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Role of remote ischaemic preconditioning on myocardial injury in stable patients undergoing percutaneous coronary intervention: a randomised case-control study

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KEYWORDS

- percutaneous coronary intervention
- periprocedural myocardial infarction
- remote ischaemic preconditioning
- troponin I

Abstract

Aims: Remote ischaemic preconditioning (RIPC) has been shown to reduce the incidence of myocardial injury in patients undergoing percutaneous coronary intervention (PCI) in preclinical and limited clinical trials. Our objective was to assess the applicability of RIPC before PCI in the effective reduction of myocardial injury among stable patients.

Methods and results: This was a single-centre, case-control, randomised study where 108 patients undergoing PCI were randomised to either RIPC or control group (n=54 each). Along with levels of troponin I and C-reactive protein (CRP), the incidence of PCI-related myocardial infarction (MI) was recorded at baseline, six, 12 and 24 hours after PCI. A significant reduction in troponin I release was seen in the RIPC group at both 12 (0.08±0.13 vs. 0.16±0.19 ng/ml, p=0.01) and 24 hours (0.06±0.04 vs. 0.22±0.3 ng/ml, p<0.01) post PCI as compared to that in the control group. RIPC was also found to be instrumental in reducing CRP levels in the RIPC group as compared to the control group at both 12 (p=0.04) and 24 hours (p=0.04) post PCI. A significant reduction in the incidence of PCI-related MI in the RIPC group was also noted when compared to the control group at 24 hours post PCI (14.8% vs. 38.9%, p<0.01), which however was found comparable at both six hours and 12 hours post PCI (p>0.05).

Conclusions: RIPC, administered by transient upper limb ischaemia, significantly reduces troponin I and CRP release at 12 and 24 hours post PCI, resulting in a significant reduction in the incidence of PCI-related MI at 24 hours post PCI.

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Introduction

Troponin release is a sensitive and specific marker of myocyte necrosis and infarction resulting from a form of ischaemia/reperfusion injury, downstream embolisation of atheromatous material, and coronary side branch occlusion[1]. In addition to the strong diagnostic role of cardiac troponins, their prognostic value has become increasingly well established for patients presenting with acute coronary syndrome[2,3]. The inflammatory response and enzyme leakage during coronary angioplasty is increasingly becoming a recognised issue[4-6]. Elective percutaneous coronary intervention (PCI) is associated with troponin release in approximately one third of cases[7], and this troponin release is independently and significantly predictive of an increased risk of adverse events[8-11].

Transient sublethal episodes of ischaemia before a prolonged ischaemia/reperfusion injury, known as ischaemic preconditioning (IPC), have been shown to reduce the extent of myocardial injury[12]. Therefore, remote ischaemic preconditioning (RIPC) is a phenomenon in which brief episodes of ischaemia followed by reperfusion in one organ seem to provide systemic protection from prolonged ischaemia in the myocardial muscle and also to limit the myocardial infarction (MI) size[13]. This phenomenon has been observed in an animal model[13]. IPC has been used during cardiac surgery[14]. IPC has also been applied during angioplasty (regional vessel preconditioning) to reduce inflammation[15] and enzyme leakage[16,17]. A novel way to apply preconditioning via remote organ (e.g., limb) ischaemia reperfusion cycles has been described[18]. An added advantage is that the entire heart may thus be preconditioned, that is to say, globally, not regionally[19]. RIPC has been shown to protect against endothelial ischaemia/reperfusion injury[11] and the extent of MI after adult coronary bypass surgery[20,21], paediatric surgery[22], and non-cardiac surgery[23]. However, some studies failed to demonstrate a beneficial effect of RIPC during PCI[24].

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The aim of our study was to determine whether RIPC before PCI reduces the cardiac enzyme release in stable patients (troponin I negative) with coronary artery disease.

