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Protective Role of Single Versus Multiple Remote Ischemic Preconditioning in Elective Percutaneous Coronary Interventions

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Abstract

Background: One common approach to treat the symptoms of coronary artery disease is percutaneous coronary intervention (PCI). Unfortunately, the myocardium is vulnerable to ischemia-reperfusion damage whenever a previously blocked coronary artery is reopened.

Aim: The study aims to compare the efficacy of single and multiple remote ischemic preconditioning (RIPC) in preventing post-PCI chest discomfort, ST-segment deviation, and myocardial infarction.

Patients and methods: In this prospective interventional trial, 125 patients were included who had been diagnosed with coronary artery disease and were candidates for PCI. Four groups of patients were studied separately. Fifty individuals made up group I; they were all treated with repeated cycles of RIPC for their upper and lower extremities. Groups II, III, and IV comprised 25 patients, each of them received a single cycle of RIPC on the upper limb, a single cycle of RIPC on the lower limb, or no RIPC, respectively. The authors assessed cardiac troponin levels before and after PCI as well as major cardiac cerebrovascular events.

Results: Compared with group I, II, and III, group IV displayed a significant (more than threefold) increase in cardiac troponin I levels 24 h post-PCI ($P = 0.010$), coupled with a higher incidence of chest pain and transient ST-segment elevation during PCI ($P < 0.001$). Moreover, on the fifth day and 3 months later creatinine levels were higher in group IV ($P = 0.001$ and 0.002 , respectively).

Conclusion: RIPC has a valuable role in protecting myocardial injury post-PCI. Both modes of single and multiple RIPC provided similar defense outcomes. The authors advocate the routine application of RIPC before an elective PCI.

Keywords: Chest pain, Coronary artery disease, Percutaneous coronary intervention, Remote ischemic preconditioning cardiac troponin, ST-Segment elevation

1. Introduction

Myocardial infarction (MI) and ischemia/reperfusion damage may be reduced by a technique called ischemic preconditioning (IPC).^{1,2} The application of IPC to a remote organ before myocardial ischemia has been shown to minimize the MI size. This technique is known as remote ischemic preconditioning (RIPC).^{3,4} Repeatedly inflating and deflating a blood pressure cuff on a leg causes a brief period of ischemia (about 4–5 min). Signaling pathways activated by cells in response to

brief ischemia protect them against further, prolonged ischemia, such as that which occurs during percutaneous coronary intervention (PCI).⁵

Due to its low cost, lack of side effects, and ease of administration, RIPC is gaining popularity. In addition, RIPC may be handled while patients wait in the catheterization lab before their PCI procedures. RIPC is applicable to both the upper and lower limbs, and it provides cardioprotection after PCI.⁶ Many studies have cited the reduction in infarct size attributable to IPC as evidence that troponin (cTnI) release is an accurate measure of myocyte necrosis.

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About one-third of elective PCI patients have troponin release, which is linked to future cardiovascular events.^{7,8}

After PCI, RIPC has been shown to minimize cTnI release and, presumably, future cardiovascular events.⁹ The purpose of this study was to compare the effects of a single RIPC with those of numerous RIPCs on cTnI release in the 24 h after elective PCI.

2. Patients and methods

The current study was a prospective interventional study that enrolled 125 patients with documented coronary artery disease requiring elective PCI from October 2019 to August 2021. The patients were divided into four groups. Group I included 50 patients who received multiple cycles of RIPC on both upper and lower limbs. Group II, III, and IV comprised 25 patients. Group II and III received a single cycle of RIPC on the upper limb and a single cycle of RIPC on the lower limb, respectively. Group IV used a control group in which no RIPC was applied. Ethical approval was obtained from the ethics committee at the pertained institutes.

Study protocol and definitions:

- (1) RIPC: the selected leg underwent RIPC by inflating a blood pressure cuff to 200 mm Hg for 5 min. Upper and lower limb ischemia cycles were obtained, and each cycle was broken by 5 min of cuff deflation.
- (2) Time window: time between removal of the cuff and the first balloon inflation that did not exceed 15 min.
- (3) PCI: PCI was done using 6 or 7 F guiding catheters through femoral or radial artery access. At least 6 h before PCI, all patients received 300 mg of aspirin and 600 mg of clopidogrel, and following arterial sheath insertion, a heparin bolus (70–100 U/kg) was administered to prevent blood clots.

