Impact of Remote Ischemic Postconditioning during Primary Percutaneous Coronary Intervention on Left Ventricular Remodeling after Anterior Wall ST-Segment Elevation Myocardial Infarction: A Single-Center Experience

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Abstract

The role of remote ischemic postconditioning (RIPostC) in improving left ventricular (LV) remodeling after primary percutaneous coronary intervention (PCI) is not well established. To determine the efficacy and safety of RIPostC in improving LV remodeling and cardiovascular outcomes after primary PCI for anterior ST-elevation myocardial infarction (STEMI). Seventy-one patients with anterior STEMI were randomized to primary PCI with RIPostC protocol ($n = 36$) versus conventional primary PCI ($n = 35$). Primary outcomes included LV remodeling and LV ejection fraction (LVEF) at 6 month follow-up using transthoracic echocardiography. Secondary outcomes included infarct size, ST-segment resolution (STR) $\geq$70%, Thrombolysis in Myocardial Infarction (TIMI) flow grade, and myocardial blush grade (MBG). Major adverse cardiac events (MACEs) were also assessed at 6 months. Safety outcome included incidence of acute kidney injury (AKI) postprimary PCI. Sixty patients completed the study. At 6 months, there was no significant decrease in the incidence of LV remodeling with RIPostC group ($p = 0.42$). Similarly, RIPostC failed to show significant improvement in LVEF. However, STR $\geq$ 70% after primary PCI was achieved more in the RIPostC group ($p = 0.04$), with a trend toward less AKI in the RIPostC group ($p = 0.08$). All other secondary end points, including MACEs at 6 months, were similar in both groups. RIPostC might be associated with better STR after reperfusion as well as less incidence of AKI in patients undergoing primary PCI for anterior wall STEMI, indicating potential benefit in those patients. Whether this role can be translated to better outcomes after primary PCI warrants further investigation.

Keywords

- coronary artery disease
- acute anterior wall myocardial infarction
- primary PCI
- reperfusion Injury
- remote ischemic postconditioning
- remodeling

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Primary percutaneous coronary intervention (PCI) is the recommended treatment for ST-segment elevation myocardial infarction (STEMI).[1] Despite the proven role of primary PCI in patients with STEMI, this benefit is attenuated by what is known as "reperfusion injury."[2] Reperfusion injury is caused by abrupt restoration of blood flow, resulting in lethal injury of the recently ischemic myocardial cells, leading to worsening of left ventricular (LV) remodeling. In preclinical studies, the impact of reperfusion injury was strongly correlated to the final infarct size.[2] Multiple trials were conducted on various techniques to help reduce reperfusion injury. In 1986, Murry et al[3] described ischemic preconditioning (IPC) where brief periods of local ischemia and reperfusion before target organ ischemia were found to exert a protective role against reperfusion injury. The protective role of IPC was also validated in other studies.[4,5] However, this technique can be applied only to cases in which the onset of ischemia can be predicted. This led to the invention of a modified technique of applying brief cycles of coronary artery occlusion/reperfusion at the onset of myocardial reperfusion, known as ischemic postconditioning (IPostC). The first promising experimental results on this topic were released in 2003 by Zhao et al.[6] Considerable drawbacks of both techniques are being invasive and time-consuming especially during primary PCI for STEMI.

Another technique was implicated after the novel idea of remote ischemic conditioning (RIC) by Przyklenk et al in 1993.[7] This technique aimed at applying cycles of brief ischemia and reperfusion to an organ remote from the heart, simply by inflating and deflating a blood pressure cuff placed on one of the limbs, either before the onset of ischemia (remote ischemic preconditioning [RIPC]) or at the onset of reperfusion (remote ischemic postconditioning [RIPostC]).[7]

Few clinical trials proved the role of RIC at the time of primary PCI for patients with STEMI.[8,9] However, the impact of RIPostC on LV remodeling in patients with STEMI was not evaluated in previous trials. LV remodeling has been shown to reflect infarct size after acute myocardial infarction (MI).[10] In this study, we sought to determine the impact of RIPostC on LV remodeling, as well as its efficacy and safety in patients undergoing primary PCI for acute anterior STEMI.

