

Different postconditioning cycles affect prognosis of aged patients undergoing primary percutaneous coronary intervention

Jie Zhang¹, Xin Zhang², Yuqi Cui³, Misbahul Ferdous³, Lianqun Cui³, Peng Zhao³

¹Department of Nutrition, Shandong Provincial Hospital affiliated to Shandong University, Jinan, China

²Department of Radiology, Police General Hospital of Shandong Province, Jinan, China

³Department of Cardiology, Shandong Provincial Hospital affiliated to Shandong University, Jinan, China

Abstract

Background: Postconditioning can affect the infarct size in acute myocardial infarction (AMI). However, few studies show an effect of different postconditioning cycles on AMI aged patients. This study sought to assess the effect of different postconditioning cycles on prognosis in aged patients with AMI who underwent primary percutaneous coronary intervention (PCI).

Methods: Seventy four aged patients were randomly assigned to three groups. Control group; PC-1 group accepted postconditioning 4 cycles of 30 s inflation and 30 s deflation; PC-2 group accepted postconditioning 4 cycles of 60 s. Creatine kinase MB (CK-MB), troponin I (cTnI), high-sensitive C-reactive protein (hs-CRP) and corrected Thrombolysis in Myocardial Infarction (TIMI) frame counts (CTFC) were analyzed before and after treatment. All patients received an echocardiographic examination for whole heart function, wall motion score index (WMSI) and single-photon emission computed tomography (SPECT) examination at 7 days and 6 months after treatment.

Results: The peak of CK-MB, postoperative 72 h cTnI and CTFC were significantly attenuated by postconditioning when compared with the control group. The hs-CRP of the postconditioning group was lower than the control group 24 h postoperative. No difference was observed between PC-1 and PC-2 group about the effect described above. At 7 days, heart function in the postconditioning group was improved when compared with the control group. At 6 months, the WMSI and SPECT score significantly reduced in the PC-2 group compared with the control and PC-1 groups, but there was no difference among the three groups about echo data except the left ventricular end-systolic diameter.

Conclusions: Postconditioning is significantly beneficial to prognosis in aged patients with AMI. The cardiac protective effect of 4 cycles of 60 s procedure was observed in WMSI and SPECT. It is favorable to implement this procedure in aged patients with AMI in clinic. (Cardiol J 2018; 25, 6: 666–673)

Key words: aged, acute myocardial infarction, primary percutaneous coronary intervention, postconditioning cycles

Introduction

With the occurrence of lessening or interruption of coronary artery flow corresponding myocardial ischemia also happens. It can result in acute myocardial infarction (AMI) which has a high

mortality rate. Early restoring of infarct-related coronary artery (IRA) can save myocardium, rescue heart function and improve survival rate. This is the main goal in the care of AMI patients. Both thrombolysis and primary percutaneous coronary intervention (PCI) permits the rescue of myocardial

Address for correspondence: Peng Zhao, MD, PhD, Department of Cardiology, Shandong Provincial Hospital affiliated to Shandong University, 324 Jingwuweiqi road, Jinan, 250021, China, tel: (86) 531-6877-3121, e-mail: pengalfie@163.com

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tissue for AMI patients. Primary PCI can reperfuse the IRA timely and effectively. It is recommended as the preferred treatment by American College of Cardiology/American Heart Association (ACC/AHA) Guide [1]. While primary PCI and thrombolysis are able to restore blood flow and benefit patients, some reversible and irreversible damage to the myocardium can still be observed. It is defined as reperfusion injury. Experimental studies of AMI have revealed that up to half of infarct size may be due to reperfusion injury rather than initial ischemic insult [2]. Many proof-of-concept trials continue to demonstrate control of reperfusion injury as a therapeutic target.

Postconditioning is a sequence of ischemia-reperfusion episodes induced by repeating cycles of balloon inflation and deflation immediately after restoring blood flow of the occluded vessel. It has been proposed as a valid alternative to reduce infarct size. Zhao et al. [3] reported that short cycles of ischemia and reperfusion could alleviate reperfusion injury and reduce infarct size by as much as 44% in a canine model. This was the first evidence of infarct size reduction associated with postconditioning. Since then, many postconditioning strategies to alleviate reperfusion injury have been applied. Many published papers were reviewed in Jivraj et al' literature [4]. The author collected 20 randomized controlled trials of ischemic postconditioning in patients with ST-segment elevation myocardial infarction (STEMI) over the past 10 years. Four of them carried out 2 or 3 cycle strategies. The remainder of them employed a 4 cycle strategy.