Methods

STUDY POPULATION

This was a single-centre, prospective, randomised, case-control study. Patients (n=108) having stable angina (with negative troponin I) undergoing angioplasty were enrolled in the study during the period between March and December 2013. The present study was a one of a kind, a pilot project which attempted to explore the benefits of RIPC among subjects of Indian ethnicity. Thus, all qualifying patients were included for a flat 10-month recruitment period, and formal sample size calculation was reserved to the planned validation study with an increased follow-up duration (study still ongoing). After confirmation of their eligibility, all subjects duly consented and were then randomised to either RIPC or control group using sealed envelopes. Two clinicians from our author group, who were in charge of randomisation, prepared randomly generated treatment allocations within uniform sealed and opaque envelopes. Once the subject consented to the study, an envelope was opened and the patient was then placed in either the RIPC or the control group. These two clinicians were also responsible for administration of actual and mock preconditioning to the subjects. Other members of the study team were blinded to the procedures, including allotment of preconditioning/mock preconditioning and its administration to cases and controls. Patients with acute myocardial infarction, unstable angina, having elevated troponin I before PCI, additional cardiac disease, women of child-bearing age, nicorandil or glibenclamide use (preconditioning mimetic and preconditioning blocking medication, respectively), renal and hepatic insufficiency, malignancy, rheumatoid arthritis, active infection and severe comorbidity (estimated life expectancy <6 months) were excluded from this study.

PROCEDURAL INTERVENTIONS

During the time of admission, patients were instructed to avoid any strenuous activity which could provoke angina before their procedure. A baseline ECG was carried out in all patients. LV ejection fraction was calculated using Simpson's method of disc by echocardiography.

Patients randomised to RIPC had a blood pressure cuff placed around their non-dominant upper arm. The cuff was inflated to 200 mmHg pressures for five minutes followed by five minutes of deflation, to allow reperfusion. This was repeated for three cycles. Control patients had a similar cuff placed around the upper arm, but it was not inflated (mock preconditioning). These procedures were administered accordingly among the patient and control cohorts at 60-180 minutes prior to PCI with a mean duration of 95.15±27.36 minutes. Thereafter, all patients underwent PCI performed by an interventionist blinded to the study group allocation.

PCI was performed via the radial arterial approach using 6 Fr guiding catheters. All patients received 600 mg clopidogrel at least six hours before PCI. Patients were anticoagulated with a heparin bolus (70 to 100 U/kg) after arterial sheath insertion to achieve an activated clotting time >250 seconds. Glycoprotein IIb/IIIa antagonists were administered at the discretion of the primary operator. Stent inflation and balloon dilations were done in accordance with current clinical practice. For each patient, the number of vessels treated, number and type of stent, baseline and intraprocedural TIMI flow were noted. Aspirin and clopidogrel were advised to all patients after angioplasty as per standard practice. The severity of CAD was assessed by quantitative coronary angiography, and lesions were classified qualitatively according to the modified ACC/AHA classification[25] into type A, B and C. Chest pain severity during PCI was graded on a scale of zero for no pain to 10 for the most severe discomfort.

All patients were followed up after 30 days for any adverse event (death, reinfarction, stent thrombosis, recurrence of angina). Endpoint assessment was carried out by a team of two clinicians who were completely blinded to the whole randomisation process.

BIOCHEMISTRY

Venous blood samples were taken at the time of admission (baseline) and six, 12 and 24 hours after PCI for troponin I and C-reactive

protein (CRP). Serum creatinine samples at baseline and 24 hrs post PCI were also taken. Troponin I was analysed with an automated immunoassay (Triage® Cardiac panel; Biosite/Inverness Medical Innovations Inc., San Diego, CA, USA, now manufactured and distributed by Alere, Waltham, MA, USA). The 99th percentile of the troponin I level in a reference population (upper reference limit) of healthy volunteers was below the lower limit of detection of 0.04 ng/ml. The variation coefficient, a measure of precision within the analytical range was <10%, complying with the European Society of Cardiology/American College of Cardiology consensus requirements[25]. The analytical range was 0.05 to 30 ng/ml, with an assay sensitivity of 0.006 ng/ml. According to the joint task force of the European Society of Cardiology, American College of Cardiology Foundation, American Heart Association and World Heart Federation, a PCI-related MI (MI 4a) is defined as a rise in troponin >0.12 ng/ml (three times the upper reference limit)[26]. The World Health Organization definition for MI for this assay was ≥0.78 ng/ml. The lower limit for detection of CRP was 0.32 mg/dl.

STATISTICAL ANALYSIS

SPSS Version 16.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for data entry and subsequent statistical analysis. Continuous data are represented as mean±standard deviation. Categorical data are represented as number (percentage). Difference of means between independent groups was analysed with the Student's t-test. Categorical variables were analysed with the chi-square test. Significance (two-tailed) was taken at a p-value of <0.05.