Methods

Study Population

Ninety-one patients who presented to our tertiary medical center in the period from February 2014 to December 2014 with acute anterior wall STEMI were enrolled. Patients were included if the onset of symptoms was $\leq$12 hours and they were eligible for primary PCI. Anterior STEMI was defined as new ST elevation at the J point in at least two contiguous leads of $\geq$2 mm (0.2 mV) in men or $\geq$1.5 mm (0.15 mV) in women in leads V2 to V3 and/or of $\geq$1 mm (0.1 mV) in other anterior chest leads in a 12-lead electrocardiogram (EKG).[1]

Patients were excluded if they: (1) presented with non-anterior wall STEMI, (2) presented with cardiogenic shock (Killip class IV),[11] (3) had a history of PCI or coronary artery bypass grafting (CABG), (4) had inadequate two-dimensional (2D) transthoracic echocardiography (TTE) evaluation, (5) initially received fibrinolytic therapy, or (6) had a history of severe peripheral artery disease. All patients were followed up with an office visit at 6 months during which clinical assessment and repeat TTE were performed.

Study Design

This is a single-center, randomized, controlled, parallel group, open-label trial, with blinded evaluation of the end points. Out of the 91 patients, only 71 met our inclusion criteria and were randomized 1:1 into two groups. The first group ($n = 36$) received RIPostC protocol during primary PCI (RIPostC group), whereas the second group ($n = 35$) underwent conventional primary PCI (control group). All patients received aspirin 300 mg, clopidogrel 600 mg before the index procedure, and 70 IU/kg unfractionated heparin during the procedure. Primary PCI was performed through femoral approach, and the use of adjunctive therapy such as thrombectomy and glycoprotein IIb/IIIa inhibitors was left to the operators' discretion. Aspirin, angiotensin-converting enzyme inhibitors, β-blockers, and statins were prescribed after PCI in the absence of contraindications. Clopidogrel 75 mg was continued daily for at least 12 months after PCI. Local institutional review board and ethics committee approved the study, and this study conformed to the Declaration of Helsinki. All the participants signed a written consent before enrolment in the study.

Remote Ischemic Postconditioning Protocol

Patients in the RIPostC group were prepared with a thigh-sized limb cuff before arterial puncture contralateral to site of femoral access. The protocol was started within 1 minute from restoration of blood flow in culprit vessel (after wire passing, thrombectomy, or balloon inflation). The lower limb was exposed to three cycles of ischemia through cuff inflation at 200 mm Hg for 5 minutes, alternating with three cycles of reperfusion through complete cuff deflation for 5 minutes. Study personnel involved in RIPostC protocol were not involved in the assessment of the end points.

Outcomes and Definitions

The primary outcomes included adverse LV remodeling and LV ejection fraction (LVEF) at 6 months follow-up duration evaluated using 2D TTE. Two-dimensional TTE studies were performed by a cardiac imaging certified physician, using the Vivid 5 system (GE, Vingmed, Horten, Norway). Baseline 2D TTE was performed for all patients within 3 days of presentation. Five views were obtained for evaluation: parasternal long-axis, parasternal short-axis, apical two-chamber, apical three-chamber, and apical four-chamber views. LV end diastolic diameter (LVEDD) and LV end systolic diameter (LVESD) were calculated using parasternal short-axis view at the level of papillary muscles by M-mode.[12] LV end diastolic volume (LVEDV) and LV end systolic volume (LVESV) were acquired using the arithmetic mean of the biplane Simpson method in both the four- and two-chamber projections.[13] LVEF was also calculated using biplane Simpson's method.[14] LV remodeling was defined as an increase in LV

end-diastolic volume ≥20% at 6 months from baseline.[15] LVEF improvement was defined as increase of LVEF more than 5% at 6 months follow-up. Parameters evaluation was conducted by two separate physicians who were blinded to randomization. Discrepancies secondary to interobserver variability were resolved by consensus of the physicians.

