European Review for Medical and Pharmacological Sciences 2017; 21: 4642-4648

Effects of remote ischemic preconditioning on myocardial injury and endothelial function and prognosis after percutaneous coronary intervention in patients with acute coronary syndrome

F.-Z. ZHOU[1,2], W. SONG[2], L.-H. YIN[2], Z.-F. SONG[2], S. YANG[2], F.-B. YANG[2], J.-F. LIU[2], Y.-G. SONG[2], H.-Y. ZHANG[2], Z.-M. ZHANG[1]

[1]Medical Examination Center of Qilu Hospital of Shandong University, Jinan, Shandong, China
[2]Department of Cardiology, Taian City Central Hospital, Taian, Shandong, China

Abstract. – OBJECTIVE: To explore the effects of remote ischemic preconditioning on myocardial injury and prognosis after percutaneous coronary intervention (PCI) in patients with acute coronary syndrome.

PATIENTS AND METHODS: The study was a single center, prospective, randomized, controlled study. A total of 184 patients with unstable angina undergoing elective PCI were randomly assigned to remote ischemic preconditioning group (induced by four times of 5-min inflations of a blood pressure cuff to 200 mmHg around the upper arm, followed by 5-min intervals of reperfusion at 1 h before PCI therapy) or control group (an uninflated cuff around the arm). Successful completion of the PCI eventually included 130 cases of patients, including 72 cases in the remote ischemic preconditioning group and 58 cases in the control group. CK-MB, cTnI, sICAM-1, sVCAM-1 and Hs-CRP levels were measured at 6 am. of the day operating PCI and at 24 h after PCI in the two groups. Major adverse cardiac events were recorded of two groups of patients in the postoperative 6 months. (MACE, including recurrence of angina pectoris, myocardial infarction and death).

RESULTS: There were no statistically significant differences in baseline indicators between the 2 groups. CK - MB, cTnI, sICAM-1, sVCAM-1 and Hs-CRP levels in patients with remote ischemic preconditioning group were significantly lower than those form the control group after PCI ($p < 0.05$), but there were no significant differences between the occurrence of MACE in the postoperative 6 months ($p > 0.05$).

CONCLUSIONS: Remote ischemic preconditioning can reduce PCI related myocardial injury and protect vascular endothelial function.

Key Words:
Remote ischemic preconditioning, Percutaneous coronary intervention, Myocardial injury, Vascular endothelial function.

Introduction

Acute coronary syndrome is caused by coronary atherosclerotic plaques resulting in coronary stenosis, further leading to myocardial ischemia, causing chest pain symptoms, severe cases can lead to myocardial infarction. Percutaneous coronary intervention (PCI) can relieve coronary stenosis and open the coronary artery occlusion. It is the most effective mean of reperfusion therapy in the world. However, PCI can lead to myocardial injury, and the increase of myocardial markers is often associated with postoperative myocardial ischemia. According to the Global Definition of Myocardial Infarction in 2007, patients with normal baseline troponin levels were treated with PCI, the myocardial damage marker (preferred cTn) increased by more than 3 times the normal reference value after receiving PCI treatment, and was identified as PCI related myocardial infarction[1]. Therefore, it is particularly important to find ways to improve myocardial injury after PCI. Some studies have shown that ischemic preconditioning (IPC) is an effective endogenous protective measure against myocardial ischemia[2], but the IPC operation of coronary artery is complicated and traumatic, so it is not suitable for clini-

Corresponding Author: Zhimian Zhang, MD; e-mail: zhangzhimian@126.com

cal application. Remote ischemic preconditioning (RIPC), which is an easy method to operate, is also concerned with the protection of myocardial injury. However, there is a lack of large-scale clinical studies in RIPC, and there are different opinions on myocardial protection. The purpose of this study was to investigate the protective effects of remote ischemic preconditioning on myocardial injury and endothelial function after PCI and its impact on major adverse cardiovascular events (MACE).

