Original Article

Effect of Ischemic Postconditioning during Primary Percutaneous Coronary Intervention for Patients with ST-segment Elevation Myocardial Infarction: A Single-center Cross-sectional Study

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Abstract

Background and Objective: Reperfusion therapy for acute myocardial infarction has been shown to reduce mortality, yet it may also have deleterious effects, including myocardial necrosis and no-reflow. Postconditioning is known measure for cardioprotection from reperfusion injury in animal model. Postconditioning is known measure for cardioprotection from reperfusion injury in animal model and human studies have shown inconsistent results. **Materials and Methods:** From February 2013 through October 2014, at Institute of Postgraduate Medical Education and Research, Kolkata Cardiology department, we randomized 43 patients with acute ST-segment elevation myocardial infarction (STEMI) who were undergoing conventional primary percutaneous coronary intervention (PCI) (22 patients) and PCI with postconditioning by repeated transient balloon occlusion after establishment of flow (21 patients). Total creatine kinase-muscle/brain (CPK-MB) released within 72 h was compared as a surrogate marker of infarct size. Myocardial blush grade between two groups was also compared. **Results:** The area under curve of serum creatine kinase (CK) release during the 1st 72 h of reperfusion was significantly reduced (P = 0.0347) in the postconditioned group compared with the control group, averaging 9632 IU in postconditioned compared with 13493 IU in control group which represented 29% of reduction of infarct size. The peak of CPK-MB release was markedly lower in the postconditioned (290 ± 16.24 IU/L) than in the control (414.2 ± 51.34 IU/L) group ($P \leq 0.0001$). Blush grading was also significantly improved in postconditioned group (P = 0.005). Mean ST-segment deviation at 48 h between cases and control groups was 0.87 ± 0.68 and 1.4 ± 0.94, respectively (P = 0.08). **Conclusion:** In patients with STEMI, postconditioning significantly improves blush grading and enzymatic infarct size reduction with a trend toward significant reduction of mean ST-segment deviation.

Keywords: *Ischemic postconditioning, reperfusion injury, primary percutaneous coronary intervention, ST-segment elevation myocardial infarction*

Introduction

Infarct size is an important determinant of the short- and long-term outcome after acute myocardial infarction (AMI).[1,2] Reperfusion therapy for AMI has been shown to reduce mortality, yet it may also have deleterious effects, including myocardial necrosis and no-reflow.[3-5] Although not all animal models have consistently shown a benefit of postconditioning on infarct size, there are compelling data in humans. In 2005, Staat *et al*.[6] published a landmark study of postconditioning. This was a multicenter randomized controlled trial of 30 patients with ST-segment elevation myocardial infarction (STEMI) involving the left anterior descending coronary artery or the right coronary artery that was undergoing percutaneous coronary intervention (PCI). Their protocol of postconditioning consisted of 4 cycles of 1 min balloon inflation followed by 1 min of balloon deflation within 1 min of reflow after deployment of a coronary stent. Patients in the postconditioning group were found to have significant reduction of CK release. Restoration of coronary blood flow during primary PCI can paradoxically induce additional myocardial damage, making reperfusion a "double-edged sword."[7] Reperfusion injury is a complex phenomenon mediated by several factors, including oxidative stress, intracellular calcium accumulation, rapid restoration of pH, inflammation, and involves, at least partly, opening of the so-called

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mitochondrial permeability transition pore.[8] Clinically identified features of this reperfusion injury may be reversible and transient, such as arrhythmias or myocardial stunning, or irreversible, such as myocardial infarction or microvascular obstruction.[7]

Materials and Methods

Study design

From February 2013 through October 2014, 43 patients with diagnosis of STEMI at our institute, Postgraduate Medical Education and Research (IPGME and R), Kolkata Cardiology department were undergoing randomization. The study was approved by the Ethics Committee of IPGME and R, Kolkata. It was a case–control, randomized, single-blinded, cross-sectional hospital-based study.