The pace of the aging population around the world is increasing dramatically. According to the World Health Organization (WHO) "Definition of an older or elderly person" published in 2016, the United Nations describes the general definition that 60+ years may be usually denoted as old age. This is the first attempt at an international definition of old age. Between 2015 and 2050, the proportion of world population over 60 years of age will nearly double from 12% to 22% according to the WHO report. By 2050, world population aged 60 years of age and older is expected to total 2 billion. There will be almost 120 million living in China alone. The rising number of aged population means the morbidity of coronary heart disease is increasing accordingly. More attention should be paid to this susceptible population. In this study recruited patients were older than 60 as the observed subjects.

To date, many studies manifested evidence that postconditioning benefit to cardiac function not only in the laboratory but also in clinic [5–7]. However, there remain paradoxical views about this [8, 9]. Firstly, there is no consensus on strategy. Secondly, few reports have observed the effect of different postconditioning cycles on patients with AMI. Thirdly, there is no data regarding aged patients, especially from China. All of the aforementioned drives a deepening of research about postconditioning. Therefore, in this study the influence of different postconditioning cycles on prognosis in aged patients with AMI who were undergoing primary PCI was observed.

Methods

Study population

The population of this study consisted of 86 patients admitted to hospital between January 2015 and June 2016. 12 patients were lost in follow-up or did not have the data sought during the study. One had mild heart failure. Three had angina and were readmitted. No sudden cardiac death or ischemic stroke occurred. All of the 74 patients who completed the follow-up who were enrolled were beyond 60 years of age. The mean age was 73 ± 9 . They underwent revascularization within 12 h of the onset of STEMI. The symptoms of AMI were chest pain lasting > 30 min, persistent ST-segment elevation > 0.1 mV in two or more contiguous electrocardiogram (ECG) leads and elevated serum levels of cardiac isoenzymes or troponins. All IRA regained Thrombolysis in Myocardial Infarction (TIMI) 3 flow and there was no evidence of re-infarction during the follow-up period. Exclusion of complication criteria was made as follows in order to keep the research subjects homogeneous: 1) hyperthyroidism, 2) moderate-severe rheumatic valvular disease, 3) infectious diseases, immune system diseases and sepsis, 4) using of anti-inflammatory drugs and antioxidant therapy recently, 5) combined liver and kidney dysfunction and other serious systemic diseases, 6) combined hypertension and diabetes mellitus not treated effectively, 7) other acute or chronic diseases of the blood and cancer, 8) psychotic. The institutional review committee approved the study, and all patients gave informed consent.

Treatment protocol

All patients were randomly divided into three groups, control group, postconditioning-1 group

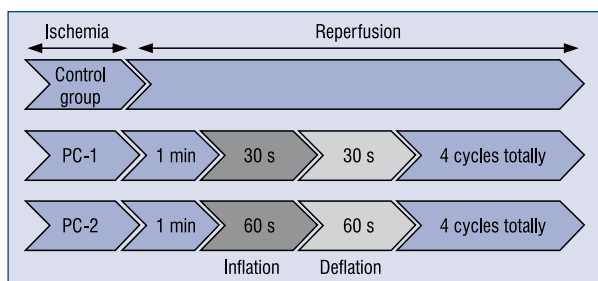


Figure 1. Treatment protocol; PC-1 — postconditioning-1 group; PC-2 — postconditioning-2 group.

(PC-1 group) and postconditioning-2 group (PC-2 group). Vascular access was obtained using the femoral or radial approach. All patients were premedicated with 300 mg acetylsalicylic acid and 300–600 mg clopidogrel before catheterization. An initial intravenous bolus of heparin (6000 U) and additional doses of 3000 U were given to patients during the procedure every 1 h long. Within 1 min of reflow, PC-1 group accepted postconditioning procedure: 4 cycles of 30 s low-pressure (4–6 atm) inflation and 30 s deflation of angioplasty balloon. PC-2 group accepted postconditioning procedure: 4 cycles of 60 s low-pressure (4–6 atm) inflation and 60 s deflation of angioplasty balloon (Fig. 1).