Patients and Methods

Patients

This study was a single center, prospective, randomized, controlled study. A total of 184 patients with acute coronary syndrome undergoing PCI from 2014 Mar to 2016 Feb in Tai'an Central Hospital were collected and randomly divided into remote ischemic preconditioning group (94 cases) and control group (90 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 remote ischemic pretreatment group and 4 cases in control group did not undergo PCI treatment, as coronary angiography showed severe lesions in three coronary arteries. 16 cases in remote ischemic pretreatment group and 28 cases in the control group did not have to undergo PCI due to coronary artery stenosis less than 75%. 130 patients (72 cases in remote ischemic pretreatment group and 58 cases in control group) underwent elective PCI successfully and finally were included in this study.

Inclusion Criteria

(1) The clinical manifestations of patients according to Canadian Cardiovascular Society (CCS) angina pectoris grade II-IV; (2) the patients undergoing selective coronary angiography and were determined at least l coronary artery stenosis, and the degree was more than 75% (diameter method); (3) the location of the stenosis was the definition of ACC/AHAof A or B lesions.

Exclusion Criteria

(1) Preoperative cardiac troponin I (cTnI) elevation higher than 0.09 ng/ml; (2) aspirin or clopidogrel is not tolerated; (3) congenital malformations associated with myocardial ischemia such as the left coronary artery derived from the pulmonary artery, congenital coronary stenosis or atresia, the coronary artery derived from the anomalous origin of the contralateral coronary sinus, coronary artery fistula and myocardial bridge; (4) congenital heart disease; (5) rheumatic heart disease; (6) dilated and hypertrophic cardiomyopathy; (7) coronary heart disease and heart failure (NYHA grade III\IV); (8) acute infection; (9) rheumatic fever; (10) malignant tumor; (11) severe liver and kidney dysfunction; (12) inflammatory muscle activity diseases and infectious diseases; (13) mental diseases, etc.

Baseline Materials

Demographic characteristics of the patients were collected and recorded in detail, including gender, 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 remote ischemic preconditioning group and control group according to the random number table. Two groups were treated with antiplatelet agents, statins, angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), β-receptor blockers, calcium antagonists and nitrates and other conventional treatment. The remote ischemic preconditioning group received remote ischemic preconditioning at 1 h prior to PCI, the specific method was 5-min inflations of a blood pressure cuff to 200 mmHg around the upper arm, followed by 5-min intervals of reperfusion by four times. The control group was not treated. CK-MB, cTnI, sICAM-1, sVCAM-1 content and Hs-CRP level were measured at 6 am of PCI surgery day and 24 h after operation, and recurrent angina, myocardial infarction, death and major adverse cardiovascular events (MACE) were recorded in 6 months after operation.

Operation Procedures

All patients underwent coronary angiography. Coronary stent implantation was performed in patients with coronary artery stenosis great-

er than 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 TIMI 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; ECG changes and vital signs were monitored during the operation.

Statistical Analysis

All the data were analyzed by SPSS19.0 (Version X; IBM, Armonk, NY, USA) 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, while the rank sum test was used in non-normal distribution. Enumeration data was analyzed with χ^2 test. The difference was statistically significant with $p < 0.05$.

Results

Basic Data for the Enrolled Participants

As shown in Table I, there was no significant difference in risk factors such as age, sex, BMI, blood lipid, fasting blood glucose and past medical history. There was no statistical difference between the two groups in the routine drug treatment, the operation of PCI, the type and number of lesion blood vessels, the characteristics of stent implantation, the amount of contrast agent and the complications of operation. (Table I).

CK-MB, cTnI, sICAM-1, sVCAM-1 and Hs-CRP Level Changes

There were no significant differences of CK-MB, cTnI, sICAM-1, and Hs-CRP ($p > 0.05$) between two groups before PCI ($p > 0.05$). The level of CK-MB, cTnI, sICAM-1, sVCAM-1and Hs-CRP in two groups of patients 24h after PCI was higher than that before operation ($p < 0.01$). The difference between the remote ischemic preconditioning group and the control group was statistically significant postoperative ($p < 0.05$), as showed in Table II.