Study participant

The trial enrolled consecutive patients of age ≥18 years of age who were diagnosed as STEMI according to American College of Cardiology/American Heart Association electrocardiography (ECG) criteria who presented within 12 h of symptom onset[9] and who are candidates for primary angioplasty.[9] The culprit coronary artery had to be occluded at the time of admission (Thrombolysis in Myocardial Infarction [TIMI] 0 flow grade) and had to be adequately reperfused (TIMI 2–3 flow grade) after percutaneous transluminal coronary angioplasty (PTCA). Patients with cardiac arrest, cardiogenic shock, or previous AMI were not included in this study. Patients with evidence of coronary collaterals (Rentrop grade ≥2) to the risk region were excluded from the study. The patients who had left main or equivalent disease were also excluded from the study.

Study protocol

All patients were premedicated with loading doses of ecosprin (325 mg) and clopidogrel (600 mg) and atorvastatin (80 = mg) given to the patients. Coronary angiography was performed using a standard Seldinger technique. Iohexol (Omnipaque) was used as contrast agent for coronary angiography. Coronary angiography allowed identification of the culprit coronary artery and checked that reperfusion had not occurred before PTCA (TIMI 0 flow grade) and that no collateral filling from homolateral or contralateral coronary vessels was present. Coronary angioplasty was performed according to the direct stenting technique. Thrombosuction catheter was used. Predilatation of the lesion was avoided. Gp2b/3a was used as per operator's discretion. After implantation of the coronary stent, the angioplasty balloon was quickly deflated and withdrawn just up-stream of the stent; then, reperfusion was checked by a single contrast shot. Only patients with a TIMI Grade 2–3 TIMI coronary flow after stent implantation were kept in the study.

In the control group, no additional intervention was performed during the 1st 8 min of reperfusion. In the postconditioned group, within 1 min of reflow after the direct stenting, the angioplasty balloon was positioned just upstream of the implanted stent (so that it would not be damaged and to prevent possible thrombi embolization during in-stent balloon reinflation) and reinflated 4 times for 1 min with low-pressure (4–6 atm) inflations, each separated by 1 min of reflow [Figure 1].[10] This sequence of four brief episodes of ischemia-reperfusion was chosen arbitrarily because it was recently demonstrated that a similar regimen triggers postconditioning in the rabbit heart.[11] When the balloon was positioned just upstream of the implanted stent in the postconditioned group, care was taken not to encompass a coronary branch. At minute 8, coronary angiography was performed in both groups to assess coronary patency and to estimate the myocardial perfusion index using the blush grade evaluation.[12] The angioplasty procedure was then completed according to physician judgment with respect to patient status.

Standard 12-lead ECGs were recorded at admission and 48 h later. Maximal ST-segment change was measured by a cardiologist unaware of the patient's group. At all-time points, ST-segment shift was measured 80 ms after the J point. Blood samples were taken at admission, after 4 h of opening of the artery, then after 8 h, 24 h, 48 h, and 72 h. Area under the curve (AUC; arbitrary units) of serum creatine kinase CK release (Beckman Kit, expressed in IU/L) was measured in each patient by computerized planimetry and used as a surrogate marker of infarct size.

Study outcomes

The objective of the present study was to determine whether brief episodes of ischemia-reperfusion (postconditioning) performed during the 1st min of reperfusion by PTCA in patients with ongoing AMI can reduce the creatine kinase-muscle/brain (CPK-MB) release after the procedure which indeed a surrogate marker of myocardial damage. Comparison of myocardial blush grading during primary PCI and maximum ST-segment deviation between the two groups at 48 h after the procedure was done.

Results

From February 2013 through October 2014, 117 patients with acute STEMI were screened for eligibility, in which

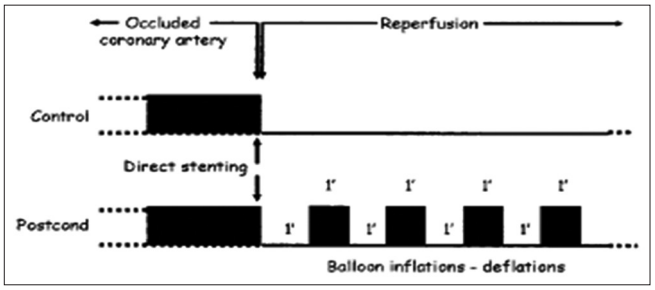


Figure 1: Experimental protocol

10 patients did not give the consent, 16 patients were in cardiogenic shock, 8 patients had left main or equivalent disease, 6 patients had collateral of Rentrop Grade ≥2, 22 patients had TIMI flow more than zero on initial angiography, and 12 patients did not had TIMI flow 2 or 3 after PTCA, so they were excluded from randomization.