Detection of CK-MB, cTnI and hs-CRP

Blood samples were withdrawn for measuring creatine kinase MB (CK-MB), troponin I (cTnI) and high-sensitive C-reactive protein (hs-CRP) with automatic biochemistry analyzer. CK-MB analysis was performed at 0, 8, 16, 24, 36, 48, and 72 h after PCI. Postoperative 72 h cTnI concentration was detected. hs-CRP assay was performed on admission and 24 h after PCI.

Echocardiography

All studies were performed with echocardiography equipment (Sonos 5500, Philips Medical Systems, Bothell, WA, USA) to patients at 7 days and 6 months after PCI [10]. Left ventricular end-diastolic diameters (LVEDD) and left ventricular end-systolic diameters (LVESD) were obtained by M-mode echocardiography from the parasternal long axis view as recommended by American Society of Echocardiography. The ejection fraction (EF) and cardiac output (CO) were calculated by a modified Simpson method. Data from 3 to 5 consecutive cardiac cycles were used for analysis.

Corrected TIMI frame counts

The corrected TIMI frame counts (CTFC) is a simple, reproducible, objective and quantitative index of coronary flow velocity. Intracoronary nitroglycerin (200 μg) was administered before CTFC counting to preserve a state of maximum vasodilation [11]. The TFC was measured blindly by two medically qualified observers. CTFC for left anterior descending artery (LAD) was calculated by dividing by 1.7 because of its higher length [12].

Wall motion score index

The wall motion score index (WMSI) is a visual semi-quantitative assessment of regional wall motion [13]. The left ventricle was divided into 16 segments. On the basal (mitral) and midventricular (papillary muscle) level, the circumference is divided into 6 segments and on the apical level into 4 segments. The score for each segment is graded according to a classical system: 1 — normal, 2 — hypokinetic, 3 — akinetic, 4 — paradoxical movement and 5 — ventricular aneurysm. WMSI is calculated by dividing total WMS of the polar map by 16 [14].

SPECT imaging

All patients underwent rest myocardial perfusion single-photon emission computed tomography (SPECT) 7 days and 6 months after PCI as previously described [14]. Briefly, patients were injected ^{99m}Tc-MIBI (Jiangyuan Pharmaceutical Factory, Jiangsu Institute of Nuclear Medicine, China). SPECT (Discovery NM/CT 670, GE, USA) was equipped with high-resolution collimators set at 140 Kev energy level, 10% window width, matrix 128 × 128 and amplifying factor 1.00. Short-axis, long-axis and vertical-axis images from the heart were analyzed for radionuclide distribution. The left ventricle was divided into 17 segments to calculate the total defect score using the following five-grade assessment: 0 — normal uptake; 1 — mildly reduced uptake; 2 — moderately reduced uptake; 3 — severely reduced uptake; 4 — no uptake. The summed score was calculated accordingly.

Statistical analysis

Data were mean ± standard error of mean (SEM) and analyzed by using GraphPad Prism 5.0 statistical analysis software. Differences were assessed using analysis of variance (ANOVA) followed by Tukey post hoc test or Student’s t test. Categorical variables were compared using the χ² or Fisher exact test. A p value < 0.05 was considered statistically significant.

Table 1. Comparison of demographic characteristics ($x \pm s$). The baseline characteristics of the three groups were not statistically significant; $p > 0.05$.