MACE Events

Telephone follow-up and patient outpatient visits and hospitalization. 6 cases (2 cases in remote ischemic preconditioning group) were lost, accounted for 3.8%. As shown in Table III, the occurrence rate of adverse cardiovascular events in remote ischemic preconditioning group is low compared with the control group, but no significant difference is shown.

Table I. Comparison of basic situation between RIPC group and control group.

Item	Control group (n = 58)	RIPC group (n = 72)	$\chi^{2/t}$	*p*-value
Age	59.27 ± 9.35	60.22 ± 9.06	0.5859	0.5590
Gender (male/female)	24 (41.38)	22 (30.56)	1.646	0.200
BMI (kg/m^2)	24.97 ± 0.72	25.13 ± 0.61	1.3714	0.1726
Triglyceride (mmol/L)	1.71 ± 0.41	1.58 ± 0.37	1.8974	0.0600
Total cholesterol (mmol/L)	4.41 ± 0.57	4.29 ± 0.72	1.0345	0.3029
LDl-C (mmol/L)	2.59 ± 0.65	2.56 ± 0.73	0.2445	0.8072
HDL-C (mmol/L)	1.07 ± 0.16	1.08 ± 0.23	0.2808	0.7793
Fasting plasma glucose (mmol/L)	5.67 ± 0.52	5.79 ± 0.46	1.3948	0.1655
Smoke [n (%)]	38 (65.52)	36 (50.00)	3.154	0.076
Hypertension (n (%))	46 (93.10)	56 (77.78)	0.045	0.833
Diabetes mellitus [n (%)]	30 (65.52)	34 (47.22)	0.260	0.610
Total balloon dilation time (s)	40.97 ± 19.58	42.71 ± 21.16	0.4817	0.6308
Number of implants [n (%)]				
n = 1	45	60	0.683	0.409
n = 2	11	9	1.032	0.310
n ≥ 3	2	3	0.000	1.000
Total length of stent (mm)	29.49 ± 18.67	32.54 ± 20.42	0.8793	0.3809
Amount of contrast agent (mL)	118.86 ± 41.25	125.15 ± 43.21	0.8418	0.4015
The stent falls off or improperly positioned	0	0	–	–

Table II. Comparison of relative indexes between RIPC group and control group before and after PCI.

Index	Control group (n = 58)	RIPC group (n = 72)	*t*	*p*-value
CK-MB				
Preoperative	12.27 ± 3.54	12.09 ± 2.81	0.3233	0.7450
Postoperative	17.45 ± 8.42	13.21 ± 7.59	3.0151	0.0031
CTNI				
Preoperative	0.012 ± 0.006	0.013 ± 0.007	0.8622	0.3902
Postoperative	0.066 ± 0.007	0.048 ± 0.006	15.7816	< 0.0001
sICAM-1				
Preoperative	17.16 ± 2.93	16.53 ± 3.12	1.1758	0.2419
Postoperative	37.12 ± 3.31	23.83 ± 2.33	26.8157	< 0.0001
sVCAM-1				
Preoperative	18.75 ± 2.23	18.91 ± 2.69	0.3634	0.7169
Postoperative	43.19 ± 3.86	26.38 ± 2.89	28.3829	< 0.0001
Hs-CRP				
Preoperative	4.26 ± 2.71	4.53 ± 3.02	0.5302	0.5969
Postoperative	8.63 ± 3.43	7.12 ± 2.73	2.7954	0.0060

Adverse Reactions of Remote Ischemic Preconditioning

Remote ischemic preconditioning group had 3 patients with upper arm ischemic discomfort, 5 patients suffered distal skin ecchymosis or petechia due to blood pressure cuff compression. However, those reactions did not affect the pretreatment process.