Primary endpoint: the chief objective of our study was to detect the cardiac troponin level 24 h after the PCI among the study groups.

Secondary endpoints: we proposed many secondary endpoints of our study, chest pain score and/or ST shift during balloon inflation as well as cardiac, and cerebral renal events at 3 months among the study groups.

The study was approved by the Research Ethical Committee of Al-Azhar University and the patients were given all the information they need about the trial. An informed written consent was taken from each participant in the study. This work has been carried out in accordance with The Code of Ethics of

the World Medical Association (Declaration of Helsinki) for studies involving humans.

2.1. Inclusion criteria

All patients admitted at our institutes with evidence of coronary artery disease requiring elective PCI were enrolled if there was no contraindication.

2.2. Exclusion criteria

Patients with one or more of the following criteria were excluded from the study:

Cardiac troponin I (cTnI) before PCI was elevated (corresponding >0.04 ng/ml in the measurement assay used).

Patients were on nicorandil or glibenclamide use (preconditioning-mimetic and preconditioning-blocking medication, respectively).

Patients with cardiogenic shock with hypotension or undetected blood pressure, hypoperfusion, and unfelt peripheral pulsation.

Patients with acute coronary syndrome.

Patients with chronic renal failure.

Patients with lower limb ischemia proving peripheral artery disease or *a priori* fracture or lower limb edema or lymphatic obstruction.

Patients not willing to participate in the study.

2.3. Tools

All patients were subjected to full history taking, clinical examination, and 12-lead surface electrocardiogram before and after the PCI.

2.4. Laboratory investigations

Baseline troponin I.

Troponin I, 24 h post-PCI.

Baseline creatinine clearance, 5 days and 3 months post-PCI.

Arrhythmias before, during, and after PCI were recorded. Arrhythmias that were taken into consideration are ventricular tachycardia, ventricular fibrillation, and atrial fibrillation.

Clinical follow-up for 3 months of any major cardiocerebrovascular events such as MI, heart failure, or stroke.

2.5. Statistical analysis

The Statistical Software for the Social sciences, version 23.0, was used to evaluate the collected data (SPSS Inc., Chicago, Illinois, USA). Quantitative

information was shown using conventional means and variances. Quantitative and percentage data were also supplied for qualitative characteristics. The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to look at the data and see whether they followed the normal distribution.

The following tests were done:

Independent-samples *t*-test of significance was used when comparing two means.

Mann–Whitney *U*-test: for two-group comparisons in nonparametric data.

A one-way analysis of variance when comparing more than two means.

Post-hoc test: Tukey's test was used for multiple comparisons between different variables.

Kruskal–Wallis test: for multiple-group comparisons in nonparametric data.

χ^2 -test of significance was used to compare proportions between qualitative parameters.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the probability (*P* value) was considered significant as the following: *P* value less than 0.05 was considered significant; *P* value less than 0.001 was considered highly significant; *P* value greater than 0.05 was considered insignificant.

3. Results

Baseline demographic characteristics are presented in Table 1. The majority of the patients were males in all groups with no statistically significant differences noted regarding demographic parameters.

Table 2 displays the reference troponin and creatinine levels before PCI; there was no statistically significant difference among the four groups.

Table 3 demonstrates significant increase of more than three times basal level of cTnI 24 h post-PCI in the placebo group as opposed to the multiple RIP group, single RIP upper limb group, and single lower limb RIP group, respectively (*P* = 0.010). We also noted significant ST elevation in the placebo group compared with the three interventional groups during balloon inflation (*P* = 0.001). We assessed the creatinine level 5 days post-PCI and documented a significant troponin rise in the placebo group (*P* = 0.001).