Secondary outcomes included:

- *Major adverse cardiac events (MACEs) at 6 month follow-up duration* defined as all-cause mortality, nonfatal MI, and target vessel revascularization (TVR).
- *Achievement of full ST-segment resolution (STR) after primary PCI* defined as ≥ 70% resolution of the ST-segment elevation.[16] ST-segment elevation was evaluated in 12-lead EKG performed within 10 minutes of first medical contact and at 90 minutes after reperfusion in the lead of maximum ST-segment elevation. PR segment was the reference baseline. Evaluation was conducted by a single investigator blinded to randomization.
- *Infarct size after primary PCI* assessed by peak levels of creatinine kinase-myocardial band (CK-MB) enzymes. CK-MB levels were documented on presentation and every 4 to 6 hours for the first 48 hours, then every 12 hours till 72 hours.
- *Thrombolysis In Myocardial Infarction (TIMI) flow grade and myocardial blush grade (MBG) after primary PCI*: Outcome measure of achieving TIMI III flow was defined as grade III antegrade flow into the bed perfused by the infarct-related vessel occurring as promptly as antegrade flow into comparable areas not perfused by infarct-related vessel.[17] MBG was evaluated in the left lateral view after the PCI, and outcome measure of achievement of MBG III was defined as the opacification of the myocardium cleared normally at the end of the washout phase, similar to that in the noninvolved territory.[18]
- *Acute kidney injury (AKI) after primary PCI*: AKI was defined as absolute (≥0.5 mg/dL) or relative (≥ 25%) increase in serum creatinine within 96 hours after PCI compared with baseline serum creatinine values, when alternative causes for renal impairment have been excluded.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation. Categorical variables were presented as counts and percentages. Inferential analyses were performed for quantitative variables using independent *t*-test in cases of two independent groups with parametric data and one-way analysis of variance for two or more means. Inferential analyses were performed for qualitative data using chi-square test. Pearson correlation was used to measure the correlation (linear dependence) between two variables.

Results

We enrolled 91 patients presenting with anterior STEMI. Of the 91 patients, 20 met one of the exclusion criteria, including previous PCI, previous CABG, or cardiogenic shock, and 71 patients were randomized into two study groups. Only 60 patients completed the study and were included in the analysis as 7 patients were lost to follow-up and 4 patients did not have adequate TTE images. ►**Fig. 1** illustrates the study flowchart.

