrial subpopulations, should be investigated in future studies.

In our recent study, we investigated the expression of β-tubulin in non-culprit arteries and the effect of ramipril on lesion progression. Our results indicated that a sympathetic nervous system catecholamine/AgII/Cx43/β-tubulin pathway may participate in the progression of non-culprit lesions.\(^{15}\) In this study, we also found increased expression of AT1, Cx43, and β-tubulin mRNA in non-culprit coronary arteries after IR. IP may decrease the ratio of apoptotic cells and expression of AT1, Cx43, and β-tubulin mRNA in non-culprit coronary arteries, thus inhibiting non-culprit lesion progression. Moreover, our results indicated that IP inhibited the sympathetic catecholamine/AgII/Cx43/β-tubulin pathway.

**CONCLUSION**

Apoptosis and mRNA expression of AT1, Cx43, and β-tubulin in non-culprit coronary arteries were increased after IR. However, IP may decrease apoptosis and expression of these factors in non-culprit coronary arteries, thus inhibiting their pathological progression. In clinical practice, IP may be used to inhibit non-culprit lesion progression.

**Data availability statement** Data are available on reasonable request. All data were available in database of Aerospace Center Hospital, Peking University Aerospace School of Clinical Medicine.

**Table 2** Effect of IP on the expression of Cx43 in non-culprit coronary arterial tissues (Cx43/β-actin optical absorption ratio)

|                | n=10 The control group | n=10 The sham group | n=10 IR group | n=10 IP group |
|----------------|------------------------|---------------------|--------------|--------------|
| Cx43/β-actin optical absorption ratio | 0.51±0.13               | 1.05±0.11*          | 1.69±0.21†  | 0.81±0.15†  |

*Compared with normal control group, p<0.0001.
†Compared with the sham group, p<0.0001.
‡Compared with IR group, p<0.0001.

Cx43, connexin 43; IP, ischemic postconditioning; IR, ischemia-reperfusion.

**Figure 5** Effect of ischemic postconditioning (IP) on the expression of Cx43 in non-culprit coronary arterial tissues. n=10/group. From left to right: normal control group, sham group, IR group, IP group. Cx43, connexin 43; IP, ischemic postconditioning; IR, ischemia-reperfusion.
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