

Effects of remote ischemic preconditioning on contrast induced nephropathy after percutaneous coronary intervention in patients with acute coronary syndrome

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Abstract

Objective: The aim of this study was to explore the clinical effects of remote ischemic preconditioning (RIPC) on contrast-induced nephropathy after percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS).

Patients and Methods: The study was a single-center, prospective, randomized, controlled study. A total of 161 patients with ACS and the rate of estimate glomerular filtration (eGFR) 15 to 70 mL/min/1.73 m² undergoing PCI were randomly assigned to RIPC group (induced by 4 times of 5-minute inflations of a blood pressure cuff to 200 mmHg around the upper arm, followed by 5-min intervals of reperfusion at 1 hour before PCI therapy) or control group (an uninflated cuff around the arm). Successful completion of the PCI eventually included 107 cases of patients, including 50 cases in the RIPC group and 57 cases in the control group. The level of serum creatinine (Scr), CystatinC (CysC), blood neutrophil gelatinase-associated lipocalin (NGAL), eGFR were measured in all patients at 6 AM before the day of PCI, and 4-hour NGAL, 24-hour CysC, 72-hour Scr, and eGFR after PCI in the 2 groups. The incidence of major adverse events in the kidney (including the incidence of CIN, the need for dialysis, or renal replacement therapy after using contrast agent) and the composite endpoint of cardiovascular events were recorded at 6 months after PCI.

Results: There were no statistically significant differences in baseline indicators between the 2 groups. Scr, CysC, and blood NGAL levels and the incidence of CIN in patients with RIPC group were significantly lower than those from the control group after PCI ($P < .05$), but there were no significant differences between the average value of eGFR and occurrence of Major cardiovascular events in the postoperative 6 months ($P > .05$).

Conclusions: RIPC can reduce PCI-related CIN and protect renal function in patients with ACS. The benefits of these patients by RIPC may be related to the reduction of the NGAL and CysC.

Abbreviations: ACS = acute coronary syndrome, BMI = body mass index, CIN = contrast-induced nephropathy, CysC = cystatinC, eGFR = estimated glomerular filtration rate, ESCMDDRD = Modification of Diet in Renal Disease, NGAL = blood neutrophil gelatinase-associated lipocalin, PCI = percutaneous coronary intervention, RIPC = remote ischemic preconditioning, Scr = serum creatinine.

Keywords: acute coronary syndrome, contrast-induced nephropathy, percutaneous coronary intervention, remote ischemic preconditioning, renal insufficiency

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1. Introduction

Acute coronary syndrome (ACS) is caused by coronary atherosclerotic plaques resulting in coronary stenosis; it can lead to myocardial infarction. Percutaneous coronary intervention (PCI) is the most effective means in the treatment of ACS in the world.^[1] In recent years, with the development of clinical diagnosis and interventional therapy, the dose of contrast agent in PCI is increasing, and PCI can lead to contrast-induced nephropathy (CIN). Therefore, CIN has become a common complication of PCI, and has become the third leading cause of acute renal failure in hospital.^[2,3] The diagnostic criteria of CIN was that the absolute value of serum creatinine (Scr) in 48 to 72 hours after the injection of contrast agent was increased by >44.2 mmol/L or above the base value of 25%, and was not associated with other renal damage.^[4,5] In addition to hydration, there is still no effective prophylactic regimen available to prevent occurrence of CIN recently.^[6] Therefore, it is urgent to explore new methods to reduce the incidence of CIN. At present, most of the research evidence show that CIN is the result of renal hypoxia injury and the direct cytotoxicity of contrast agents to the

kidney.^[7] Renal ischemia and reperfusion injury play a key role in the occurrence of CIN.^[8,9] So prevention of renal ischemia reperfusion injury may be an effective measure to prevent CIN. Ischemic preconditioning is a kind of measure that can effectively protect the ischemic reperfusion injury. Przyklenk et al, on the basis of ischemic preconditioning, first proposed the concept of remote ischemic preconditioning (remote ischemic preconditioning, RIPC) in 1993.^[10] It can reduce the ischemia and reperfusion injury of target organs by stimulating endogenous protection. This method was less invasive and stronger feasibility than in situ ischemic preconditioning. It has a good application prospect. Therefore, it is particularly important to find ways to prevent CIN after PCI in patients with ACS. At present, the reports showed that RIPC can reduce myocardial ischemia reperfusion injury in the field of animal experimental research. However, there is a lack of large-scale clinical studies in RIPC, and there are different opinions on prevention of CIN. The purpose of this study was to investigate the protective effects of RIPC on prevention of CIN after PCI and its impact on major adverse events in patients with ACS, to provide new measure for the prevention of CIN.