Discussion

Over the past 30 years, PCI has become the most effective means of revascularization in patients with acute coronary syndromes, but PCI is often accompanied by myocardial and endothelial damage. Many studies have shown that myocardial injury after PCI is associated with poor prognosis[3-6]. At present, creatine kinase isoenzyme and troponin are widely recognized as serum markers for the diagnosis of myocardial injury. C- reactive protein (CRP) is a sensitive marker of atherosclerosis. It can be directly involved in the formation of atherosclerosis and the development of cardiovascular disease. Elevated CRP predicts plaque vulnerability. CRP can promote the expression of focal adhesion factor, reduced endothelial nitric oxide bioavailability, change the uptake of LDL by the macrophages activation, promotes vascular inflammation and thrombosis, and ultimately exacerbate coronary atherosclerosis. Numbers of studies have shown that PCI can induce and exacerbate inflammation[7,8], and the study also showed that the levels of inflammatory markers (hs-CRP) were increased immediately after PCI[9]. Related studies have confirmed that the causes of myocardial and endothelial injuries were related to balloon dilatation and stent release during PCI, which resulting in transient coronary ischemia and microcirculatory disturbances[10,11]. The total balloon dilation time, total stent length, stent number and stent shedding were compared between the 2 groups during PCI in this study, the differences were not statistically significant.

Recent studies[12,13] showed that serum sICAM-1 and sVCAM-1 reflect the endothelial function by regulating adhesion between cells, causing vascular endothelial injury and activating neu-

Table III. Comparison of major adverse cardiovascular events between the RIPC group and the control group 6 months after PCI.

MACE	Control group (n = 58)	RIPC group (n = 72)
Recurrent angina [n (%)]	8 (13.79%)	4 (5.55 %)[a]
Myocardial infarction [n (%)]	6 (10.34%)	4 (5.55 %)[a]
Death [n (%)]	0 (0%)	0 (0 %)[a]

Note: There was no significant difference between the RIPC group and the control group in the 6-month MACE event ($p^a > 0.05$).

trophil, starting immune response and inducing apoptosis of endothelial cells. PCI can enhance endothelial cell injury, promote the expression of sICAM-1 and sVCAM-1in vascular endothelial cells, tightening the interaction between cells, vascular adhesion molecules and adhesion molecule of leukocytes, participating in myocardial ischemia and reperfusion injury, thus aggravating microcirculation dysfunction. Typically, involved in inflammation and adhesion reaction, sICAM-1 and sVCAM-1 were little or none expressed in normal vessels, but highly expressed in patients in the postoperative PCI. They were related with the level of endothelial dysfunction and restenosis, and can be in a certain extent of endothelial injury. SICAM-1 and sVCAM-1 can activate white blood cells to produce and release oxygen free radicals, leukotrienes and platelet activating factor of vasoactive substances. These products promoted the development of inflammation, caused vascular endothelial injury and induced vasoconstriction and hypoxic ischemic myocardium, resulting in vascular cavity occlusion and promoting the progression of disease in patients with PCI after operation.

In 1986, Murry et al[14] found that prior to clamping the canine circumflex coronary artery for 5 min, then reperfusion 5 min, repeat 4 times, then 40 min occlusion, myocardial infarction area decreased 75% compared with the control group. They call this phenomenon as ischemic preconditioning (ischemic, preconditioning, IPC). But the local ischemic preconditioning treatment may cause damage to the local tissue, this limits the application of the technology in a certain extent. If IPC does not affect the local tissue blood supply situation, it will make more patients benefit. In 1993, Przyklenk et al[15] found that the circumflex coronary artery ischemia can reduce the infarct size in the anterior descending branch of the blood supply area, suggesting that local ischemia can improve the ability of other parts of the same organ to adapt to ischemia. Subsequently, Lang et al[16] found that renal transient ischemia can protect against myocardial infarction, and Gho et al[17] reported the protective effects of intestinal ischemia on the myocardium. Other studies have also demonstrated that transient ischemia in multiple organs can significantly protect against subsequent ischemia-reperfusion injury[18-21]. Similar to myocardial ischemic preconditioning, transient ischemia in the extra cardiac tissues and organs can protect the autologous myocardium and reduce infarct size after prolonged ischemia. This preconditioning is, therefore, known as remote ischemic preconditioning (remote ischemic preconditioning, RIPC), because it occurs outside the heart, which is different from classical myocardial ischemic preconditioning. Remote ischemic preconditioning and ischemia can play a similar role in pretreatment, thus greatly expanded the scope of application of ischemic preconditioning. It had simple and easy implementation, no damage, does not affect the operation characteristics, is easily accepted by people in ethics, so it has a certain clinical feasibility[22]. However, there is disagreement about the protective effect of distal ischemic preconditioning on myocardial injury after PCI, and there is no large-scale clinical study and the impact on the prognosis has not been reported. This study through randomized, prospective control methods, compared myocardial injury index of CK-MB, cTnl, sICAM-1, sVCAM-1 and Hs-CRP changes in remote ischemic preconditioning group and control group. The results suggest that PCI can lead to myocardial injury, but myocardial ischemia and myocardial injury can be alleviated by remote ischemic preconditioning, which can protect the heart of PCI patients.

