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The Effect of Remote Ischemic Preconditioning on The Outcome of Elective Percutaneous Coronary Intervention

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Abstract
Background: Remote ischemic preconditioning (IPC) is a potential cardioprotective strategy in the context of elective percutaneous coronary intervention (PCI). This study aimed to assess its impact on post-procedural cardiac myonecrosis, as measured by cardiac troponin I (cTnI), and its association with major adverse cardiac events (MACE) at 6-month follow-up. The objective of this study was to investigate whether remote IPC, administered prior to elective PCI, reduces cTnI levels, ischemic symptoms, ECG evidence of ischemia, and the occurrence of MACE. **Methods:** This prospective study was conducted involving 200 patients with significant coronary artery stenosis who underwent elective PCI. Patients were divided into two groups: Group A received remote IPC through blood pressure cuff inflations and deflations, while Group B served as the control. Various parameters, including patient demographics, cardiac risk factors, ECG findings, lesion complexity, and MACE rate, were assessed. **Results:** Both groups exhibited similar baseline characteristics, with no significant differences in age, gender, cardiac risk factors, ECG findings, and lesion complexity. Remote IPC was associated with a significant reduction in cTnI levels at 24 hours post-PCI and a lower incidence of unstable angina and overall MACE. No significant differences were observed in other procedural outcomes or adverse events between the groups. **Conclusions:** This study suggests that remote IPC administered prior to elective PCI has the potential to mitigate post-procedural cardiac damage, as indicated by reduced cTnI levels, and may be associated with a lower incidence of MACE.

Keywords: Remote Ischemic Preconditioning, Percutaneous Coronary Intervention, Cardiac Troponin I, Major Adverse Cardiac Events.

1. Introduction

Elective percutaneous coronary intervention (PCI) is associated with troponin release in approximately one-third of cases. Troponin release serves as a sensitive and specific marker for myocyte necrosis and infarction resulting from ischemia/reperfusion injury, downstream embolization of atheromatous material, and coronary side-branch occlusion [1].

Numerous studies have demonstrated that procedure-related troponin release is associated with subsequent cardiovascular events [2, 3].

Conditioning the heart to tolerate the effects of acute ischemia-reperfusion injury can be initiated through the application of various mechanical and pharmacological strategies, inducing brief non-lethal episodes of ischemia and reperfusion to the heart. This can occur either prior to or even after an episode of sustained lethal myocardial ischemia, resulting in a significant reduction in myocardial injury [4]. This phenomenon is termed ischemic preconditioning (IPC) or postconditioning, respectively. However, a randomized study suggests that post-conditioning during primary PCI does not reduce infarct size or improve myocardial function recovery at both short- and long-term follow-up and might have a potential harmful effect [5].

Since the description of ischemic preconditioning as the most powerful intrinsic modality against ischemia–reperfusion injury, methods are being developed for optimal clinical use. Pharmacological preconditioning has not gained much clinical ground, and ischemia–reperfusion cycles have been used during cardiac surgery [6]. Although ischemic preconditioning has also been applied during angioplasty (regional vessel preconditioning) to reduce inflammation and enzyme leakage, concerns about proximal vessel damage and embolization have been raised. More recently, a novel approach to applying preconditioning via remote organ (e.g., limb) ischemia–reperfusion cycles has been described [7].

Transient sublethal episodes of ischemia before prolonged ischemia/reperfusion injury, known as ischemic preconditioning (IPC), have been shown to reduce the extent of myocardial infarction. This protection not only acts locally but can also protect distant tissues, a phenomenon known as remote IPC, and limits MI size in animal models. Remote ischemic preconditioning, induced by repeated brief periods of limb ischemia before index ischemia, reduces myocardial injury in patients exposed to predictable ischemia [8, 9].

This study aimed to assess the effect of remote ischaemic preconditioning on cardiac myonecrosis as measured by quantative

cardiac troponin I (cTnI) after elective percutaneous coronary intervention (PCI) and its correlation with major adverse cardiac event rate (MACE Rate) at 6 months follow up.

2. Patients and Methods

Patients:

This was a prospective study that included 200 patients with significant coronary artery stenosis, as confirmed by coronary angiography, who were referred for elective percutaneous coronary intervention (PCI) at Benha University Hospital and Alexandria Police Hospital between January 2020 and January 2023. Approval of Cardiovascular Medicine Department and Ethics Committee in the Faculty of Medicine, Benha University was obtained before preceding the study. An informed written consent was obtained from parents, and they received an explanation of the purpose of the study and had a secret code number.