Table 1. Baseline demographic and clinical profile of patients.

Parameters	Whole cohort (n=108)	RIPC (n=54)	Control (n=54)	*p*-value*
Age, years (mean±SD)	57.67±8.82	57.19±7.31	58.15±10.16	0.57
BMI (kg/m^2)	24.14±3.12	24.04±3.04	24.23±3.22	0.76
Male, n (%)	92 (85.2)	50 (92.6)	42 (77.8)	0.06
Diabetes, n (%)	40 (37.0)	18 (33.8)	22 (40.7)	0.55
Smoker, n (%)	32 (29.6)	14 (25.9)	18 (33.3)	0.53
Hypertension, n (%)	68 (63.0)	30 (55.6)	38 (70.4)	0.16
Dyslipidaemia, n (%)	42 (38.9)	24 (44.4)	18 (33.3)	0.32
LVEF, % (mean±SD)	51.59±12.4	49.67±12.8	53.54±11.7	0.11
History of ACS/MI, n (%)	54 (50.0)	30 (55.6)	24 (44.4)	0.34
NYHA I/II, n (%)	86 (79.6)	42 (77.8)	44 (81.5)	0.81
NYHA III/IV, n (%)	22 (20.4)	12 (22.2)	10 (18.5)	0.81
Statins, n (%)	108 (100)	54 (100)	54 (100)	1.00
β-blockers, n (%)	106 (98.1)	54 (100)	52 (96.3)	0.50
ACE-I/ARB, n (%)	100 (92.6)	48 (88.9)	52 (96.3)	0.27
GP IIb/IIIa inhibitor use, n (%)	42 (38.9)	18 (33.3)	24 (44.4)	0.32
Prior PTCA, n (%)	8 (7.4)	2 (3.7)	6 (11.1)	0.27
Troponin I (ng/ml), (mean±SD)	0.051±0.002	0.050±0.002	0.051±0.003	0.41
CRP (mg/dl), (mean±SD)	0.43±0.27	0.46±0.24	0.39±0.29	0.22
Serum creatinine (mg/dl), (mean±SD)	1.10±0.40	1.12±0.53	1.08±0.20	0.64

*_p_-value shown is between RIPC group and control group; value of <0.05 considered as statistically significant. ACE-I: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; BMI: body mass index; LVEF: left ventricle ejection fraction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; PTCA: percutaneous transluminal coronary angioplasty

Results

One hundred and eight patients were randomised to RIPC and control arms (54 in each group). Normal distribution among the case and control groups was observed (p>0.05). RIPC was successfully administered to all 54 patients without any complication. The mean age of the study population was 57.67±8.82 years among which the majority were males (85.2%). Among conventional risk factors for CAD in our study cohort, around 37% of subjects had diabetes, 63% had hypertension, 29.6% had a history of smoking and 38.9% were dyslipidaemics. Both the study groups were comparable in terms of mean age, basal metabolic index (BMI) and gender distribution. The distribution of conventional risk factors for CAD was also found to be comparable among the two groups. The mean left ventricular ejection fraction (LVEF) of the whole cohort was 51.59±12.4%, which was also found to be comparable between the two groups **(Table 1)**.

Table 2 shows the angiographic parameters of the whole cohort and their distribution between both study groups. The left anterior descending (LAD) was found to be the most commonly treated artery (48.1%). A total of 25.9% of cases had double or triple-vessel percutaneous transluminal coronary angioplasty (PTCA), the distribution of which between RIPC and control groups was comparable. A total of 140 lesions were treated (68 in the RIPC group and 72 in the control group). Most of the treated lesions were type B1/B2 or type C (51.9% and 5.6%, respectively). The mean stent diameter and length used in the whole cohort was 3.07±0.33 mm and 20.55±6.36 mm, respectively. The mean lengths and diameters of the stents used were comparable between the two study groups. The subjects in the whole cohort were treated by a mean number of 1.54±0.84 stents/patient. Most (96.29%) of the subjects in the whole cohort were treated with at least one drug-eluting stent, the distribution of which was comparable between the two study groups (p>0.05) **(Table 2)**.