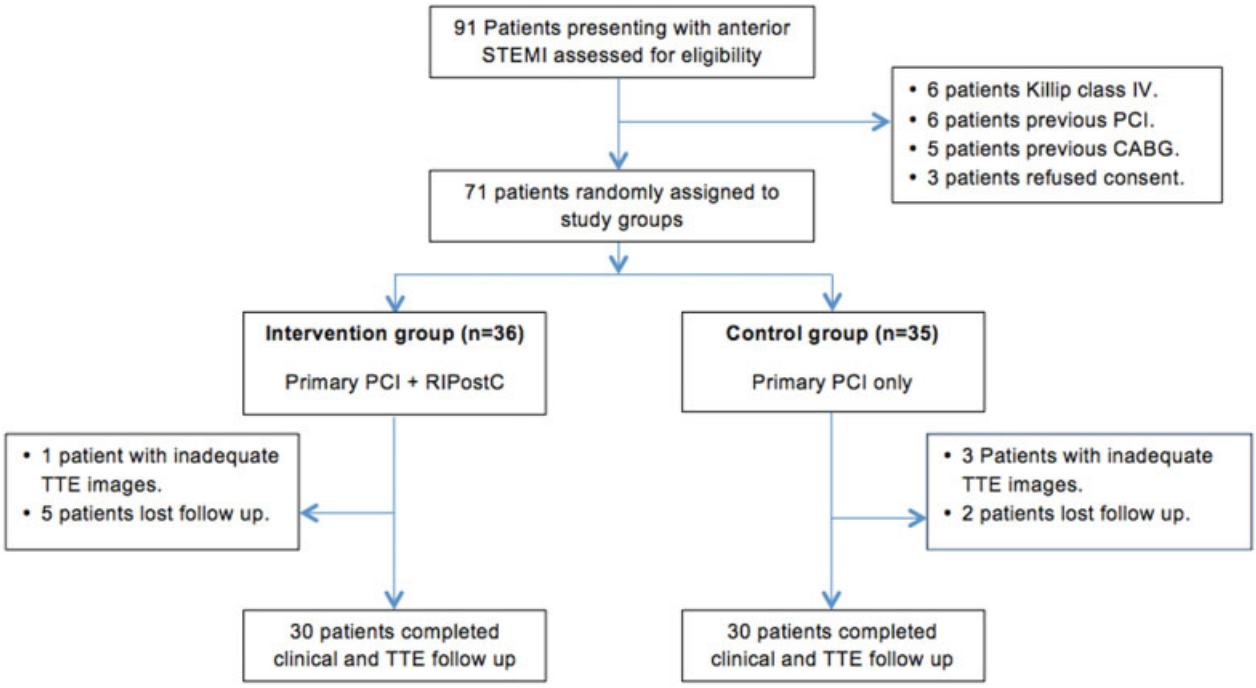

Fig. 1 The study flowchart. CABG, Coronary artery bypass grafting; PCI, percutaneous coronary intervention; RIPostC, remote ischemic postconditioning; STEMI, ST-segment elevation myocardial infarction; TTE, transthoracic echocardiography.

Table 1 Baseline clinical and echocardiographic characteristics

	Control group ($n = 30$)	RIPostC group ($n = 30$)	*p*-Value
Age, y (mean ± SD)	50.1 ± 7.3	53.0 ± 7.5	0.14
Female, *n* (%)	5 (16.7)	5 (16.7)	0.99
Smoking, *n* (%)	23 (76.7)	19 (63.3)	0.26
Dyslipidemia, *n* (%)	24 (80.0)	22 (73.3)	0.54
DM, *n* (%)	13 (43.3)	12 (40.0)	0.79
HTN, *n* (%)	8 (26.7)	12 (40.0)	0.27
FH of CAD, *n* (%)	11 (36.7)	10 (33.3)	0.79
BMI $\geq$ 30 kg/m^2, *n* (%)	6 (20.0)	9 (30.0)	0.37
CKD, *n* (%)	4 (13.3)	3 (10.0)	0.69
CVD, *n* (%)	2 (6.7)	3 (10.0)	0.64
PVD, *n* (%)	9 (30.0)	4 (13.3)	0.12
SBP, mm Hg (mean ± SD)	131.0 ± 12.4	134.7 ± 15.9	0.32
DBP, mm Hg (mean ± SD)	83.2 ± 7.9	81.7 ± 6.9	0.44
HR, bpm (mean ± SD)	95.3 ± 12.1	95.4 ± 9.6	0.98
Killip classification			
Class I, *n* (%)	25 (83.3%)	24 (80.0%)	0.74
Class II, *n* (%)	5 (16.7%)	6 (20.0%)	
Class III, *n* (%)	0 (0.0%)	0 (0.0%)	
Echocardiographic measurements			
LVEDV, mm^3 (mean ± SD)	89.0 ± 29.6	87.1 ± 24.8	0.79
LVESV, mm^3 (mean ± SD)	54.4 ± 21.8	50.0 ± 17.2	0.39
LVEDD, mm (mean ± SD)	54.3 ± 4.0	52.9 ± 6.4	0.31
LVESD, mm (mean ± SD)	43.3 ± 3.9	40.5 ± 5.6	0.03
LVEF, % (mean ± SD)	38.7 ± 6.7	40.9 ± 6.0	0.18

Abbreviations: BMI, body mass index; bpm, beats per minute; CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; FH, family history; HR, heart rate; HTN, hypertension; LVEDD, left ventricular end diastolic dimension; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic dimension; LVESV, left ventricular end systolic volume; PVD, peripheral vascular disease; RIPostC, remote ischemic post conditioning; SBP, systolic blood pressure; SD, standard deviation.

The baseline characteristics and risk factors were similar in both groups. In ►**Table 1**, we report the baseline clinical characteristics as well as echocardiographic measurements in both groups.