Inclusion criteria were patients with significant coronary artery stenosis confirmed by coronary angiography and referred for elective PCI. Age 18 years or older.

Exclusion criteria were those requiring emergency PCI, patients with elevated levels of cardiac troponin I (cTnI) before PCI, as measured at the preadmission clinic, women of child-bearing age, patients using nicorandil or glibenclamide (preconditioning-mimetic and preconditioning-blocking medications, respectively), individuals with severe co-morbidities or an estimated life expectancy of less than 6 months, patients with a left ventricular ejection fraction less than 40%, individuals with left main stem stenosis requiring coronary bypass surgery, patients with systemic hypotension (systolic blood pressure <90 mmHg) or in a state of cardiogenic shock.

Patients were divided into two groups:

Group A: This group included 100 patients who received multiple remote ischemic preconditioning (IPC) before arriving in the catheter laboratory, induced by three 5-minute inflations of a blood pressure cuff to 200 mm Hg around the upper arm, followed by 5-minute deflations to allow reperfusion. **Group B:** This group included 100 patients who did not receive remote IPC and served as the control group.

Methods:

All patients underwent the following assessments:

A: History taking: Collection of patient's name, age, and sex. Evaluation of risk factors, including hypertension, diabetes mellitus, dyslipidemia, smoking history, and the presence of a positive family history in first-degree relatives. Documentation of presenting symptoms. Recording of current medications, including ACE inhibitors (ACEI), beta-blockers (BB), statins, aspirin (ASA), and clopidogrel.

B: Clinical Examination: Physical examination, including general and local assessments, was performed for all patients.

C: Electrocardiography (ECG): A 12-lead ECG was conducted for all patients to evaluate heart rate, rhythm, and S-T deviations both before and after PCI.

D: Laboratory findings: Serum creatinine levels were assessed at the preadmission clinic. Venous blood samples were obtained at the preadmission clinic (baseline) and again 24 hours after PCI for the measurement of cTnI. cTnI levels were analyzed using an automated immunoassay method, with the upper reference limit based on the 99th percentile of a reference population of healthy volunteers, below the lower limit of detection of 0.04 ng/mL. The analytical range for cTnI was 0.02 to 50 ng/mL.

E: Percutaneous Coronary Intervention: PCI was performed via a femoral arterial approach with 6F or 7F guiding catheters. All patients received either clopidogrel 300 mg 24 hours before PCI or clopidogrel 600 mg 6 hours before PCI and were anticoagulated with a heparin bolus (70 to 100U/kg) after arterial sheath insertion. All patients received aspirin 75 mg indefinitely and clopidogrel 75 mg for 4 weeks after bare metal stent implantation or at least 6 months after drug-eluting stent implantation, following local practice. The attending physician prescribed all other medications, and the PCI strategy was determined by the treating interventional cardiologist according to conventional practice.

The following interventional data were recorded: the number of vessels affected, lesion characteristics in each vessel, including the percent of stenosis and lesion complexity classified as A, B, or C according to the American College of Cardiology/American Heart Association classification. Type A lesions (high success, greater than 85%; low risk) were defined by specific characteristics, Type B lesions (moderate success, 60% to 85%; moderate risk) had their own criteria, and Type C lesions (low success, less than 60%; high risk) were defined by a separate set of characteristics. Procedural details in each vessel, including pre-dilatation with balloon size, duration of inflation, and pressure, as well as stenting and direct stenting, were recorded.

The outcome of PCI, whether it was successful or not, including TIMI flow, was documented. Additionally, intervention-related complications, such as major arrhythmias, bleeding, side branch compromise or occlusions, arterial dissection, thrombus formation, use of Glycoprotein IIb/IIIa antagonists, abrupt vessel closure, and slow/no-reflow, were recorded. The severity of chest pain during PCI was assessed on a scale from 0 for no pain to 10 for the most critical discomfort ever experienced, and ECG ST-segment deviation during stent deployment was observed and recorded when possible.

G: MACE Rate (Major Adverse Cardiac Event): Patients were contacted 6 months after PCI to record adverse events, including hospital admissions with acute coronary syndrome, heart failure, emergency coronary artery bypass surgery, and sudden cardiac death.