A total of 43 patients were randomized, with 21 patients were undergoing postconditioning (postconditioned group) and 22 patients conventional primary PCI (control group). One patient from postconditioned group and two patients from the control group were died during index period of hospitalization. Twenty patients from postconditioned group were compared with 20 patients from the control group. The characteristics of the patients at baseline were similar in the two groups [Table 1]. Among cases, 10 patients (50%) had blush Grade 3, 8 patients (40%) had blush Grade 2, and 2 patients (10%) had blush Grade 1, respectively, after primary PCI. Among control group, 3 patients (15%) had blush Grade 3, 9 patients (45%) had blush Grade 2, and 8 patients (40%) had blush Grade 1, respectively, after primary PCI. There was statistically significant difference between two groups (P = 0.0057) [Figure 2]. Mean ST-segment deviation at 48 h between postconditioned and control group were 0.87 ± 0.68 and 1.4 ± 0.94, respectively. There was a trend toward significant improvement in ST-segment deviation in postconditioned group but did not reach the level of statistical significance [Figure 3]. The AUC of serum CK release during the first 72 h of reperfusion was significantly reduced (P = 0.0347) in the postconditioned group compared with the control group, averaging 9632 in postconditioned compared with 13,493 in the control group which represented 29% of reduction of infarct size [Figure 4]. The peak of CPK MB release was markedly lower in the postconditioned (290 ± 16.24 IU/L) than in the control (414.2 ± 51.34 IU/L) group ($P \leq 0.0001$) [Figure 5]. Summary of changes of different parameters after primary PCI has been summarized in Table 2.

Table 1: Baseline characteristics of the study population

	Postconditioned	Control	*P*
Age	56±11	57±11	NS
Sex male/female	11/9	14/6	NS
BMI	31±6	31±5	NS
Hypertension (%)	40	50	NS
Smoker (%)	30	40	NS
Dyslipidemia (%)	60	50	NS
Diabetes (%)	20	15	NS
Ejection fraction	46±6	45±7	NS
Distribution of culprit vessel (%) (LAD/LCX/RCA)	50/15/35	55/10/35	NS
Maximum ST-segment deviation at 0 h	4.3±0.9	4.2±0.8	NS

BMI: Body mass index, RCA: Right coronary artery, LAD: Left anterior descending, LCX: Left circumflex, NS: Not significant

Table 2: Summary of changes of parameters after primary primary percutaneous coronary

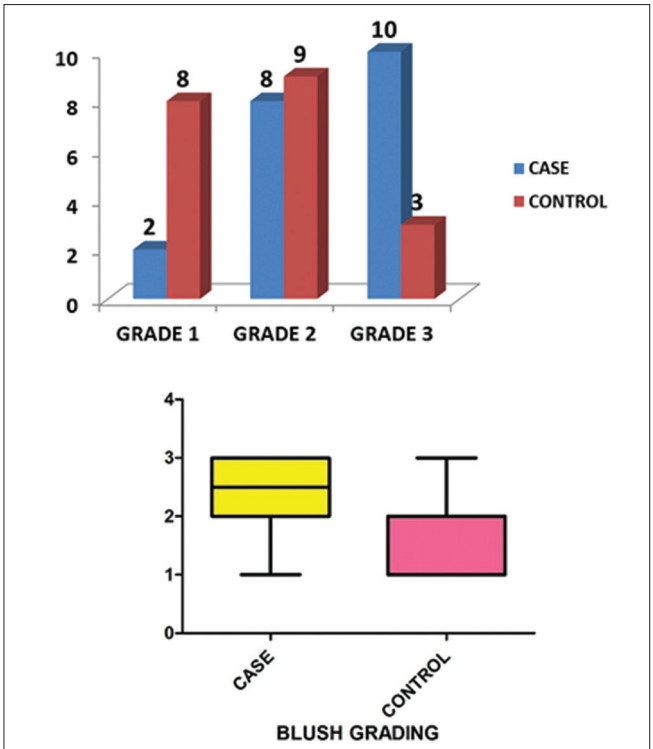
	Postconditioned	Control	*P*
Maximum ST-segment deviation at 48 h	0.8±0.7	1.4±0.9	0.085
Blush grading % (Grade 1/Grade 2/Grade 3)	10/40/50	40/45/15	0.005
AUC of CPK MB release in first 72 h	9632±117	13493±163	0.034
Peak CPK MB release	290±16	414±51	<0.0001

