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Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP Stent) Study

A Prospective, Randomized Control Trial

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Background—Myocyte necrosis as a result of elective percutaneous coronary intervention (PCI) occurs in approximately one third of cases and is associated with subsequent cardiovascular events. This study assessed the ability of remote ischemic preconditioning (IPC) to attenuate cardiac troponin I (cTnI) release after elective PCI.

Methods and Results—Two hundred forty-two consecutive patients undergoing elective PCI with undetectable preprocedural cTnI were recruited. Subjects were randomized to receive remote IPC (induced by three 5-minute inflations of a blood pressure cuff to 200 mm Hg around the upper arm, followed by 5-minute intervals of reperfusion) or control (an uninflated cuff around the arm) before arrival in the catheter laboratory. The primary outcome was cTnI at 24 hours after PCI. Secondary outcomes included renal dysfunction and major adverse cardiac and cerebral event rate at 6 months. The median cTnI at 24 hours after PCI was lower in the remote IPC compared with the control group (0.06 versus 0.16 ng/mL; $P=0.040$). After remote IPC, cTnI was <0.04 ng/mL in 44 patients (42%) compared with 24 in the control group (24%; $P=0.01$). Subjects who received remote IPC experienced less chest discomfort ($P=0.0006$) and ECG ST-segment deviation ($P=0.005$) than control subjects. At 6 months, the major adverse cardiac and cerebral event rate was lower in the remote IPC group (4 versus 13 events; $P=0.018$).

Conclusion—Remote IPC reduces ischemic chest discomfort during PCI, attenuates procedure-related cTnI release, and appears to reduce subsequent cardiovascular events. **(*Circulation*. 2009;119:820-827.)**

Key Words: ischemia ■ myocardial infarction ■ prognosis ■ remote ischemic preconditioning ■ stents ■ troponin

Elective percutaneous coronary intervention (PCI) is associated with troponin release in approximately one third of cases.[1] Troponin release is a sensitive and specific marker of myocyte necrosis and infarction resulting from a form of ischemia/reperfusion injury, downstream embolization of atheromatous material, and coronary side-branch occlusion.[2–4] A number of studies have demonstrated that procedure-related troponin release is associated with subsequent cardiovascular events.[5–9]

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Transient sublethal episodes of ischemia before a prolonged ischemia/reperfusion injury, known as ischemic preconditioning (IPC), have been shown to reduce the extent of myocardial infarction (MI).[10] This protection not only acts locally but also can protect distant tissues, a phenomenon known as remote IPC, and limits MI size in animal models.[11] In humans, remote IPC protects against endothelial ischemia/reperfusion injury[12] and the extent of MI after adult coronary bypass surgery,[13,14] pediatric surgery,[15] and noncardiac surgery.[16] However, a small study failed to demonstrate protection from remote IPC during PCI,[1] and there are limited outcome data. The present study investigated the ability of remote IPC to attenuate cardiac troponin I (cTnI) release after elective PCI in a single-center, randomized controlled trial.

Methods

Identification and Recruitment of Patients

Consecutive patients were identified from the waiting list for elective PCI between July 2006 and November 2007 and invited to participate in the study during their attendance at the routine preadmission

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Clinical trial registration information—URL: http://www.ukcrn.org.uk. Registration number: UKCRN 4074.

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clinic at a single-specialist cardiothoracic center. All patients ≥18 of age who were undergoing elective PCI and able to give informed consent were eligible for study. Exclusion criteria were (1) emergency PCI, (2) elevation of cTnI before PCI taken at the preadmission clinic, (3) women of child-bearing age, (4) nicorandil or glibenclamide use (preconditioning-mimetic and preconditioning-blocking medication, respectively), and (5) severe comorbidity (estimated life expectancy <6 months). The subjects received written information about the study and, after confirmation of eligibility, were randomized to either control treatment or remote IPC. No changes were made to the clinical care of the patients enrolled in this study. The local research ethics committee approved the study protocol (LREC reference, 06/Q0106/20), and the study conformed to the principles outlined in the Declaration of Helsinki. The study was registered on the UKCRN database (UKCRN 4074).

Procedural Interventions

Remote IPC and Control Interventions

At the preadmission clinic, participants were instructed to avoid any strenuous activity that could provoke angina before their procedure. Consent was confirmed on the day of admission for PCI, and ≈1 hour before the procedure, those patients randomized to remote IPC had a blood pressure cuff placed around their nondominant upper arm. The cuff was inflated to 200-mm Hg pressure for 5 minutes, followed by 5 minutes of deflation, to allow reperfusion. This was repeated 2 more times. Control patients had a similar cuff placed around the upper arm, but it was not inflated. Thereafter, all patients underwent PCI by an interventionist blinded to the study allocation.