Procedural Data

The mean pain-to-door time was 4.8 ± 2.6 hours in the RIPostC group versus 5.9 ± 2.3 hours in the control group ($p = 0.07$), and door-to-balloon time was 44.0 ± 11.9 minutes in the RIPostC group versus 38.8 ± 16.9 minutes in the control group ($p = 0.18$).There was no difference between both study groups in the mean value of preprocedural TIMI flow (0.13± 0.08 in the RIPostC group versus 0.23 ± 0.09 in the control group; $p = 0.381$) or the mean value of post-procedural TIMI flow (2.73± 0.52 in the RIPostC group versus 2.70 ± 0.53 in the control group; $p = 0.795$). The RIPostC group had more patients with three-vessel disease compared with the control group ($p = 0.01$). The study protocol was generally tolerated by all patients. Balloon predilatation was significantly lower in the RIPostC group compared with the control group (13.3 vs. 51.7%, respectively; $p = 0.002$). On the contrary, balloon postdilatation was more in the RIPostC group compared with the control group (36.7 vs. 10.0% respectively; $p = 0.02$). Use of adjunctive therapy was similar in both groups. In ►**Table 2**, we summarize the procedural data in both groups.

Primary Outcomes

The LVEDV was not significantly different between the RIPostC and control groups at baseline (87.1 ± 24.8 vs. 89.0 ± 29.6 mm^3, respectively; $p = 0.79$) or at 6 months follow-up (96.7 ± 30.2 vs. 98.2 ± 27.4 mm^3, respectively; $p = 0.84$). The incidence of adverse LV remodeling was similar in both groups at 6 months follow-up duration (30.0% in the RIPostC group vs. 40.0% in the control group; $p = 0.42$). The LVEF was similar between the RIPostC and

Table 2 Procedural data

	Control group ($n = 30$)	RIPostC group ($n = 30$)	p-Value
P-D time, h (mean ± SD)	5.9 ± 2.3	4.8 ± 2.6	0.07
D-B time, min (mean ± SD)	44.0 ± 11.9	38.8 ± 16.9	0.18
Aspiration thrombectomy, *n* (%)	18 (60.0)	13 (43.3)	0.19
GP IIb/IIIa inhibitors, *n* (%)	7 (23.3)	6 (20.0)	0.75
Thrombus burden			0.24
Grade I, *n* (%)	0 (0.0)	0 (0.0)	
Grade I, *n* (%)	0 (0.0)	0 (0.0)	
Grade III, *n* (%)	2 (6.7)	0 (0.0)	
Grade IV, *n* (%)	4 (13.3)	7 (23.3)	
Grade V, *n* (%)	24 (80.0)	23 (76.7)	
Balloon predilatation, *n* (%)	16 (51.7)	4 (13.3)	0.002
Balloon postdilatation, *n* (%)	3 (10.0)	11 (36.7)	0.02
One-vessel disease, *n* (%)	15 (50.0)	14 (46.7)	0.79
Two-vessel disease, *n* (%)	15 (50.0)	10 (33.3)	0.19
Three-vessel disease, *n* (%)	0 (0.0)	6 (20.0)	0.01

Abbreviations: D-B, door-to-balloon; GP, glycoprotein; P-D, pain-to-door; RIPostC, remote ischemic post conditioning; SD, standard deviation.

control groups at baseline (40.9 ± 6.0 vs. 38.7 ± 6.7%, respectively; $p = 0.18$) and at 6 months follow-up (43.6 ± 10.9 vs. 42.5 ± 8.2, respectively; $p = 0.66$). LVEF was improved in 50% of the patients in the RIPostC group versus 53.3% of patients in the control group ($p = 0.79$). At 6 months follow-up, there was no difference between the RIPostC and control groups in LVESV (56.2 ± 27.3 vs. 53.7 ± 16.3 mm^3, respectively; $p = 0.67$), LVEDD (54.9 ± 5.2 vs. 56.4 ± 4.3 mm, respectively; $p = 0.24$), and LVESD (41.7 ± 5.3 vs. 42.2 ± 3.6 mm, respectively; $p = 0.67$). Primary outcomes are illustrated in ►**Fig. 2**.

Secondary Outcomes

At 6 months follow-up, the incidence of MACEs was similar between both groups (13.3% in the RIPostC group versus 6.7% in the control group; $p = 0.39$). No mortality was reported among patients in both groups. Nonfatal MI occurred in 10.0% of patients in the RIPostC group versus 6.7% of patients in the control group ($p = 0.64$). TVR was performed in 3.0% of patients in the RIPostC group, whereas no patients in the control group required TVR ($p = 0.31$).