Table 3 shows the clinical and angiographic parameters during PCI of the total study population and both groups. Blood pressure and heart rate during PCI were comparable between both groups. A total of 15 (13.9%) patients had chest pain during PCI. Significantly more patients, i.e., 12 (22.2%), in the control group had a chest pain score >1 as compared to three (5.5%) patients in the RIPC group (p=0.02). Only seven (6.5%) patients had TIMI flow <3 during the procedure. However, the distribution of this was not significantly different between both groups, but it suggested a trend towards a lower incidence of cases with TIMI flow <3 during the procedure in the RIPC group (one [1.8%] vs. six [11.1%], p=0.12, in the RIPC and control group, respectively) **(Table 3)**.

Table 4 shows the troponin I, CRP levels and the incidence of PCI-related MI at six, 12 and 24 hours after PCI. Mean troponin I

Table 2. Angiography and angioplasty-related parameters.

Variable		Whole cohort (n=108)	RIPC (n=54)	Control (n=54)	*p*-value*
Target vessel	Left main only, n (%)	2 (1.8)	0 (0)	2 (3.7)	0.48
	LAD/ramus only, n (%)	52 (48.1)	28 (51.9)	24 (44.4)	0.56
	LCX only, n (%)	12 (11.1)	8 (14.8)	4 (7.4)	0.36
	RCA only, n (%)	14 (12.9)	4 (7.4)	10 (18.5)	0.15
	Double/triple-vessel PTCA, n (%)	28 (25.9)	14 (25.9)	14 (25.9)	1.00
Lesion classification (according to AHA/ACC)	Type A, n (%)	46 (32.8)	22 (32.3)	24 (33.3)	0.90
	Type B1/B2, n (%)	80 (57.1)	41 (60.3)	39 (54.2)	0.57
	Type C, n (%)	14 (10.0)	5 (7.3)	9 (12.5)	0.46
Stent diameter, mm (mean±SD)		3.07±0.33	3.07±0.32	3.07±0.33	0.97
Stent length, mm (mean±SD)		20.55±6.36	21.11±6.30	19.99±6.43	0.37
No. of stents (mean±SD)		1.54±0.84	1.44±0.74	1.63±0.92	0.25
DES, n (%)		104 (96.29)	50 (92.59)	54 (100)	0.13

**p*-value shown is between RIPC group and control group; value of <0.05 considered as statistically significant. AHA: American Heart Association; ACC: American College of Cardiology; DES: drug-eluting stent; LAD: left anterior descending artery; LCX: left circumflex artery; PTCA: percutaneous transluminal coronary angioplasty; RCA: right coronary artery

level was comparable between the two groups at six hours post PCI (p=0.14), but significantly lower in the RIPC group as compared to the control group at 12 and 24 hours post PCI (0.08±0.13 vs. 0.16±0.19 ng/ml, p=0.01, and 0.06±0.04 vs. 0.22±0.31 ng/ml, p<0.01, respectively). The CRP levels were also found to be comparable between the two groups at six hours post PCI (p=0.09) but significantly lower in the RIPC group as compared to the control group at 12 and 24 hours after PCI (0.46±0.35 vs. 0.71±0.78 mg/dl, p=0.04, and 0.53±0.48 vs. 1.16±2.26 mg/dl, p=0.04, respectively).

The incidence of PCI-related MI (MI 4a) was found to be comparable in the RIPC group at six hours (two [3.7%] vs. four [7.4%], p=0.68) and 12 hours (six [11.1%] vs. four [7.4%], p=0.74). However, RIPC seemed to have reduced the incidence of PCI-related MI (MI 4a) as compared to the control group at 24 hrs post PCI (eight [14.82%] vs. 21 [38.89], p<0.01) **(Table 4)**.

The distribution of subjects with undetectable troponin I was comparable between the RIPC group and the control group both at six hours (46 [85.2%] vs. 41 [75.9%], p=0.33) and 12 hours (45 [83.3%] vs. 36 [66.7%], p=0.08) post PCI, respectively, but was found to be significantly higher at 24 hours post PCI in the RIPC group as compared to the control group (42 [77.7%] vs. 28 [51.9%], p<0.01, respectively) **(Figure 1)** .

At 30-day follow-up, no patient in either group had any adverse cardiac event (death, reinfarction, stent thrombosis, recurrence of angina).