AUC: Area under the curve, CPK MB: Creatine kinase-muscle/brain

Discussion

Abnormalities associated with increasing myocardial perfusion, as assessed by the myocardial blush grade (MBG), correlate with unfavorable ventricular remodeling and risk of mortality even after adjusting for the presence of TIMI Grade 3 flow or a normal TIMI frame count.[13,14] They are better indicator of microvascular integrity. In this study, short-term or long-term clinical outcomes were not assessed; instead, laboratory markers were assessed for successful reperfusion and cardiac injury. Myocardial blush grading is one of the markers of successful reperfusion at microvascular level. In our study, there was a significant improvement of myocardial blush grading in the postconditioned group indicating favorable result with postconditioning. Although previous studies on postconditioning showed similar effect,[6] recently, a large study conducted by Hahn *et al*. did not find any significant difference of MBG between postconditioned and control group.[15] In their study postconditioning was not performed as per protocol in around 10% of patients and balloon occlusion for ischemic postconditioning was performed before stenting, so there may be a possibility of incomplete establishment of flow before postconditioning violating the basic principle of postconditioning. In our study, we performed postconditioning in all patients after achieving TIMI flow 2 or 3 after stenting. Moreover, they used predilatation balloon and thrombosuction catheter for the establishment of flow in most of the patients. In our study, we have used only thrombosuction catheter and excluded patients for whom we had to use predilatation balloon for establishing flow. The reason being that by the use of predilatation balloon we are actually allowing more thrombus to migrate toward distal microcirculation causing more damage which is against the principle of direct stenting which should be a preferred strategy for management of STEMI. We have used thrombosuction catheter in almost all patients for establishing flow. The advantage of thrombosuction catheter over predilatation balloon is that chances of distal thrombus migration are much less. In our institution, we use predilatation balloon for establishing flow only when thrombosuction fails to establish the flow.

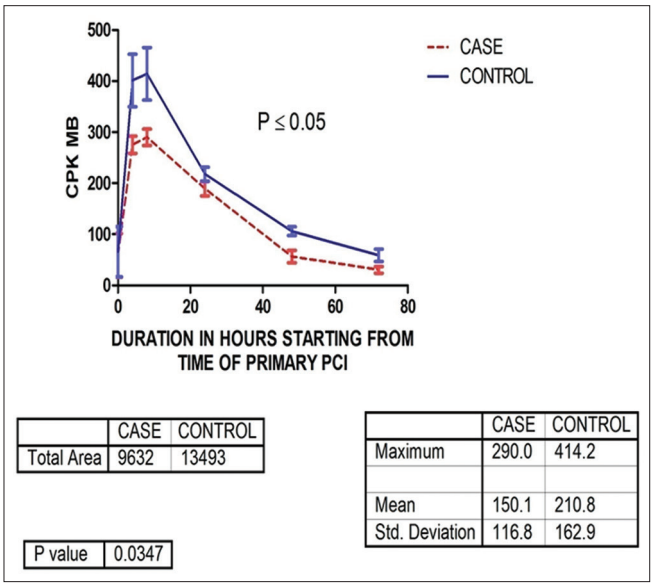
The major finding of this study is that postconditioning reduced infarct size by 29%. The reduced enzymatic infarct size observed here closely resembles that reported in the