Outcomes:

The primary outcome was to assess whether remote IPC 1 hour before elective PCI reduced cTnI concentration at 24 hours. Secondary outcomes included evaluating the effect of remote IPC on ischemic symptoms, ECG evidence of ischemia during coronary balloon occlusion on the monitor, and major adverse cardiac events (MACE) at 6 months.

Statistical analysis:

Data were analyzed using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA) and MedCalc© version 13 (MedCalc© Software bvba, Ostend, Belgium). The normality of numerical data distribution was assessed using the D'Agostino-Pearson test. Numerical variables were presented as mean (SD) if normally distributed or as median (interquartile range) if skewed. Categorical variables were displayed as ratios or as percentages. Comparison of normally distributed numerical data was conducted using one-way analysis of variance (ANOVA), with the Student-Newman-Keuls test employed for multiple post hoc pairwise comparisons when the ANOVA test indicated a statistically significant difference among the groups. For skewed data, the Kruskal-Wallis test was used, with the Conover test applied for multiple post hoc pairwise comparisons upon detection of a statistically significant difference by the Kruskal-Wallis test. Categorical data were compared using the Pearson chi-squared test or Fisher's exact test when appropriate, while ordinal data were assessed using the chi-squared test for trend. A two-sided p-value <0.05 was considered statistically significant.

3. Results

Both groups were of matched age (P=0.153) and gender (P=0.225)**.** Also, there was no statistically significant difference between the two groups regarding cardiac risk factors history of hypertension (P=0.145), DM (P= 0.157), smoking (P=0.258), premature CAD (P=0.638), and Obesity (P=0.119). **Table 1**

Table (1) Demographic data and risk factors of the studied groups

		Group A (n=100)	Group B (n=100)	P value
Age (years)	**Mean ± SD**	55.44 ± 10.64	53.4 ± 9.42	0.153
	Range	38 – 72	39 – 78	
Sex	**Male**	72 (72%)	64 (64%)	0.225
	Female	28 (28%)	36 (36%)	
DM	**Yes**	56 (56%)	46 (46%)	0.157
	No	44 (44%)	54 (54%)	
HTN	**Yes**	67 (67%)	57 (57%)	0.145
	No	33 (33%)	43 (43%)	
Smoking	**Yes**	48 (48%)	56 (56%)	0.258
	No	52 (52%)	44 (44%)	
Overweight	**Yes**	58 (58%)	47 (47%)	0.119
	No	42 (42%)	53 (53%)	
Family history	**Yes**	30 (30%)	27 (27%)	0.638
	No	70 (70%)	73 (73%)	

DM: Diabetes myelitis, HTN: Hypertension.

All patients suffered from previous chest pain in both groups. There was no significant difference between groups as regard presenting symptom. **Table 2**

Table (2) Presenting symptom in the two study groups

Variable	RIPC group (n=100)	Control group (n=100)	p-value

Chest pain	100 (100%)	100 (100%)	-
Dyspnea	0 (0%)	0 (0%)	-
Palpitations	0 (0%)	0 (0%)	-
Syncope	0 (0%)	0 (0%)	-

ECG rhythm before and after PCI and ECG Changes before and after PCI (ST-segment deviation) were insignificantly different between both groups. **Table 3**

Table (3) Electrocardiography before and after PCI of the studied groups

		Group A (n=100)	Group B (n=100)	P value
ECG rhythm before PCI	**Abnormal**	10 (10%)	8 (8%)	0.621
	Normal	90 (90%)	92 (92%)	
ECG rhythm after PCI	**Abnormal**	8 (8%)	5 (5%)	0.237
	Normal	92 (92%)	95 (95%)	
ECG Changes before PCI (ST-segment deviation)	**Yes**	61 (61%)	67 (67%)	0.377
	No	39 (39%)	33 (33%)	
ECG Changes after PCI (ST-segment deviation)	**Yes**	40 (40%)	51 (51%)	0.118
	No	60 (60%)	49 (49%)	

*Significantly different as P value ≤0.05. ECG: Electrocardiography, PCI: Percutaneous coronary intervention,