In our investigation, remote ischemic preconditioning was performed in patients with acute coronary syndromes undergoing elective PCI surgery. RIPC was observed to attenuate myocardial and endothelial damage after PCI surgery in patients with acute coronary syndromes through repeated blood blocking and recovery of upper limb ischemic preconditioning. The mechanism of remote ischemic preconditioning is still unclear; studies have shown that remote ischemic preconditioning may reduce the inflammatory reaction[23,24], but most of the researches are still in the field of animal studies and difference exists between species. In this study, we detected the expression of Hs-CRP, sICAM-1 and sVCAM-1, and we investigated the reaction of RIPC with intravascular disease dermatitis. The results showed that remote ischemic preconditioning could significantly reduce the levels of Hs-CRP, sICAM-1 and sVCAM-1 after PCI, alleviate the related inflammatory reaction after PCI, protect the vascular endothelial function and alleviate the myocardial injury.

Conclusions

This study is a randomized, controlled and single center prospective study of small sample cas-

es, the sample size is relatively small, the related indexes is limited, such as only one inflammation index hs-CRP. Taking into account issues such as patient compliance, we measured related indicators measured only after 24 h in this study, without observing the change process related indicators. There may also be bias in the experimental results. Due to time limitations, the occurrence of adverse events was followed up for only 6 months. The time of follow-up is relatively short and the clinical outcome of records is relatively small. Therefore, the reliability of this study should be further confirmed by larger and longer clinical observations.

Acknowledgements

This study was supported by the grants from the Natural Science Foundation of Shandong Province, China (No. ZR2015HL005) and the Medical and Health development Project of Scientific and Technological Development of Shandong Province, China (NO.2015WS0117) to Prof Fazhan Zhou.