2. Patients and methods

2.1. Patients

This study was a single-center, prospective, randomized, controlled study. A total of 161 patients with ACS undergoing PCI from March 2014 to March 2016 in Tai'an Central Hospital were collected and randomly divided into RIPC group (72 cases) and control group (89 cases). This study was approved by the Ethics Committee of Tai'an Central Hospital. Signed written informed consents were obtained from all participants before the study. Of these, 54 patients were excluded because they did not undergo PCI. There were 6 cases in RIPC group and 4 cases in control group did not undergo PCI, as coronary angiography showed severe lesions in 3 coronary arteries. Sixteen cases in RIPC group and 28 cases in control group did not undergo PCI, owing to coronary artery stenosis <75%. A total of 107 patients (50 cases in RIPC group and 57 cases in control group) underwent elective PCI successfully and finally were included in this study.

2.2. Inclusion criteria

The inclusion criteria were the clinical manifestations of patients according to Canadian Cardiovascular Society angina pectoris grade II–IV; the patients undergoing selective coronary angiography and were determined at least I coronary artery stenosis, and the degree was >75% (diameter method); the location of the stenosis was the definition of ACC/AHA of A or B lesions; coexist renal inadequacy (that rate of estimate glomerular filtration [eGFR] is between 15 and 70 mL/min/1.73 m²).

2.3. Exclusion criteria

Exclusion criteria were allergic to contrast media patients; patients who use of nephrotoxic drugs in the last 1 month; with malignant tumor patients; severe liver damage and maintenance hemodialysis patients with renal failure; renal transplant patients; mental diseases, among others.

2.4. Baseline materials

Demographic characteristics of the patients were collected and recorded in detail, including sex, age, height, weight, body mass

index (BMI), risk factors for coronary heart disease, combined disease, drug treatment, and physical examination results.

All patients completed the routine examination, including routine blood test, liver and kidney function, blood glucose and blood lipid, myocardial enzymes, cardiac markers, ion biochemistry, coagulation system, thyroid function, glycosylated hemoglobin by fasting hemospasia at 6 AM. All patients signed informed consent. The patients were divided into RIPC group and control group according to the random number table. Two groups were treated with antiplatelet agents, statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β -receptor blockers, calcium antagonists, and nitrates and other conventional treatment. According to the 2006 International CIN expert consensus recommended,^[11] standard hydration was used as preventive treatment to all patients before and after PCI. As a standardized treatment, all patients received 0.9% normal saline intravenously 6 hours before the coronary angiography and 12 hours after the operation. Special patients were adjusted according to the cardiac function and urine volume. Diabetes patients before 48 hours of the operation change metformin to insulin therapy. The RIPC group received remote ischemic preconditioning at 1 hour before PCI; the specific method was 5-minute inflations of a blood pressure cuff to 200 mmHg around the upper arm, followed by 5-minute intervals of reperfusion by 4 times. The control group was not treated.

2.5. Operation procedures

All patients underwent coronary angiography. Coronary stent implantation was performed in patients with coronary artery stenosis >75%. The stents were all drug-eluting stents. Vascular lesions, balloon expansion pressure, the expansion time, the number of stents, stent length, postoperative blood flow Thrombolysis in myocardial infarction and the amount of contrast agent, coronary artery dissection, collateral vascular compression, reflow, coronary artery spasm, thrombosis, and other complications for coronary artery were recorded; electrocardiogram changes and vital signs were monitored during the operation.

2.6. Biochemical measurement

All patients were detected Scr, CystatinC (CysC), blood neutrophil gelatinase related lipid carrier protein(NGAL) on an empty stomach one day before operation, and the simplified Modification of Diet in Renal Disease (MDRD) equation was used to calculate eGFR. After angiography, all patients measured blood NGAL in 4 hours, blood CyC in 24 hours, serum creatinine and eGFR in 72 hours. The levels of Scr and CysC in the department were determined in Clinical Laboratory of Tai'an Central Hospital. Blood NGAL was detected by latex-enhanced turbidimetric immunoassay; the reagent was provided by Beijing nine strong Biotechnology Co. Ltd. The tests were performed in strict accordance with the instructions of the reagents and equipment suppliers.