EF was insignificantly different between both groups. **Figure 1**

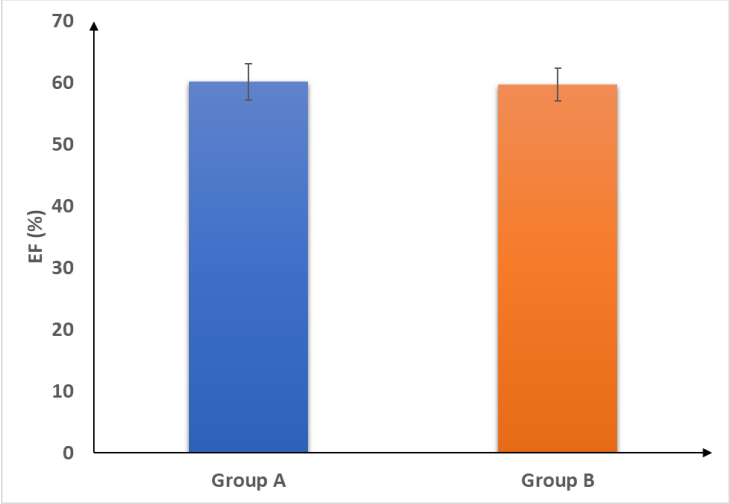

Fig. (1) EF of the studied groups

Serum creatinine was insignificantly different between both groups. Troponin was insignificantly different at baseline between both groups and was significantly lower at 24h in Group A than in Group B (P value <0.001). **Table 4**

Table (4) Serum creatinine and troponin of the studied groups

			Group A (n=100)	Group B (n=100)	P value
Serum creatinine (mg/dL)		**Mean ± SD**	1.02 ± 0.28	0.99 ± 0.26	0.331
		Range	0.58 - 1.5	0.61 - 1.44	
Troponin (ng/ml)	**Baseline**	**Mean ± SD**	0.02±0.01	0.02±0.01	0.103
	24 h	**Mean ± SD**	0.04±0.03	0.07±0.05	**<0.001***

*Significantly different as P value ≤0.05

Degree of stenosis, lesion complexity, intervention, ECG during deployment of stent and TIMI flow were insignificantly different between both groups. **Table 5**

Table (5) Interventional data of the studied groups

	Group A (n=100)	Group B (n=100)	P value

Degree of stenosis (%)	**Mean ± SD**	83.35 ± 6.98	82.43 ± 8.07	0.39
	Range	71 - 95	70 - 96	
Lesion complexity	**Type A**	63 (63%)	56 (56%)	0.135
	Type B	21 (21%)	33 (33%)	
	Type C	16 (16%)	11 (11%)	
Intervention	**Ballon predilatation**	57 (57%)	55 (55%)	0.776
	Direct stenting	43 (43%)	45 (45%)	
ECG during deployment of stent	**ST deviation**	22 (22%)	26 (26%)	0.508
	No change	78 (78%)	74 (74%)	
TIMI flow	**I**	0 (0%)	0 (0%)	---
	II	0 (0%)	0 (0%)	
	III	100 (100%)	100 (100%)	

Arrhythmia, bleeding and dissection were insignificantly different between both groups. Side branch compromise/ occlusion, thrombus formation and no reflow were not present in any patients in both groups. Unstable angina and Overall incidence of MACE were significantly lower in Group A than in Group B (P value= 0.032 and 0.024 respectively). MI, heart failure and mortality were insignificantly different between both groups. Emergency CABG didn't happen to any patients in both groups. **Table 6**

Table (6) Complications of intervention and MACE Rate of the studied groups

		Group A (n=100)	**Group B (n=100)**	**P value**
Arrhythmia	**Yes**	23 (23%)	20 (20%)	0.606
	No	77 (77%)	80 (80%)	
Bleeding	**Yes**	4 (4%)	3 (3%)	1.000
	No	96 (96%)	97 (97%)	
Side branch compromise/ occlusion	**Yes**	0 (0%)	0 (0%)	---
	No	100 (100%)	100 (100%)	
Dissection	**Yes**	6 (6%)	8 (8%)	0.579
	No	94 (94%)	92 (92%)	
Thrombus formation	**Yes**	0 (0%)	0 (0%)	---
	No	100 (100%)	100 (100%)	
No reflow	**Yes**	0 (0%)	0 (0%)	---
	No	100 (100%)	100 (100%)	
MACE Rate				
Unstable angina	**Yes**	10 (10%)	21 (21%)	**0.032***
	No	90 (90%)	79 (79%)	
MI	**Yes**	0 (0%)	1 (1%)	1.000
	No	100 (100%)	99 (99%)	
Heart failure	**Yes**	1 (1%)	2 (2%)	1.000
	No	99 (99%)	98 (98%)	
Emergency CABG	**Yes**	0 (0%)	0 (0%)	---
	No	100 (100%)	100 (100%)	
Mortality	**Yes**	0 (0%)	1 (1%)	1.000
	No	100 (100%)	99 (99%)	
Overall incidence of MACE	**Yes**	11 (11%)	23 (23%)	**0.024***
	No	89 (89%)	77 (77%)	