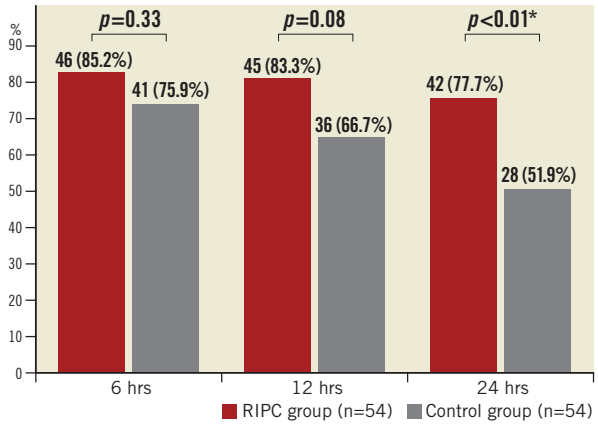

Figure 1. *Frequency of subjects with undetectable troponin I (<0.05 ng/ml) among RIPC group and controls.*

Table 3. Periprocedural clinical and angiographic parameters.

Variable		Whole cohort (n=108)	RIPC (n=54)	Control (n=54)	*p*-value*
SBP, mmHg (mean±SD)		124.9±11.40	124.3±11.84	125.6±11.01	0.57
DBP, mmHg (mean±SD)		82.2±6.33	81.3±5.87	83.2±6.67	0.11
Heart rate, bpm (mean±SD)		73.8±8.01	74.1±8.12	73.6±7.9	0.78
Chest pain score >1, n (%)		15 (13.9)	3 (5.5)	12 (22.2)	0.02*
ECG ST deviation >1 mm, n (%)		10 (9.3)	2 (3.7)	8 (14.8)	0.09
TIMI flow grade	0-2, n (%)	7 (6.5)	1 (1.8)	6 (11.1)	0.12
	3, n (%)	101 (93.5)	53 (98.1)	48 (88.9)	

**p*-value shown is between RIPC group and control group; value of <0.05 considered as statistically significant. DBP: diastolic blood pressure; HR: heart rate; SBP: systolic blood pressure; TIMI: Thrombolysis In Myocardial Infarction

Table 4. Post-procedure troponin I and CRP values (at 6, 12 and 24 hours) and the incidence of MI.

Variable	6 hours			12 hours			24 hours		
	RIPC (n=54)	Control (n=54)	*p*-value	RIPC (n=54)	Control (n=54)	*p*-value	RIPC (n=54)	Control (n=54)	*p*-value
Troponin I, ng/ml (mean±SD)	0.06±0.03	0.07±0.04	0.14	0.08±0.13	0.16±0.19	0.01*	0.06±0.04	0.22±0.31	<0.01*
CRP, mg/dl (mean±SD)	0.37±0.09	0.46±0.38	0.09	0.46±0.35	0.71±0.78	0.04*	0.53±0.48	1.16±2.26	0.04*
MI 4a, n (%) ¶	2 (3.7)	4 (7.4)	0.68	6 (11.1)	4 (7.4)	0.74	8 (14.82)	21 (38.89)	<0.01*

**p*-value of <0.05 was considered as statistically significant. ¶ The joint task force of the European Society of Cardiology, American College of Cardiology Foundation, American Heart Association and World Heart Federation, defined PCI-related MI (MI 4a) as a rise in troponin >0.12 ng/ml (three times the upper reference limit)

Discussion

Our study showed that remote IPC, administered by transient upper limb ischaemia, significantly reduces all signs of post-procedural myocardial injury, including PCI-related troponin I (p<0.01), CRP (p=0.04) release and the incidence of PCI-related MI (p<0.01) at 24 hrs after PCI.

Several studies have shown that PCI-related troponin I release is associated with a worse prognosis, especially in those patients with the most marked elevation in troponin I concentration[8,10-12]. A post-procedure increase in troponin concentration of fivefold baseline levels is an independent predictor of a composite of death, MI, and revascularisation at one year (hazard ratio=2.39; 95% CI: 1.09-5.26)[11]. As discussed earlier, a PCI-related MI (MI 4a) is defined as >0.12 ng/ml (3 times the upper reference limit)[26]. Gadolinium late enhancement with cardiac magnetic resonance has demonstrated that procedural troponin I release is due to MI both downstream of the stented lesion and adjacent to the implanted stent[1,27].