2.7. End event

- (1) The primary end point was to detect the difference of Scr, Cysc, eGFR, NGAL levels of 2 groups of patients before and after PCI and the incidence of CIN in the 2 groups.
- (2) The secondary end points were adverse renal outcomes including the number of patients with renal failure undergoing dialysis or kidney transplantation, readmission, and death.

2.8. Postoperative follow-up

Patients were followed up for 6 months after coronary angiography. The major adverse renal events (renal failure owing to dialysis or renal transplantation) and composite cardiovascular end points (readmission and death) in the 2 groups were recorded.

2.9. Statistical analysis

All the data were analyzed by SPSS19.0 (Ver-sion X; IBM, Armonk, NY) statistical software. The measurement data were expressed to mean±standard deviation. Before the comparison between groups, the normality test and the homogeneity of variance test were carried out. Paired data *t* test and independent sample *t* test were used to measure the normal distribution and homogeneity of population variance, whereas the rank sum test was used in non-normal distribution. Enumeration data were analyzed with χ^2 test. The difference was statistically significant with *P* < .05.

3. Results

3.1. Basic data for the enrolled participants

As shown in Table 1, there was no significant difference in risk factors such as age, sex, BMI, blood lipid, fasting blood glucose, and medical history. There was no statistical difference between the 2 groups in the routine drug treatment, the operation of PCI, and the amount of contrast agent (Table 1).

3.2. Scr, Cys C, NGAL, and eGFR level changes

There were no significant differences of Scr, Cys C, NGAL, and eGFR (*P* > .05) between 2 groups before PCI (*P* > .05). The level of patients postoperative with 72-hour Scr, 24-hour CysC, 4-hour NGAL in 2 groups was higher than that before operation

(*P* < .05).The eGFR of 72 hours was significantly lower than that before operation (*P* < .05). The levels of 72-hour creatinine (Cr), 24-hour CysC, 4-hour NGAL in the control group were higher than that in RIPC group (*P* < .05).The postoperative 72-hour eGFR of control group was lower than that of RIPC, but the difference was not statistically significant (*P* > .05), as shown in Table 2.

3.3. Comparison of CIN incidence

As shown in Table 3, 2 groups of patients with CIN occurred in control group of 15 cases, RIPC group of 5 cases, and the incidence of RIPC group was lower than that of the control group (*P* < .05).

3.3.1. Comparison of major adverse renal events and cardiovascular events in patients with RIPC group and control group. After 6 months of PCI, the patients were followed up. A total of 5 patients in RIPC group and control group were admitted to hospital, including RIPC group of 3 cases, the control group of 2 cases. The results showed that there was no significant difference between the 2 groups in readmission, renal dialysis, or transplantation, and death (*P* > .05) as shown in Table 4.

3.3.2. Adverse reactions of RIPC. RIPC group had 3 patients with upper arm ischemic discomfort, and 5 patients suffered from distal skin ecchymosis or petechia owing to blood pressure cuff compression. However, those reactions did not affect the pretreatment process.

4. Discussion

With the extensive development of cardiac intervention, CIN has become a common complication of cardiovascular angiography and interventional therapy.^[12] Early detection and prevention of CIN are of great significance. At present, it is considered that the

Table 1
Comparison of the general information between the control group and the RIPC group.