Table 4 illustrates very few events and complications during and immediately postprocedure. It was noticeable that patients in the placebo group experienced more frequent chest pain with each balloon inflation during PCI. Other complications such as acute heart failure, stroke bleeding, or death were very scanty in all groups.

4. Discussion

In the latest years, many clinical studies have recognized that remote ischemic preconditioning affords effective myocardial protection in patients undergoing elective PCI.¹⁰ Our study was a bit unique as we studied four groups of patients with a multimodality technique (group I with multiple RIP in the four limbs; group II utilized single upper limb RIP, either right or left limb; group III used single lower limb RIP, either right or left

Table 1. Baseline demographic characteristics of the study groups.

Demographic data	Group I: multiple RIP (<i>n</i> = 50) [<i>n</i> (%)]	Group II: single RIP/UL (<i>n</i> = 25) [<i>n</i> (%)]	Group III: single RIP/LL (<i>n</i> = 25) [<i>n</i> (%)]	Group IV: placebo (<i>n</i> = 25) [<i>n</i> (%)]	<i>P</i> value
Age (years)					0.665
Mean ± SD	59.90 ± 9.51	60.04 ± 5.45	57.96 ± 8.01	60.64 ± 7.00	
Sex					0.296
Male	35 (70.0)	17 (68.0)	22 (88.0)	17 (68.0)	
Female	15 (30.0)	8 (32.0)	3 (12.0)	8 (32.0)	
DM	21 (42.0)	11 (44.0)	13 (52.0)	18 (72.0)	0.089
HTN	35 (70.0)	21 (84.0)	19 (76.0)	21 (84.0)	0.430
Smoking	30 (60.0)	9 (36.0)	15 (60.0)	14 (56.0)	0.223
Dyslipidemia	43 (86.0)	21 (84.0)	24 (96.0)	24 (96.0)	0.292
Family history	15 (30.0)	4 (16.0)	3 (12.0)	7 (28.0)	0.250

DM, diabetes mellitus; HTN, hypertension; LL, lower limb; RIP, remote ischemic preconditioning; UL, upper limb.

Table 2. Reference troponin and creatinine levels before PCI.

Parameter	Group I: multiple RIP (<i>n</i> = 50)	Group II: single RIP/UL (<i>n</i> = 25)	Group III: single RIP/LL (<i>n</i> = 25)	Group IV: placebo (<i>n</i> = 25)	<i>P</i> value
Initial cTnI (mean ± SD)	0.016 ± 0.006	0.016 ± 0.006	0.016 ± 0.005	0.018 ± 0.005	0.620
Initial creatinine	1.02 ± 0.14	1.00 ± 0.13	0.98 ± 0.13	1.06 ± 0.20	0.278

cTnI, cardiac troponin I; LL, lower limb; RIP, remote ischemic preconditioning; UL, upper limb.

Table 3. Revolution in ST-segment, troponin, and creatinine levels after PCI.

Parameter	Group I: multiple RIP (n = 50)	Group II: single RIP/UL (n = 25)	Group III: single RIP/LL (n = 25)	Group IV: placebo (n = 25)	P value
24-h cTnI (mean ± SD)	0.039 ± 0.017	0.045 ± 0.027	0.037 ± 0.020	0.061 ± 0.048	0.010
Transient ST elevation during ballooning (mean ± SD)	0.08 ± 0.18	0.06 ± 0.17	0.08 ± 0.20	0.42 ± 0.48	0.001
Creatinine level fifth day (mean ± SD)	1.10 ± 0.10	1.09 ± 0.12	1.10 ± 0.14	1.26 ± 0.25	0.001
Postcreatinine at 3 months (mean ± SD)	1.05 ± 0.14	1.05 ± 0.12	1.04 ± 0.13	1.18 ± 0.20	0.002

cTnI, cardiac troponin I; LL, lower limb; RIP, remote ischemic preconditioning; UL, upper limb.

Table 4. Periprocedural events/complications.