Baseline clinical characteristics	Control group (n = 23)	PC-1 group (n = 26)	PC-2 group (n = 25)
Clinical presentation			
Gender (male/female)	15/8	17/9	17/8
Age [years]	72 ± 11	74 ± 8	73 ± 10
Systolic pressure [mmHg]	129 ± 24	130 ± 22	134 ± 19
Diastolic pressure [mmHg]	83 ± 17	89 ± 21	85 ± 19
Body mass index [kg/m ²]	26.9 ± 10.3	25.5 ± 8.6	26.1 ± 9.4
Medical history			
Previous stroke/TIA	3 (13.0%)	4 (15.4%)	4 (16.0%)
Previous vascular diseases	4 (17.4%)	3 (11.5%)	3 (12.0%)
Risk factor			
Hypertension	12 (52.2%)	13 (50.0%)	14 (56.0%)
Diabetes mellitus	9 (39.1%)	10 (48.5%)	10 (40.0%)
Smoking	11 (47.8%)	11 (42.3%)	10 (40.0%)
Current or recent medication			
Beta-blocker	7 (30.4%)	8 (30.8%)	7 (28.0%)
Calcium-channel blocker	10 (43.5%)	11 (42.3%)	9 (36.0%)
ACEI/ARB	8 (34.8%)	8 (30.8%)	8 (32.0%)
Diuretic	3 (13.0%)	2 (7.6%)	3 (12.0%)
Admission and treatment			
Ischemia time [h]	6.9 ± 1.1	7.6 ± 1.4	7.2 ± 1.8
Single/multiple vessel stenosis [%]	69.6/30.4	65.4/34.6	64.0/36.0
Culprit artery LAD	14 (60.9%)	16 (61.5%)	16 (64.0%)
Aspiration	7 (30.4%)	10 (38.4%)	8 (32.0%)
Maximum ST shift [mm]	5.9 ± 1.1	5.2 ± 0.8	5.6 ± 1.5
Average number of stents	1.4 ± 0.6	1.3 ± 0.8	1.2 ± 0.5

ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker; LAD — left anterior descending artery; PC-1 group — postconditioning-1 group; PC-2 group — postconditioning-2 group; TIA — transient ischemic attack

Results

Baseline characteristics of patients

As shown in Table 1, the mean age of the study population was 73 ± 9 years, and 66.2% of patients were men. Three groups of patients admitted to hospital diagnosis. Age, gender, risk factors, medical history, current or recent medication and treatment were not statistically significant. Nevertheless hypertension and diabetes were the more prevalent comorbidities. More than half of the patients, the LAD was the culprit artery. The ischemia time was approximately 6 h prior to being admitted to hospital.

Results of blood biochemical marker in three group patients

The levels of peak CK-MB in two PC groups were significantly lower than the control group,

respectively ($p < 0.05$). It was associated with a lower level cTnI 72 h after PCI than the control group. Compared with control group, postoperative 24 h hs-CRP was significantly lower in PC groups ($p < 0.05$). However, there were no significant differences between PC-1 and PC-2 group ($p > 0.05$) of the above three markers. The results indicated that postconditioning had positive effect on cardiac injury after AMI (Fig. 2).

Results of echocardiography in the three groups of patients

Patients performed echo exam at 7 days and 6 months after PCI. As Table 2 shows HR, LVEF and CO levels were improved in PC groups compared with control group ($p < 0.05$). But there was no difference at 6 months except the LVESD ($p > 0.05$) (Table 3). These results demonstrate