General information	Control group (n=57)	RIPC group (n=50)	<i>t</i> or χ^2 value	<i>P</i>
Age	69.14 ± 7.80	69.42 ± 7.07	-0.193	.847
Sex (male/female)	35/22	30/20	0.022	.882
BMI, kg/m ²	25.61 ± 4.12	25.35 ± 3.98	0.331	.740
Smoke, n (%)	10 (17.54)	12 (16.00)	0.045	.831
Hyperlipidemia, n (%)	15 (26.32)	12 (24.00)	0.076	.783
Diabetesm n (%)	27 (47.37)	24 (48.00)	0.004	.948
Hypertension, n (%)	32 (56.14)	28 (56.00)	0.000	.988
Old myocardial infarction, n (%)	6 (10.53)	8 (16.00)	0.702	.402
PCI history, n (%)	10 (17.54)	9 (18.00)	0.040	.951
Contrast agent dosage, mL	108.82 ± 43.25	114.76 ± 44.22	-0.701	.485
Medication				
Aspirin, n (%)	57 (100)	50 (100)	—	—
Clopidogrel, n (%)	57 (100)	50 (100)	—	—
Statins, n (%)	55 (96.49)	47 (94.00)	0.023	.881
β-blockers, n (%)	40 (70.18)	38 (76.00)	0.457	.499
ACEI or ARB, n (%)	38 (66.67)	35 (70.00)	0.137	.712
Calcium antagonist, n (%)	20 (35.08)	16 (32.00)	0.114	.736
Diuretic, n (%)	20 (35.09)	22 (44.00)	0.000	.988
Spirolactone, n (%)	8 (14.03)	9 (18.00)	0.313	.576
Insulin, n (%)	14 (24.56)	12 (24.00)	0.005	.946
Hypoglycemics, n (%)	16 (28.07)	12 (24.00)	0.048	.826
IIb/IIIa receptor antagonist, n (%)	0 (0.00)	0 (0.00)	—	—

ACEI=angiotensin-converting enzyme inhibitor, ARB=angiotensin II receptor blocker, BMI=body mass index, PCI=percutaneous coronary intervention, RIPC=remote ischemic preconditioning.

Table 2

Comparison of postoperative renal function index in control group and RIPC group.

Index	Control group (n=57)	RIPC group (n=50)	t value	P
Scr, μmol/L				
Preoperative	93.526 ± 19.114	90.420 ± 17.464	0.873	.385
72 h after operative	108.772 ± 35.83*	95.980 ± 24.300* [†]	2.183	.031
CysC, mg/L				
Preoperative	1.157 ± 0.188	1.119 ± 0.169	1.073	.286
24 h after operative	1.333 ± 0.366*	1.178 ± 0.184* [†]	2.814	.006
NGAL, ng/mL				
Preoperative	175.614 ± 53.275	174.440 ± 45.030	0.122	.903
4 h after operative	228.509 ± 74.394*	198.260 ± 56.714* [†]	2.381	.019
eGFR, mL/min/1.73 m ²				
Preoperative	68.023 ± 10.168	69.994 ± 8.908	-1.059	.292
72 h after operative	60.948 ± 18.441*	67.088 ± 14.837*	-1.880	.630

CysC=cystatinC, eGFR=estimated glomerular filtration rate, NGAL=blood neutrophil gelatinase-associated lipocalin, RIPC=remote ischemic preconditioning, Scr=serum creatinine.

*Was compared with the preoperative, P<.05.

[†]Was compared with the control group, P<.05.

key factor of CIN is the change of renal hemodynamics caused by contrast agent, which leads to the occurrence of medulla nephric ischemia and hypoxia injury.^[13]

RIPC is an effective endogenous protective mechanism against ischemia/reperfusion injury. It protects the heart and has a protective effect on the brain, kidney, small intestine, liver, skeletal muscle and other organs, and has the universality of organs.^[14,15] In 2000, Ogawa et al^[16] found that ischemic preconditioning can alleviate the renal damage in rats after 40-minute ischemia. In the study of 924 patients with cardiac or vascular surgery, it was found that the incidence of acute renal dysfunction in the distal ischemic preconditioning group was significantly lower than that in the control group.^[17] In recent years, some researchers reported the role of limb ischemic preconditioning in preventing CIN in patients with renal insufficiency.^[18-21] However, for patients with ACS undergoing PCI, there is a lack of large-scale clinical studies to prevent CIN by RIPC. The study of preventing CIN is still in its infancy for patients with ACS undergoing PCI currently. This study shows that recirculation treatment of 5 times of 5-minute ischemia (pressure maintained at 200 mmHg) of /5 min can reduce the incidence of CIN. There were 20 cases of CIN in the study, including RIPC group of 5 cases (10%), and control group of 15 cases (26.3%). It suggests that RIPC can reduce the incidence of CIN in patients with ACS undergoing PCI.