Event/complications	Group I: multiple RIP (n = 50) [n (%)]	Group II: single RIP/UL (n = 25) [n (%)]	Group III: single RIP/LL (n = 25) [n (%)]	Group IV: placebo (n = 25) [n (%)]	P value
Anginal pain	7 (14.0)	0	3 (12.0)	11 (44.0)	<0.001
Heart failure	0	0	0	0	1.000
Stroke	0	0	1 (4.0)	0	0.258
Death	0	0	0	0	1.000

cTnI, cardiac troponin I; LL, lower limb; RIP, remote ischemic preconditioning; UL, upper limb.

limb; and group IV, the control group with no RIPC, named the control group).

We documented significant cTnI elevation (≥ 3 times of baseline level) in the control group, 24 h post-PCI, as compared with the other groups, indicating myocardial protection in the RIPC groups. The present study is consistent with Ghaemian et al.,¹¹ who documented that myonecrosis caused by PCI was reduced by 27.5% when patients had two cycles of 5-min ischemia/reperfusion of the lower leg. Moreover, our study is in agreement with Li et al.,¹² who acknowledged that a single RIPC could lead to cardioprotection. Conversely, Yölmaztepe et al.¹⁹ and Lu et al.¹⁴ failed to demonstrate the protective role of a single RIPC cycle either in human or animal studies, respectively. However, Prasad et al.¹⁵ failed to provide cardiac protection even after inducing three cycles of 3-min RIPC. A possible explanation for this unfavorable outcome is that 3 min of cuff inflation may not be enough to induce significant preconditioning due to the shorter length of ischemia.

The time between cuff deflation and PCI has been cited as a potential cause of discrepancies in studies using three cycles of ischemia.¹³ In contrast to the positive role of RIPC in cardiomyoprotection, Porto et al.⁸ reported that tricyclic bilateral upper limb ischemia preceding PCI did not generate RIPC, and there was no myocardial protection. However, they found that in low-risk individuals having single-vessel elective PCI, RIPC worsened cTnI release after PCI and boosted the inflammatory response. The varying results shown in RIPC research may be because of the many different ways the technique is implemented.

One of the most striking findings of our study is that chest pain and transient ST elevation during balloon inflation were significantly less among the patients who received RIPC ($P < 0.001$). Receptors (adenosine, bradykinin, cytokines, chemokines), intracellular signal transduction (e.g. nitric oxide), and mitochondrial activity are all involved in the intracardiac signal transduction that RIPC provides, as documented in prior basic investigations.¹

Our study demonstrated that cardiomyoprotection was coupled with kidney safety with significantly less change in creatinine levels among the interventional three groups as opposed to the control group. We assessed creatinine level on the fifth day and after 3 months of PCI, documenting significantly less creatinine levels with P less than 0.001 and less than 0.002, respectively. In agreement with our study, Alreja et al.¹⁶ conducted a meta-analysis and concluded that patients having cardiac or vascular procedures had a considerably lower risk of acute renal damage when RIPC was used. In other meta-analysis performed by D'Ascenzo et al.²⁰ and Brevoord et al.,¹⁸ the outcomes of both studies exposed that serum creatinine levels were not reduced by RIPC.

Despite the putative effects of RIPC mentioned above, the 3 months' major cardiocerebrovascular outcomes did not differ among the four groups.

4.1. Limitations of the study

The current study enrolled a relatively small number of patients. Therefore, it will be useful if these findings are confirmed by other larger randomized studies to assess the safety and feasibility of using routine remote ischemic preconditioning

before elective PCI. Also, it represents our first experience with a single center. A multicenter trial would gather additional and enhanced experience. Because of the unavailability of the physiologic assessment of the coronary blood flow Fractional flow reserve (FFR), we could not affirm the mechanism of improved chest pain and reduced ST elevation in the RIPC groups; however, the proposed mechanism from many trials is the improved coronary blood flow caused by remote ischemia.

4.2. Conclusion and recommendations

Remote ischemic preconditioning has a valuable role in protecting myocardial injury post-PCI. Both types of single and multiple RIPC provided similar protection. We advocate the routine application of RIPC before elective PCI.

Conflict of interest

Authors declare that there is no conflict of interest, no financial issues to be declared.

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