Conflict of Interest

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

References

1) Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiol 2007; 50: 2173-2195.
2) Jessup M, Brozena S. Heart failure. N Engl J Med 2003; 348: 2007-2018.
3) Cantor WJ, Newby LK, Christenson RH, Tuttle RH, Hasselblad V, Armstrong PW, Moliterno DJ, Califf RM, Topol EJ, Ohman EM. Prognostic significance of elevated troponin I after percutaneous coronary intervention. J Am Coll Cardiol 2002; 39: 1738-1744.
4) Herrmann J. Peri-procedural myocardial injury: 2005 update. Eur Heart J 2005; 26: 2493-2519.
5) Zhou M, Yu K, Wang XH, Yang CS, Lei YP, Wang YG, Xue YZ, Yao HC, Gao B. Analysis on application timing of IABP in emergency PCI treatment of patients with combined acute myocardial infarction and cardiac shock. Eur Rev Med Pharmacol Sci 2017; 21: 2934-2939.
6) Gao J, Chen Q, Liu F, Zhao Q, Chen B, Zhou Y, Zhao Q, Ma Y, Yang Y. The effects of remote ischemic conditioning in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention: a meta-analysis. Minerva Med 2017; 108: 370-380.
7) Chew DP, Bhatt DL, Robbins MA, Penn MS, Schneider JP, Lauer MS, Topol EJ, Ellis SG. Incremental prognostic value of elevated baseline C-reactive protein among established markers of risk in percutaneous coronary intervention. Circulation 2001; 104: 992-997.
8) Saleh N, Svane B, Velander M, Nilsson T, Hansson LO, Tornvall P. C-reactive protein and myocardial infarction during percutaneous coronary intervention. J Intern Med 2004; 255: 33-39.
9) Boudart C, Tabolcea I, Strachinaru M, Castro J, Noseda A, Gottignies P, Reper P. Acute coronary syndrome and platypnoea-orthodeoxia with thoracic and interauricular septal aneurysms. Eur Rev Med Pharmacol Sci 2016; 20: 301-304.
10) Grube E, Gerckens U, Yeung AC, Rowold S, Kirchhof N, Sedgewick J, Yadav JS, Stertzer S. Prevention of distal embolization during coronary angioplasty in saphenous vein grafts and native vessels using porous filter protection. Circulation 2001; 104: 2436-2441.
11) Lee L, Horowitz J, Frenneaux M. Metabolic manipulation in ischaemic heart disease, a novel approach to treatment. Eur Heart J 2004; 25: 634-641.
12) Ikata J, Wakatsuki T, Oishi Y, Oki T, Ito S. Leukocyte counts and concentrations of soluble adhesion molecules as predictors of coronary atherosclerosis. Coron Artery Dis 2000; 11: 445-449.
13) Iliodromitis EK, Andreadou I, Markantonis-Kyroudis S, Mademli K, Kyrzopoulos S, Georgiadou P, Kremastinos DT. The effects of tirofiban on peripheral markers of oxidative stress and endothelial dysfunction in patients with acute coronary syndromes. Thromb Res 2007; 119: 167-174.
14) Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 1986; 74: 1124-1136.
15) Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic "preconditioning" protects remote virgin myocardium from subsequent sustained coronary occlusion. Circulation 1993; 87: 893-899.
16) Lang SC, Elsasser A, Scheler C, Vetter S, Tiefenbacher CP, Kubler W, Katus HA, Vogt AM. Myocardial preconditioning and remote renal preconditioning--identifying a protective factor using proteomic methods? Basic Res Cardiol 2006; 101: 149-158.
17) Gho BC, Schoemaker RG, van den Doel MA, Duncker DJ, Verdouw PD. Myocardial protection by brief ischemia in noncardiac tissue. Circulation 1996; 94: 2193-2200.
18) Tokuno S, Hinokiyama K, Tokuno K, Lowbeer C, Hansson LO, Valen G. Spontaneous ischemic events in the brain and heart adapt the hearts of severely atherosclerotic mice to ischemia. Arterioscler Thromb Vasc Biol 2002; 22: 995-1001.
19) Schoemaker RG, van Heijningen CL. Bradykinin mediates cardiac preconditioning at a dis-

tance. Am J Physiol Heart Circ Physiol 2000; 278: H1571-H1576.

20) Liem DA, Verdouw PD, Ploeg H, Kazim S, Duncker DJ. Sites of action of adenosine in interorgan preconditioning of the heart. Am J Physiol Heart Circ Physiol 2002; 283: H29-H37.

21) Ates E, Genc E, Erkasap N, Erkasap S, Akman S, Firat P, Emre S, Kiper H. Renal protection by brief liver ischemia in rats. Transplantation 2002; 74: 1247-1251.

22) Attaran RR. Letter by Attaran regarding article, "Cardiac Ischemic Preconditioning in Coronary Stenting (CRISP Stent) study: A prospective, randomized control trial". Circulation 2009; 120: e132, e133.

23) Tapuria N, Junnarkar SP, Dutt N, Abu-Amara M, Fuller B, Seifalian AM, Davidson BR. Effect of remote ischemic preconditioning on hepatic microcirculation and function in a rat model of hepatic ischemia reperfusion injury. HPB (Oxford) 2009; 11: 108-117.

24) Zhou W, Zeng D, Chen R, Liu J, Yang G, Liu P, Zhou X. Limb ischemic preconditioning reduces heart and lung injury after an open heart operation in infants. Pediatr Cardiol 2010; 31: 22-29.