At present, Cr is the main criterion for CIN. It often rises to peak at 72 hours after PCI. In this study, 107 cases of patients with ACS undergoing PCI treatment, the difference of the creatinine level between 72 hours after operation and preoperation was statistically significant. CysC is a cysteine proteinase inhibitor,^[22] it has small molecular weight, and it can freely through the glomerular filtration. It can be fully absorbed by

renal tubular epithelial cells, and no longer returns to the blood, whereas the renal tubules do not secrete CysC. Because of these characteristics, CysC is superior to Cr, which is a good indicator of renal function.^[23] NGAL is a kind of trace protein; it is an early and sensitive biomarker of renal injury. It reached the peak at 4 hours after renal ischemia. Glomerular filtration rate (GFR) is the most important indicator of renal function. It cannot be directly measured; it is generally believed that the MDRD equation is an effective way to calculate GFR.^[24]

The study found that serum NGAL after PCI 4 hours was significantly higher than that before operation in the 2 groups (P<.05), and CysC postoperative 24 hours was significantly higher than preoperative (P<.05). The levels of Cr and GFR postoperative 72 hours were significantly higher than those before angiography. This indicates that the NGAL and CysC are more sensitive than Cr and GFR, and they can detect CIN early. It is of great value in the diagnosis of CIN.

The mechanism of the protective effect of RIPC is unclear. Previous studies have suggested that the mechanism of renal protection by RIPC is that it can play a role in anti-inflammatory and nerve and humoral pathways by activating a variety of factors.^[6] The latest research finds that the mechanism of effect of RIPC reduces renal damage in CIN through the activation of tumor necrosis factor α/nuclear factor-κB pathway, and then increases the high expression of renal enzymes in the body and plays the role of anti-apoptosis, anti-inflammatory, and antioxidant protection of kidney.^[25]

Therefore, RIPC, as an effective endogenous protective mechanism against ischemia/reperfusion injury, has broad prospects in the prevention of CIN for patients with ACS undergoing PCI, and provides a new effective way to prevent CIN for ACS patients undergoing PCI treatment.

Table 3

Comparison of the incidence of CIN in control group and RIPC group after CAG, n (%).

Group	Total cases	incidence of CIN
Control group	57	15 (26.3%)
RIPC group	50	5 (10.0%)
χ ² Value		4.665
P		.031

CAG=coronary angiography, CIN=contrast-induced nephropathy, RIPC=remote ischemic preconditioning.

Table 4

Comparison of major adverse events in control group and RIPC group after PCI.

Events	Control group (n=57)	RIPC group (n=50)	χ ² Value	P
Readmission, n (%)	3 (5.26)	2 (4.00)	0.000	1.000
Renal dialysis, n (%)	0 (0.00)	0 (0.00)	—	—
Renal transplantation, n (%)	0 (0.00)	0 (0.00)	—	—
Death, n (%)	0 (0.00)	0 (0.00)	—	—

PCI=percutaneous coronary intervention, RIPC=remote ischemic preconditioning.

4.1. Limitations and suggestions

This study is a randomized, controlled, and single-center prospective study of small sample cases; the sample size is relatively small, and the related indexes are limited. Taking into account issues such as patient compliance, we measured related indicators without observing the change process related indicators. Experimental results may exist bias. Because of the shorter study time, all patients were followed up for only 6 months, so the clinical results of the records were relatively small. Therefore, the reliability of this study should be further confirmed by larger and longer clinical observations.

5. Conclusions

Our research shows that RIPC has preventive effects on CIN, which can effectively reduce the incidence of CIN and protect renal function in patients with ACS undergoing PCI. The benefits of these patients by RIPC may be related to the reduction of the NGAL and CysC.