Przyklenk et al[13] demonstrated that brief episodes of ischaemia in one vascular bed (circumflex branch occlusion) protected remote virgin myocardium from subsequent sustained left anterior descending coronary artery occlusion in a canine model. Birnbaum et al[23] demonstrated that a brief remote ischaemia of a skeletal muscle induced by muscle stimulation combined with a reduction of femoral arterial blood flow reduced myocardial infarct size considerably in rabbits. A less invasive method of inducing hind limb ischaemia as an RIPC stimulus was introduced by Oxman et al who demonstrated that applying a tourniquet to the hind limb to induce 10 min of limb ischaemia had the ability to reduce reperfusion arrhythmias in a rat heart following a sustained ischaemic insult[28].

Cheung et al[22] first successfully applied RIPC in the clinical setting and reported that a standard RIPC stimulus using four five-minute cycles of lower limb ischaemia was able to reduce myocardial injury, improve airway resistance and decrease inotrope score in 17 children undergoing corrective cardiac surgery for congenital heart disease. Ali et al[21] demonstrated in abdominal aortic aneurysm repair that there was no difference in mortality between the two groups either in hospital or at discharge, but RIPC reduced the incidence of myocardial infarction and renal impairment. Kharbanda et al[29] demonstrated that transient upper limb ischaemia, induced by a blood pressure cuff inflated around the upper arm for three five-minute cycles, with intervening periods of reperfusion, ameliorated contralateral forearm ischaemia/reperfusion endothelial dysfunction in human volunteers. A pooled analysis of the four trials related to cardiovascular surgery demonstrated a statistically significant reduction in biomarkers of myocardial injury with RIPC relative to control (standardised mean difference -0.81, 95% CI: 1.29-0.33, p=0.001)[30].

During coronary angioplasty, mechanical disruption of a stable atherosclerotic plaque and possible microemboli induced by the balloon may cause a systemic inflammatory response, as reflected by a rise in CRP levels. In our study there was no significant increase in CRP level at six hours, but a significant increase was recorded at 12 and 24 hours after PCI.

The actual mechanism through which an episode of brief ischaemia and reperfusion in an organ or tissue exerts protection against a subsequent sustained insult of ischaemia-reperfusion injury in a remote organ or tissue is currently unclear. Humoral and neural hypotheses are suggested to explain RIPC. The finding that a period of reperfusion of the remote preconditioning organ was required in addition to the brief ischaemia suggested that the reperfusion period may be needed to "wash out" a substance or humoral factor generated by the preconditioning ischaemia, which was then transported to the heart[28-31]. RIPC has a biphasic pattern of myocardial protection. An early classic phase is believed to act within a few minutes to two hours after the preconditioning stimulus and is mediated through opening of mitochondrial ATP-sensitive potassium channels[32,33]. A delayed second window of protection occurs at 24 to 72 hours and is probably the result of modified gene expression that suppresses the proinflammatory response to the ischaemia/reperfusion injury. Activation of the mitogen-activated protein kinases (MAPKs) p38, Erk1/2 and JNK within the remote organ may also contribute to RIPC-induced cardioprotection. Konstantinov et al[34] noted a reduction in the extent of MI after RIPC in a porcine transplanted heart, in agreement with the original work on IPC that argued for a circulating humoral mediator.

RIPC to protect the heart from ischaemia as a therapeutic modality, particularly for elective intervention, is an attractive option. There are limited numbers of studies exploring the effect of RIPC on myocardial injury during elective PCI which are mostly small with limited data and outcomes.

Iliodromitis et al[24] reported that no myocardial protection was conferred by remote IPC induced by three five-minute cycles of bilateral upper limb ischaemia in the catheterisation laboratory immediately before PCI. In contrast, they observed that remote IPC exacerbated

troponin I release after PCI and enhanced the inflammatory response in the absence of statin therapy in low-risk patients undergoing single-vessel elective PCI. In our study, almost all patients in both groups were taking statins that nullify the beneficial effect of statin, affecting the result. The rationale for performing RIPC within one hour of PCI came from the CRISP STENT study that had shown protection is time-dependent and that the greatest benefit occurred with shorter cuff to balloon time. The CRISP STENT study[35], a prospective randomised controlled study of 202 patients, concluded that remote IPC reduces ischaemic chest discomfort during PCI, attenuates procedure-related troponin I release, and appears to reduce subsequent cardiovascular events. Also noteworthy is the study by Bøtker et al[36], who demonstrated the potential for pre-hospital use of RIPC in the setting of 333 patients of AMI (four cycles of five-minute forearm cuff inflation and deflation, delivered in the ambulance). They demonstrated an improvement in myocardial salvage index (%) at 20 days after primary PCI in the group which received preconditioning[36]. In a substudy of the same patients, RIPC delivered before hospital resulted in modest improvement in LV function among high-risk patients prone to developing large myocardial infarcts[37].