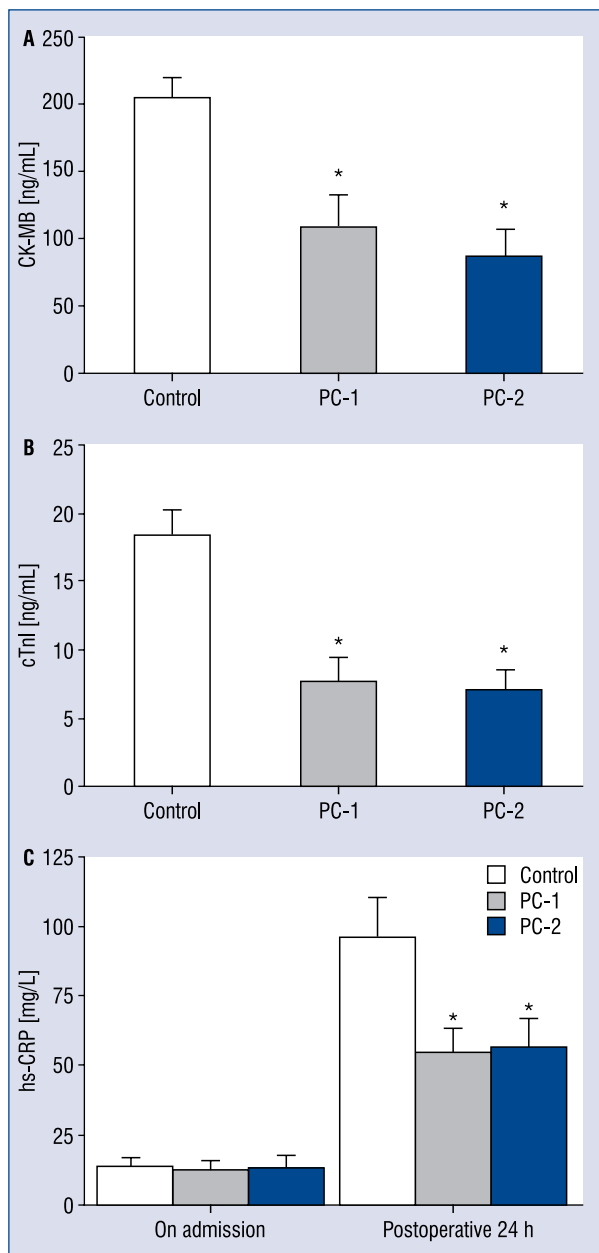


Figure 2. Comparison of creatine kinase MB (CK-MB), troponin I (cTnI) and high-sensitive C-reactive protein (hs-CRP); **A.** Peak of CK-MB; **B.** Postoperative 72 h cTnI; **C.** On admission and postoperative 24 h hs-CRP; mean ± standard error of mean; *p < 0.05 vs. control group; PC-1 — postconditioning-1 group; PC-2 — postconditioning-2 group.

postconditioning can benefit the recovery of injured AMI heart function in the short term but not over a long period in aged patients.

Results of CTFC in the three groups of patients

The CTFC can evaluate coronary artery microcirculation indirectly based on TIMI flow grades.

Table 2. Comparison of heart function of three groups at 7 days after percutaneous coronary intervention.

Index	Control group	PC-1 group	PC-2 group
HR [bpm]	84 ± 12	70 ± 9*	68 ± 11*
LVESD [mm]	40.2 ± 6.9	35.8 ± 5.7	32.6 ± 4.8*
LVEDD [mm]	54.2 ± 5.9	52.7 ± 4.6	55.7 ± 6.3
LVEF [%]	37.3 ± 5.1	48.6 ± 6.8*	47.4 ± 6.4*
CO [L/min]	4.1 ± 1.1	5.8 ± 0.6*	6.1 ± 0.8*

*p < 0.05 vs. control group, CO — cardiac output; HR — heart rate; LVEDD — left ventricular end-diastolic diameters; LVESD — left ventricular end-systolic diameters; LVEF — left ventricular ejection fraction; PC-1 group — postconditioning-1 group; PC-2 group — postconditioning-2 group

Table 3. Comparison of three groups’ heart function at 6 months after percutaneous coronary intervention.

Index	Control group	PC-1 group	PC-2 group
HR [bpm]	66 ± 13	62 ± 7	65 ± 11
LVESD [mm]	36.2 ± 6.9	32.8 ± 6.7	29.6 ± 4.9*
LVEDD [mm]	49.2 ± 7.9	42.7 ± 4.9	47.7 ± 6.7
LVEF [%]	49.4 ± 6.6	51.6 ± 6.8	50.4 ± 7.4
CO [L/min]	5.5 ± 1.0	6.1 ± 0.7	6.6 ± 0.7

*p < 0.05 vs. control group, CO — cardiac output; HR — heart rate; LVEDD — left ventricular end-diastolic diameters; LVESD — left ventricular end-systolic diameters; LVEF — left ventricular ejection fraction; PC-1 group — postconditioning-1 group; PC-2 group — postconditioning-2 group

In this study it was found that patients of the PC group had much faster CTFC than patients of the control group (p < 0.05) (Fig. 3). It appeared that CTFC in the PC-2 group was faster than the PC-1 group. There was no statistical difference however (p > 0.05).

Results of WMSI and SPECT score in the three groups of patients

WMSI and SPECT score can be used to evaluate segmental myocardial movement and function. 7 days after PCI, the WMSI improved significantly in both PC groups (p < 0.05). After 6 months of PCI, PC-2 group segmental myocardial movement and function was much better than PC-1 group (p < 0.05). The same results can be observed in SPECT score. Collectively, these two key indicators showed PC-2 protocol had a positive effect on the recovery of segmental myocardial movement and function (Fig. 4).