Maximal ST-segment elevation at baseline EKG was similar between both groups (3.13 ± 1.1 mm in the RIPostC group versus 2.97 ± 0.9 mm in the control group; $p = 0.147$). Maximal ST-segment elevation 90 minutes after PCI was lower in the RIPostC group compared with the control group (1.83± 0.8 vs. 2.14 ± 0.1 mm, respectively; $p = 0.03$). Full STR ≥ 70% was achieved more with the RIPostC protocol compared with the control group (66.7% vs. 40.0% respectively; $p = 0.04$). However, there was no difference between both groups in infarct size based on peak CK-MB levels (271.9 ± 185.9 µg/L in the RIPostC group vs. 287.7 ± 253.9 µg/L in the control group; $p = 0.79$), TIMI grade III flow (76.7% in the RIPostC group vs. 73.3% in the control group; $p = 0.77$) or MBG grade III (36.7% in RIPostC group vs. 26.7% in control group; $p = 0.41$). Baseline serum creatinine was not different between the RIPostC and control groups (1.11 ± 0.26 vs. 1.09 ± 0.22 mg/dL, respectively; $p = 0.50$). Serum creatinine done within 96 hours after PCI was nonsignificantly reduced in RIPostC group compared with the control group (1.22 ± 0.40 vs. 1.36 ± 0.32 mg/dL, respectively; $p = 0.09$). There was a trend toward less incidence of AKI in the RIPostC group compared with control group that did not reach statistical significance (3.3 vs. 16.7%, respectively; $p = 0.08$). ►**Fig. 3** reports secondary outcomes.

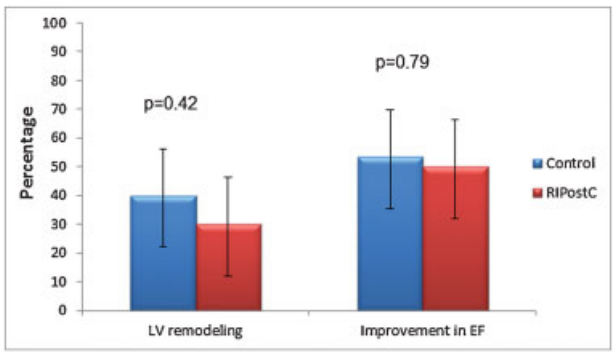

Fig. 2 Primary outcomes of the study. EF, Ejection fraction; LV, left ventricle; RIPostC, remote ischemic postconditioning.

Discussion

In this prospective randomized study of 60 patients with anterior wall STEMI, we aimed to demonstrate the safety and

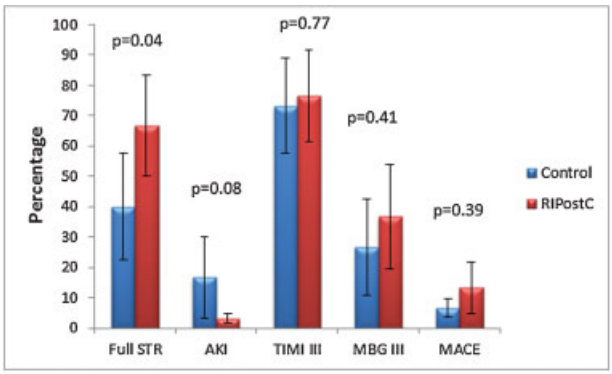

Fig. 3 Secondary outcomes of the study. AKI, Acute kidney injury; MACE, Major adverse cardiac events; MBG, myocardial blush grade; RIPostC, remote ischemic postconditioning; STR, ST-segment resolution; TIMI, Thrombolysis in Myocardial Infarction.

efficacy of RIPostC protocol in reducing the reperfusion injury phenomenon associated with primary PCI. Our study demonstrated that despite better achievement of full STR with RIPostC protocol, there was no significant improvement in adverse LV remodeling, LVEF, or TIMI grade III flow. Similarly, no difference in MACEs was seen between the two groups at 6 months follow-up. A trend toward reduced incidence of AKI after primary PCI was demonstrated with RIPostC protocol. The differences in the rate of balloon pre- and postdilatation between the two groups were attributed to various operators' discretions. The incidence of TVR was increased in the RIPostC group, however, without reaching statistical significance. This could be attributed to the severity of baseline atherosclerotic coronary artery disease in this group compared with the control group.