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References

- [1] Ye Z, Lu H, Guo W, et al. The effect of alprostadil on preventing contrast-induced nephropathy for percutaneous coronary intervention in diabetic patients. *Medicine* 2016;95:e5306.
- [2] Chang CF, Lin CC. Current concepts of contrast-induced nephropathy: a brief review. *J Chin Med Assoc* 2013;76:673–81.
- [3] Heunisch F, Chaykovska L, von Einem G, et al. ADMA predicts major adverse renal events in patients with mild renal impairment and/or diabetes mellitus undergoing coronary angiography. *Medicine* 2017;96:e6065.
- [4] Mehran R. Contrast-induced nephropathy remains a serious complication of PCI. *Interv Cardiol* 2007;20:236–40.
- [5] Jerkic H, Letilovic T, Stipinovic M, et al. Association of chronic kidney disease with periprocedural myocardial injury after elective stent implantation. *Medicine* 2016;95:e5381.
- [6] Gassanov N, Nia AM, Caglayan E, et al. Remote ischemic preconditioning and renoprotection: from myth to a novel therapeutic option. *Am Soc Nephrol* 2014;25:216–24.
- [7] Sendeski MM. Pathophysiology of renal tissue damage by iodinated contrast media. *Clin Exp Pharmacol Physiol* 2011;38:292–9.
- [8] Evans RG, Ince C, Joles JA, et al. Haemodynamic influences on kidney oxygenation: clinical implications of integrative physiology. *Clin Exp Pharmacol Physiol* 2013;40:106–22.
- [9] Persson PB, Hansell P, Liss P. Pathophysiology of contrast medium-induced nephropathy. *Kidney Int* 2005;68:14–22.
- [10] Przyklenk K, Bauer B, Ovize M, et al. Regional ischemic preconditioning protects remote virgin myocardium from subsequent sustained coronary occlusion. *J Circ* 1993;87:893–9.
- [11] McCullough PA, Stacul F, Becker CR, et al. Contrast-induced nephropathy (CIN) Consensus Working panel: executive summary. *Cardiovasc Med* 2006;7:177–94.
- [12] Huang MK, Hsu TF, Chiu YH, et al. Risk factors for acute kidney injury in the elderly undergoing contrast-enhanced computed tomography in the emergency department. *J Chin Med Assoc* 2013;76:271–6.
- [13] Fishbane S, Dutham JH, Marzo K, et al. N-acetylcysteine in the prevention of radiocontrast-induced nephropathy. *J Am Soc Nephrol* 2004;15:251–60.
- [14] Jessup M, Brazen S. Heart failure. *N Engl J Med* 2003;48:27–8.
- [15] Zhang Y, Zhang X, Chi D, et al. Remote ischemic preconditioning for prevention of acute kidney injury in patients undergoing on-pump cardiac surgery. *Medicine* 2016;95:e3465.
- [16] Ogawa T, Mimura Y, Hiki N, et al. Ischaemic preconditioning ameliorates functional disturbance and impaired renal perfusion in rat ischaemia-reperfused kidneys. *Clin Exp Pharmacol Physiol* 2000;27:997–1001.
- [17] van den Munckhof I, Riksen N, Seeger JP, et al. Aging attenuates the protective effect of ischemic preconditioning against endothelial ischemia-reperfusion injury in humans. *Am J Physiol Heart Circ Physiol* 2013;304:H1727–32.
- [18] Er F, Nia AM, Dopp H, et al. Ischemic Preconditioning for prevention of contrast-medium-induced nephropathy: randomized pilot RenPro-trial (renal protection trial)[J]. *Circulation* 2012;126:30296–303.
- [19] Igarashi G, Iino K, Watallabe H, et al. Remote ischemic pre-conditioning alle-viales contrast-induced acute kidney injury in patients with moderate chronic kidney disease. *Circ J* 2013;77:3037–44.
- [20] Zhang C. Preventive effect of limb ischemic preconditioning on contrast induced nephropathy. *J Pract Med* 2014;02:266–8.
- [21] Xu Z, Zhang D, Du J, et al. Prevention of contrast nephropathy after limb ischemia. *J Microcirc* 2016;03:16–20.
- [22] Filler G, Bokenkamp A, Hofmann W, et al. Cystatin C as a marker of GFR-history indications and future research. *Clin Biochem* 2005;38:1–8.
- [23] Laterza OF, Price CP, Scott MG. Cystatin C: an improved estimator of glomerular filtration rat[J]. *Clin Chem* 2002;48:699–707.
- [24] Ma YC, Li Z, Chen JH, et al. Modified glomerular filtration rate estimating equation for chinese patients with chronic kidney disease. *J Am Soc Nephrol* 2006;17:2937–44.
- [25] Wang F, Yin J, Lu Z, et al. Limb ischemic preconditioning protects against contrast-induced nephropathy via renalase. *EBioMedicine* 2016;10:1016–26.