In a meta-analysis of 17 clinical trials, Alreja et al reported an association of RIPC with a favourable effect on serological markers of myocardial or renal injury (troponin T or I and CK-MB) during cardiovascular interventions[38]. Similarly, in our study, PCI-related MI and troponin release were significantly reduced in the RIPC group at 24 hours after PCI. The CRP level was not significantly different between the RIPC and the control group six hours after PCI. Chest discomfort and ECG ST-segment deviation during PCI were not significantly improved after RIPC.

Another meta-analysis of five randomised clinical trials indicated that RIPC reduces the risk of periprocedural MI amongst subjects with multivessel disease[39]. Pei et al in their meta-analysis also found RIPC to be protective against post-procedural events amongst stable CAD patients, which probably validates the results of the present study[40].

The definition of post-PCI MI is, however, debatable, but elevations of cardiac biomarkers from normal (before PCI) to above five times the 99th percentile URL (after PCI) are currently considered to be indicative of a post-procedural MI[41]. This criterion has been upgraded from a >3 times increase in cardiac biomarkers[26]. Since there is no valid scientific basis for defining a biomarker threshold for such a condition and this recent increase to >5 times has been done by arbitrary convention, we decided to use the guidelines published in 2007 for this study[26]. Another reason why the criterion of >3 times the biomarkers was used in the present study is because it has been used in almost all studies published so far investigating this subject; using a different criterion would have made the present study incomparable with other similar randomised studies and their meta-analyses. Importantly, reclassification from one definition to another has not been shown to improve accuracy in the diagnosis of periprocedural MI[42].

Presently, none of the available therapeutic interventions holds sufficient promise to act against the detrimental effects of ischaemia-reperfusion injury to the myocardium (at least in ACS). The main reason for the same is that studies examining the role of RIPC in preventing ischaemia-reperfusion injury cannot possibly be designed to adjust for several known confounding factors[43]. Relevant confounding factors have been amply described in a recently published review on this subject[44]. However, most of these confounding factors do not act against the effectiveness of RIPC in stable CAD subjects, which probably explains the positive effects of the aforementioned intervention deduced in our subject cohort.

Limitations

There were some study limitations. Firstly, the study population was small. Although PCI-related MI and undetectable troponin I (at six and 12 hours) in the RIPC and in the control group were less in absolute numbers, this difference was found to be statistically insignificant. Even then, a clear trend was seen as the RIPC group had a lesser incidence of PCI-related MI with a higher frequency of subjects having undetectable troponin values at these time intervals. If the study population had been larger, even this difference could also have been statistically significant. Secondly, the pre and post balloon dilatation duration during PCI was not recorded in this study and we feel that it may have been a key factor influencing the outcome. Thirdly, long-term clinical follow-up is needed to see clinical transformation of biochemical outcome. Our study only explored PCI-related troponin release and, since symptoms were not recorded, it does not necessarily translate into PCI-related MI. This also constitutes a major limitation of our study.

Conclusions

The present study concludes that administration of remote ischaemic preconditioning prior to PCI significantly reduces troponin I and CRP release at both 12 and 24 hours post PCI. The incidence of PCI-related MI was also found to be significantly lower in the RIPC group at 24 hours after PCI. However, studies with a larger number of patients and longer clinical follow-up are warranted to establish the beneficial effect of RIPC, which could possibly help in reducing the incidence of myocardial injury during PCI.

Impact on daily practice

In the light of the presented results, we recommend the use of RIPC as an adjunctive strategy for reducing post-PCI myocardial ischaemia-reperfusion injury. Clinical applicability of RIPC becomes all the more recommendable, as none of the other examined adjunctive cardioprotective strategies (pharmacological or mechanical) has so far been able to demonstrate convincing clinical benefit.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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