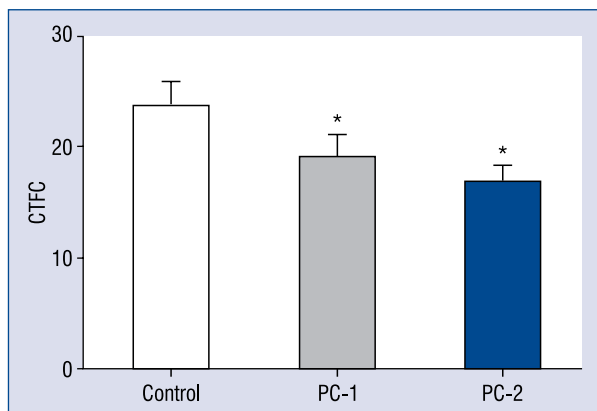


Figure 3. Difference of corrected Thrombolysis in Myocardial Infarction frame counts (CTFC) of the three groups; mean ± standard error of mean; *p < 0.05 vs. control group; PC-1 — postconditioning-1 group; PC-2 — postconditioning-2 group.

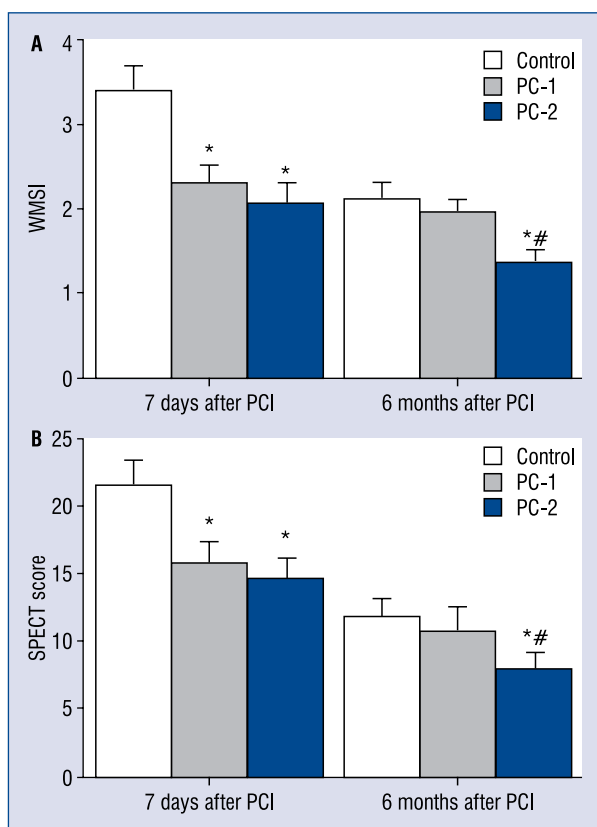


Figure 4. Comparison of wall motion score index (WMSI) and single-photon emission computed tomography (SPECT) 7 days and 6 months after percutaneous coronary intervention (PCI); **A.** WMSI; **B.** SPECT; mean ± standard error of mean; *p < 0.05 vs. control group; #p < 0.05 vs. PC-1 group; PC-1 — postconditioning-1 group; PC-2 — postconditioning-2 group.

Discussion

Myocardial remodeling occurs after myocardial infarction. The process takes about 6 months, the time at which infarct healing is complete. This research therefore implemented the abovementioned observation 6 months after AMI. One study showed that in STEMI patients treated with primary PCI the presence of chronic total occlusion is an independent predictor of long-term mortality [15]. Most studies supported the view that postconditioning is a simple and effective means to be applied in clinic. Postconditioning appears to be superior to PCI alone in reducing myocardial injury and improving left ventricular function, especially in patients who have received direct stenting in PCI [16]. However, some studies argued that postconditioning during primary PCI does not reduce infarct size or improve myocardial function recovery [8, 9, 17]. The present results revealed that the peak of CK-MB, CTFC and postoperative 72 h cTnI were significantly attenuated by postconditioning compared with the control. The hs-CRP of postconditioning group was lower than the control group though it increased 24 h after PCI compared with that on admission. At 7 days, heart rate, CO and EF in postconditioning groups were improved compared with the control group. These results are consistent with previous experimental results [18–20]. What was unexpected is that there was no difference in the effect on cardiac function recovery when applying two postconditioning cycles in aged patients with AMI who underwent PCI 6 months later. However, the WMSI and SPECT score was significantly reduced in the PC-2 group compared with the control and PC-1 group. It suggested that PC-2 protocol may have a positive effect on recovery of segmental myocardial movement and function.