*: significant as P value ≤0.05. MI: Myocardial infarction, CABG: Coronary artery bypass graft, MACCE: Major adverse cardiac event.

4. Discussion

In this study, we investigated the impact of remote ischemic preconditioning on reducing cardiac myonecrosis following elective percutaneous coronary intervention (PCI) and lowering the major adverse cardiac event rate (MACE Rate) in a cohort of 200 symptomatic coronary heart disease patients undergoing elective PCI. Patients were randomly allocated into two groups: Group A, comprising 100 patients who underwent remote Ischemic Preconditioning immediately before PCI through the upper arm, and Group B, consisting of 100 patients who did not undergo Remote Ischemic Preconditioning. Remote ischemic preconditioning was achieved through three 5-minute inflations of a blood pressure cuff to 200 mm Hg around the upper

arm, followed by 5-minute deflations to allow reperfusion.

In the current study, there were no significant group differences regarding age, sex, risk factors, family history, presenting symptoms. There was no statistically significant difference between the two groups regarding clinical examination and relevant ECG findings, troponin before intervention and serum creatinine level.

ECG changes before and after PCI (ST-segment deviation) were insignificantly different between both groups. [ECG ST Deviation >1 mm in RIPC group 40 patients (40%) versus 51 patients (51%) in the control group (p=0.118)]. Also, ECG changes during deployment of stent were insignificantly different between both groups.

This is different from the findings of **Stephen et al.** [10] who reported that the Subjects receiving remote IPC had significantly less ischemic ECG changes during stent implantation. (ECG ST Deviation >1 mm in RIPC group 37 patients (36%) versus 55 patients (56%) in control group (p= 0.005)).

In **Leesar et al.** study, Ischemic preconditioning was induced by infusion of bradykinin. Experimental studies suggest that an important trigger of ischemic PC is the activation of bradykinin B2 receptors. The ST-segment shift recorded on the surface ECG was significantly smaller in the bradykinin treated group than in the control group during balloon inflation (7 vs. 16 mm, respectively; p < 0.01). Also, chest pain score was significantly smaller in the bradykinin treated group than in the control group during balloon inflation [11].

On the contrary, **Iliodromitis et al.** study showed that no differences in segment electrocardiograph changes and in the level of chest pain at the time of interventional procedures were observed between the studied groups [12].

Regarding the Troponin level after intervention: this is consistent with the findings of **Stephen et al.** **[10]** who reported that remote IPC applied 1 hour before PCI attenuated procedure-related cTnI release, increased the number of patients who had no detectable cTnI release at 24 hours, and appeared to increase the tolerance of the myocardium to ischemia. The mean cTnI concentration at 24 hours was lower in the remote IPC group (0.06 ng/ml) than in control group (0.16 ng/ml) (P=0.04). The study failed to demonstrate any effects of RIPC on coronary microvascular resistance or coronary flow **[10]**.

In 2009, a study concluded that RIPC benefits are unaffected by coronary flow or microvascular resistance. Note that their study involved only 54 patients, with just 11 undergoing arm RIP, while the rest had coronary balloon occlusion as an RIPC stimulus **[10]**.

In 2011, Rashed et al. [13] assessed whether remote ischemic preconditioning reduces myonecrosis and inflammation in PCI patients using cardiac biomarkers (CK, CKMB, Cardiac troponin T) and CRP. The RIPC group had significantly lower post-procedural cardiac troponin T levels (0.020 vs. 0.047 ng/mL in the control group, p=0.047) and fewer post-procedural myocardial infarctions (6 vs. 12 patients in the control group).