Local IPostC by applying brief cycles of ischemia/reperfusion to the culprit artery after resuming blood flow has been the study point for many trials aiming to overcome myocardial reperfusion injury.[3–5] The results were controversial, and wide application of this invasive technique was limited due to the fact that it can lead to serious, life-threatening complications such as plaque rupture.[19,20] Hence, interest was directed to RIPostC as a safer modality to reduce reperfusion injury. Results from animal studies suggested that IPC, RIPC, and RIPostC share common signaling pathways including triggers (adenosine receptor stimulation),[21] mediators (protein kinase C activation),[22,23] and end effectors (opening of mitochondrial K-ATP channels (adenosine triphosphate-sensitive potassium channels),[24] activation of prosurvival kinases,[25] and inhibition of MPTP (mitochondrial permeability transition pore) opening as demonstrated in earlier studies[26,27]).

The efficacy of RIPostC is still an area of debate. Few studies have been conducted to date to evaluate the effect of remote conditioning in patients with acute STEMI undergoing primary PCI. Rentoukas et al[28] tested the effects of remote ischemic periconditioning initiated prior to primary PCI in patients with STEMI and showed reduction in the primary end point of full STR with remote ischemic periconditioning compared with primary PCI alone group. In another study by Crimi et al,[9] RIPostC at the time of primary PCI reduced the enzymatic infarct size assessed by the area under the curve of CK-MB release and was also associated with an improvement in the T2-weighted edema volume on contrast-enhanced cardiac magnetic resonance (CMR) as well as improvement in STR $>$ 50%.

The timing of conditioning stimulus in our study protocol, which was applied within 1 minute of restoration of flow, is similar to original preclinical model for RIPostC[29] and therefore is expected to translate the preclinical promising results into clinical world.

To the best of our knowledge, this is the first study to evaluate the impact of RIPostC on adverse LV remodeling in patients undergoing primary PCI for anterior STEMI. Our study confirmed the previous data regarding the improvement in STR with RIPostC protocol, which has been shown to be associated with improved outcomes and less infarct size after STEMI.[16,30] However, our results failed to show significant decrease in adverse LV remodeling. This could be attributed to the small sample size, which might have precluded the detection of a significant difference between both groups.

A trend toward less AKI in patients undergoing RIPostC protocol was also seen in our study, however, without a statistical significance. A posthoc analysis study by Crimi et al[31] showed that RIPostC led to lower serum creatinine levels post-PCI in patients with lower glomerular filtration rate at baseline, however, without significant reduction in AKI in RIPostC arm. In a study by Deftereos et al,[32] RIPostC was found to confer protection against AKI in patients with non-ST-segment elevation MI undergoing PCI. AKI occurring post-PCI could be due to several factors, including hypotension in severely ill patients, atheroembolic events, and contrast administration. It is suggested that the same humoral and neuronal mechanisms mediating protective effect of RIPostC on myocardium might similarly help in renal protection from ischemic injuries. Larger studies are warranted to further evaluate the role of RIPostC in cardiorenal protection after primary PCI.

Limitations

This study has few limitations. First it was conducted in a single center with a small sample size and more than 10% of the patients in both groups did not continue the study because of poor echocardiographic studies or loss of follow-up. Hence, the failure to show an improvement in the study's primary outcome of LV remodeling might be a statistical error of type II. Second, patients in the RIPostC group had more extensive atherosclerotic coronary disease, which could be a precluding factor from reaching a significant improvement in outcomes. Third, the study was not double-blinded. However, seeking to eliminate potential source of bias, investigators evaluating end points were blinded to the treatment groups. Finally, the use of CMR might have better validated the study results with its superiority in assessment of infarct size and ventricular remodeling.

Conclusions

RIPostC might be associated with better STR after reperfusion as well as less incidence of AKI in patients undergoing primary PCI for anterior wall STEMI, indicating potential benefit in those patients. Whether this role can be translated to better outcomes after primary PCI warrants further investigation. We recommend conducting a larger sample study to evaluate the long-term impact of this protocol on adverse LV remodeling, and improving LVEF using more accurate modalities such as CMR.

Conflicts of Interest
Authors have no conflicts of interest to declare.

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