The exact mechanism of postconditioning is not fully understood. A number of experimental studies were carried out in pigs, dogs, rabbits, rats and mice as the animal model of myocardial ischemia reperfusion injury. They confirmed that postconditioning can effectively improve cardiac function, reduce myocardial infarction area, inflammation, the occurrence of apoptosis and arrhythmia [21–23]. There is no conclusion about the optimal number of postconditioning cycles and cycle duration. In a study of 46 rats treated with different postconditioning it was found that postconditioning (3 cycles of 10 s inflation and 10 s deflation) decreased the area of myocardial

infarction by 23% compared to the control group. However, increasing the number of cycles (increased from 3 to 6) cannot further reduce the area of myocardial infarction [24]. Series of POST studies have not been able to obtain the myocardial protective effect of postconditioning, which may be caused by different standards, design groupings, test methods and other variables. This study, by design, had two different cycles which were compared with the PCI group alone. At 6 months, the WMSI and SPECT score was significantly reduced in the PC-2 group when compared with the control and PC-1 groups, but there was no difference among the three groups about echo data except for the LVESD. One reason for the differences between 7 days and 6 months may be due to age and collateral circulation. Aged patients may have well collateral circulation compared with younger patients. If the blockage duration of blood flow in coronary artery was not very long the old patients may not react as quickly as younger patients. We can see that the hs-CRP is not different at 7 days. This indicated that inflammation is another reason for different results between 7 days and 6 months. Postconditioning attenuates the elevation of tumor necrosis factor- α and was associated with long-term cardioprotective effects for inhibition of the inflammatory response and reperfusion injury [25]. Variations in environmental conditions and duration of ischemia may also be reasons for failing to show any meaningful difference.

As a simple and objective index of continuous variables, CTFC is gaining more attention in the evaluation of coronary blood flow. CTFC numerical level can reflect the microcirculation and myocardial reperfusion injury degree. This study confirmed that the PC group can speed up CTFC. Data hinted that postconditioning can accelerate coronary artery flow velocity and microcirculation blood supply. However, there was no difference between PC-1 and PC-2 group. The reason for a lack of difference may be due to the "delay effect". This means CTFC was observed at the point of completing PCI in this study. It was unfortunate that it was not feasible to repeat CTFC in this study 6 months subsequent to PCI. Maybe a difference could be detected 6 months after PCI. In this study, echocardiography and SPECT were used to evaluate the systolic and diastolic function and microcirculation perfusion of patients. The results showed that LVESD, LVEF and CO were improved in the PC group 7 days after the operation. The differences may be related to the restoration of

hibernating myocardium after AMI. At 6 months, however, there was no difference among the three groups with echo data except the LVESD. Based on these observations it was extrapolated that reasons for the results above were: 1) Aged patients were the observed subjects in this study and their recovery duration could be longer than younger patients; 2) In spite of having no whole heart function differences detected, the SPECT score of the PC group decreased markedly compared with the conventional PCI, suggesting that the PC group can effectively increase myocardial perfusion and reduce myocardial infarct size, especially in the PC-2 group. It means regional impaired myocardiums were rescued by postconditioning; 3) Sample size and follow-up time maybe other impact factors.

Conclusions

In summary, this study revealed that postconditioning could significantly benefit the prognosis in aged patients with AMI. The data favors the notion that the PC group can effectively increase myocardial perfusion, although there was no difference in cardiac function detected by echo between the two postconditioning cycles applied 6 months after PCI. The findings further revealed the positive role of 4 cycles of 60 s observed in WMSI and SPECT. These data should shed some light toward a better understanding of the therapeutic value of postconditioning in the management of AMI-associated cardiac dysfunction. However, more long term and larger size clinical trials are needed to clarify whether postconditioning could contribute to a reduction in long term morbidity and mortality in aged patients with AMI.

Acknowledgements

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Conflict of interest: None declared

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