In a 2003 study by **Laskey et al.** [14] IPC during PCI was induced by a 90-second balloon occlusion of the target artery, followed by 5 minutes of unobstructed reperfusion. Then, a subsequent 90-second balloon occlusion at the same pressure was performed. Patients with IPC had a significantly lower frequency of CK-MB release (11.4%) compared to those without IPC (41.5%, p < 0.0001).

Kim et al. [15] showed that RIPC during transfer to primary angioplasty modestly improved LV function and remodeling in patients at risk of large myocardial infarcts.

Hans et al. [16] demonstrated that remote ischemic conditioning before hospital admission in AMI patients increased myocardial salvage, as measured by myocardial perfusion imaging at 30 days.

Ilias et al. [17] demonstrated a significant cardio-protective effect of RIPC and morphine during primary percutaneous coronary intervention, resulting in more patients achieving full ST-segment resolution and lower peak troponin I levels.

Our study, although excluding AMI patients, provides further evidence of cardioprotection achieved by RIPC in the context of PCI, whether elective or primary PCI.

On the contrary, **Iliodromitis et al.** [12] reported that remote IPC induced by three 5-minute cycles of bilateral upper-limb ischemia immediately before PCI did not confer myocardial protection. Instead, it exacerbated CK-MB and cTnI release after PCI and enhanced the inflammatory response, especially in patients without statin therapy.

The reason for this discrepancy remains unclear but may be related to the use of bilateral arm ischemia as the RIPC stimulus and the small number of patients (41 patients) included. Furthermore, the exclusion of patients with multi-vessel disease, venous graft disease, or small vessel disease may have played a role in the differing outcomes.

Iliodromitis et al. [12] noted that it is challenging to understand why brief episodes of upper limb ischemia-reperfusion would affect enzyme release from the heart after PCI, given that ischemia-reperfusion shares common pathways with inflammation. In an environment of heightened inflammatory stimulation, such as in the RIPC group without statins, similar levels of ischemia-reperfusion of the heart might lead to greater damage and cardiac enzyme release, as observed in their study.

The translation of ischaemic preconditioning from experimental settings to clinical use requires thoughtful consideration and extensive clinical trials.

Several studies have indicated that a higher cTnI release in PCI is linked to a poorer prognosis, particularly in cases with significant cTnI elevation [18].

In our current study, the 6-month follow-up revealed that unstable angina occurred in 21% of the control group compared to 10% in the RIPC group. Those who received remote IPC before elective PCI had a lower MACE rate at 6 months, aligning with **Stephen et al.'s** findings [10], where patients receiving remote IPC had a significantly lower MACE rate at 6 months (4 acute coronary syndromes vs. 13 events in the control group: 11 acute coronary syndromes, 1 acute left ventricular failure, 1 death; p=0.018). Patients who experienced adverse events had significantly higher cTnI levels after PCI (median cTnI at 24 hours: 0.26 ng/mL vs. 0.09 ng/mL for those without events; p=0.55).

In **Laskey et al.**'s study [14], the death/non-fatal MI rate at one year was significantly lower in patients with IPC (10.6%) compared to those without IPC (17.6%; $p < 0.0001$). This increased risk in the non-IPC group became evident as early as 50 days after PCI and continued to rise during the follow-up period. Even when focusing on one-year mortality, a significantly increased risk was seen in the non-IPC group.

These results suggest that using remote IPC shortly before PCI leads to improved clinical outcomes at 3 months and a lower MACCE rate, primarily due to a reduction in acute coronary syndromes. Moreover, the magnitude of cTnI release post-PCI offers valuable prognostic information, although the exact mechanism remains unknown. Preconditioning has beneficial effects on platelet inhibition, antithrombosis, plaque stabilization, endothelial function, and inflammation reduction [19].

5. Conclusion

In conclusion, remote ischemic preconditioning is an effective, cost-efficient, and well-tolerated method for reducing post-procedural elevations of cTnI in patients undergoing PCI. These elevations often occur without identifiable angiographic adverse events, suggesting the role of distal microembolization in myonecrosis. Remote IPC enhances myocardial tolerance to ischemia, diminishes ischemic chest discomfort, reduces ST segment deviations, and lowers cTnI release after elective PCI. Additionally, it appears to reduce subsequent cardiovascular events, demonstrating sustained cardioprotection. Therefore, a larger study is warranted to investigate the potential of remote IPC in reducing major adverse cardiovascular events after PCI.

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