Mean of differences	0.6500
95% confidence interval	0.2132 to 1.087

P value	0.0057

Figure 2: Comparison of blush grading between postconditioned and control group

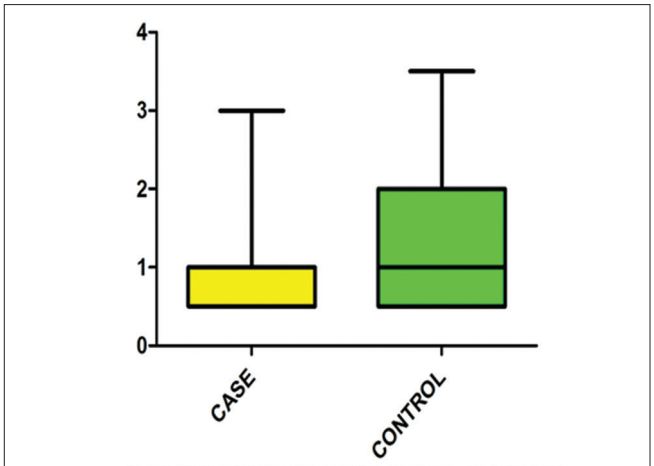


	CASE	CONTROL
Total Area	9632	13493

	CASE	CONTROL
Maximum	290.0	414.2
Mean	150.1	210.8
Std. Deviation	116.8	162.9

P value	0.0347

Figure 4: Comparison of Area under the curve of creatine kinase-muscle/brain between postconditioned and control group

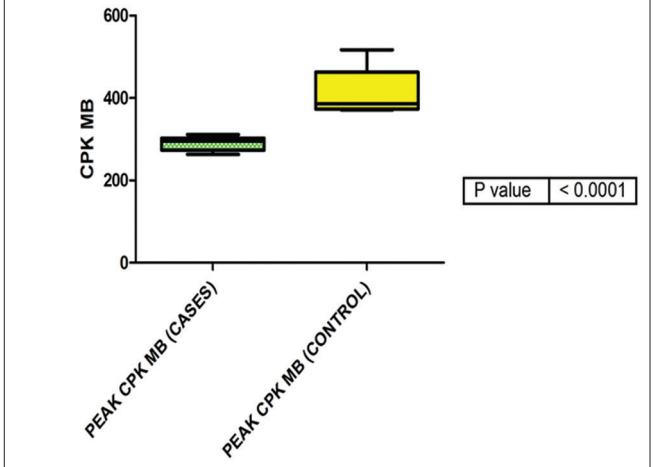


	CASE	CONTROL
Mean	0.8750	1.400
Std. Deviation	0.6859	0.9403
Std. Error	0.1534	0.2103

P value	0.0851

Figure 3: Comparison of ST-segment deviation between postconditioned and control group

	PEAK CPK MB (CASES)	PEAK CPK MB (CONTROL)
Maximum	311.0	517.0



P value	< 0.0001

	PEAK CPK MB (CASES)	PEAK CPK MB (CONTROL)
Mean	290.0	414.2
Std. Deviation	16.24	51.34
Std. Error	3.631	11.48

Figure 5: Comparison of peak creatine kinase-muscle/brain between postconditioned and control group

postconditioned human heart by Kloner *et al*.[16] and Ottani *et al*.[17] and Staat *et al*.[6] CK release is a surrogate endpoint that has been validated with respect to SPECT imaging in several studies and represents a useful and easily available technique to evaluate irreversible myocardial injury in clinical practice.[18] Overall, our data strongly suggest that enzymatic infarct size reduction was not due to a difference in either major determinant of infarct size but actually reflects a protective effect of postconditioning because we have already demonstrated that baseline variables were similar in two groups.

There are recent controversies regarding beneficial effect of postconditioning.

Hahn *et al*.[15] did not find improve myocardial reperfusion in patients with ST-segment elevation myocardial infarction undergoing primary PCI with postconditioning. They showed that there was no significant difference in peak levels of creatine kinase MB between the two groups. This is against our observation. In fact, they have used peak CPK-MB level instead of taking total amount of enzyme measured by area under curve principle released over a time period. Now, total enzyme release is a better index than taking only peak value as a surrogate marker of infarct size determination. Even meta-analysis demonstrates that there is a significant difference in reduction of AUC of CPK-MB level after postconditioning.

Previous studies with SPECT imaging shows that there is significant reduction of infarct size after postconditioning.[18] However, recent studies[15] and meta-analysis[19] which used magnetic resonance imaging (MRI) as a tool to determine infarct size failed to demonstrate any beneficial effect of postconditioning. Several factors may affect the relationship between the two approaches. Although cardiovascular magnetic resonance (CMR) shows its superiority to other methods with regard to detection and quantification of MI, different specific approaches have been employed to quantify infarct size from CMR.[20-22] Until now, there is no ideal and practical method to define infarct size by CMR available for daily clinical setting and there are a few drawbacks within all the mentioned methods. Hence, determining infarct size by MRI can be operator dependent and needs expertise.[20] This may explain the above difference of final infarct size in different studies. Besides, in the presence of reperfusion therapy, an reversible-reperfusion-injury increased permeability, but preserved integrity of the myocyte membrane is partly associated with troponin and CK release,[23,24] which would not appear as necrosis on CMR images.[22] Therefore, more studies are needed for confirmatory evidence on infarct size. Even in recent study[25] of patients with anterior STEMI, remote ischemic postconditioning at the time of primary PCI reduced enzymatic infarct size and was also associated with an improvement of T2-weighted edema volume in MRI and ST-segment resolution >50%.

There was no statistically significant difference in the mean ST-segment deviation at 48 h between two groups ($P = 0.08$). It is worth noting that the blush grade was significantly improved in the postconditioned group, whereas there was a trend, although not significant, toward a diminution of ST-segment shift at 48 h of reperfusion. Blush grade has been proposed as a marker of myocardial perfusion in the 1st min of reflow.[12,26] van't Hof *et al*.[12] reported blush grade as a marker of long-term mortality in AMI patients. Schröder[27] demonstrated that ST regression after reperfusion is another endpoint that indicates a preserved myocardial perfusion after AMI. Reduction in ST elevation was not significant ($P = 0.08$) in the present study, possibly because ECG was performed at 48 h of reflow instead of 90 min, as usually recommended, and because of insufficient statistical power.[12] On the other hand, experimental studies indicate that myocardial blood flow may vary up to 48 h after reperfusion in the area at risk after prolonged ischemia reperfusion.[28]

Limitation of the study

We used CPK-MB release over 72 h as a surrogate marker for myocardial injury. Although there are studies which show good correlation between CPK-MB release and myocardial injury demonstrated by SPECT study, recently, MRI scan has emerged as a reliable tool for estimation of myocardial edema and infarct size, though standard protocol is still lacking. Had the study been conducted by MRI or SPECT, it would have more impact on final outcome than only relying on surrogate marker, that is, AUC estimation of CPK-MB over 72 h. However, cost constraint is always a factor in conducting a study using MRI or SPECT in each patient. The study was conducted in a state medical college and hospital and maximum patients of our institute are from low socioeconomic background. Safety concerns related to possible thrombus microembolization occurring during repeated balloon inflations during postconditioning[29] to the infarct-related artery has been postulated. Some operators are now investigating the effect of remote ischemic postconditioning,[25] and result of these studies are encouraging. It was not a longitudinal study. Parameters such that all-cause mortality, hospital admission with heart failure, improves in ejection fraction were not included in this study, so the benefit of enzymatic reduction of infarct size whether it is translating into clinical benefit is not known from the study. Sample size was small and subgroup analysis was not done. Further studies with large sample size is required for answering questions like the effect of GP 2b/3a inhibitor, correlation with time of presentation after chest pain, effect of the use of thrombosuction catheter.

Conclusion

In our study, we have clearly demonstrated that we can reduce the infarct size after doing postconditioning. We can also improve the blush grading which is being considered to be an important determinant of successful primary PCI. It was a cross-sectional study; we need a large volume longitudinal study to see the exact clinical impact of postconditioning during primary PCI.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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