Percutaneous Coronary Intervention

PCI was performed via a femoral arterial approach with 6F or 7F guiding catheters. All patients received aspirin 300 mg and clopidogrel 300 mg at least 6 hours before PCI and 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 not administered. Ultravist (iopromide) (Bayer HealthCare Pharmaceuticals, Berlin, Germany) was used as the contrast agent in all cases. All patients received aspirin 75 mg indefinitely and clopidogrel 75 mg for 4 weeks after bare metal stent implantation or 1 year after drug-eluting stent implantation, in accordance with local practice. All other medication was given at the discretion of the attending physician, and the PCI strategy was at the discretion of the treating interventional cardiologist according to conventional practice.

Chest pain severity during PCI was graded on a scale of 0 for no pain to 10 for the most severe discomfort ever experienced. Angiographic success was defined as a residual stenosis of <15% by visual angiographic assessment.

Outcome Measurements

Biochemistry

Venous blood samples were taken at the preadmission clinic (baseline) and again 24 hours after PCI for cTnI, serum creatinine, and C-reactive protein. cTnI was analyzed with an automated immunoassay (Bayer ADVIA IMS Troponin-I Ultra method, Bayer, Berlin, Germany). The 99th percentile of the cTnI 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, is <10%, complying with the European Society of Cardiology/American College of Cardiology consensus requirements.[17] The analytical range was 0.01 to 50 ng/mL, with an assay sensitivity of 0.006 ng/mL. The European Society of Cardiology/American College of Cardiology/American Heart Association/World Health Federation definition of a PCI-related MI (MI 4a) was defined as >0.12 ng/mL (3 times the upper reference limit).[18] The World Health Organization definition for MI for this assay was ≥0.78 ng/mL.

An estimate of the glomerular filtration rate (expressed as mL · min^{-1} · 1.73 m^{-2} of body surface area) was calculated with the Modification of Diet in Renal Disease formula: $186 \times (\text{serum creatinine in mg/dL})^{-1.154} \times (\text{age in years})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$.[19] A significant decline in renal function after PCI was prospectively defined as an increase in serum creatinine concentration >25% above baseline at 24 hours. Vascular inflammation after PCI was assessed by the change in C-reactive protein (CRP) from baseline (ΔCRP in mg/mL). All biochemical measurements were made without knowledge of group allocation.

Angiographic Parameters

Ejection fraction was calculated by the single plane method using the end-systolic and -diastolic frames of the left ventriculogram obtained during diagnostic angiography. The myocardium at risk during PCI was assessed by reference to the target vessel,[20] collateral vessels assessed at angiography by the modified Rentrop score,[21] and a modified jeopardy score.[22] The jeopardy score is a measure of the burden of coronary disease by assigning disease in a major epicardial vessel (left anterior descending, left circumflex, and right coronary arteries) a score of 4 for proximal disease and 2 for distal disease, with a maximum of 4 in each vessel and a maximum overall total of 12. We modified this by assigning a score of 4 for PCI to the proximal vessel and 2 for distal PCI while retaining a maximum score of 12.

Angiographic lesion characteristics were classified according to the modified AHA/American College of Cardiology classification.[23] The final result of stent implantation (reference diameter, minimal lumen diameter, percent stenosis [calculated by area], residual stenosis, and acute gain in artery diameter [minimal lumen diameter after stent minus minimal lumen diameter before]) was assessed by quantitative angiography from 2 orthogonal planes (Cardiac Viewer CV-1000, version 2.1.0, Liverpool, NY). Preprocedural and postprocedural assessments of epicardial (Thrombolysis in Myocardial Infarction flow score) and microvascular integrity (Thrombolysis in Myocardial Infarction blush grade) were performed as previously described.[24] Two interventional cardiologists graded each case and were blinded to the cTnI results. Other angiographic complications (artery dissection, perforation, or jailed side branch with compromised flow) occurring during PCI were noted, as were the contrast dose, radiation exposure, and total fluoroscopic screening time. Procedural factors, including length and type of implanted stent, duration and pressure of coronary balloon inflations, and other variables, were recorded without prior knowledge of the randomization details.

Specific Objectives

The primary outcome was assessing whether remote IPC ≈1 hour before elective PCI reduced cTnI concentration at 24 hours. Secondary outcomes were the effect of remote IPC on ischemic symptoms, ECG evidence of ischemia during coronary balloon occlusion, CRP, and major adverse cardiac and cerebral events (MACCE) at 6 months.

MACCE Rate

Patients were contacted by telephone 6 months after PCI by an interviewer blinded to group allocation. Adverse events, including hospital admissions with unstable angina/acute coronary syndrome, MI, heart failure, and stroke/transient ischemic attack, were recorded. The medical notes were then reviewed to confirm the details and, when appropriate, the cause of death.

Sample Size

The sample size was determined on the basis of the primary outcome, post-PCI cTnI at 24 hours. We assumed that remote IPC would reduce the prevalence of PCI-induced cTnI release by 15%; therefore, 200 patients were recruited into the study to enable such a reduction to be detected ($\alpha=0.05$; $\beta=0.2$; statistical power=80%).

Randomization

A computer-generated, simple randomization procedure was used to allocate patients to treatment group. The allocations were kept in

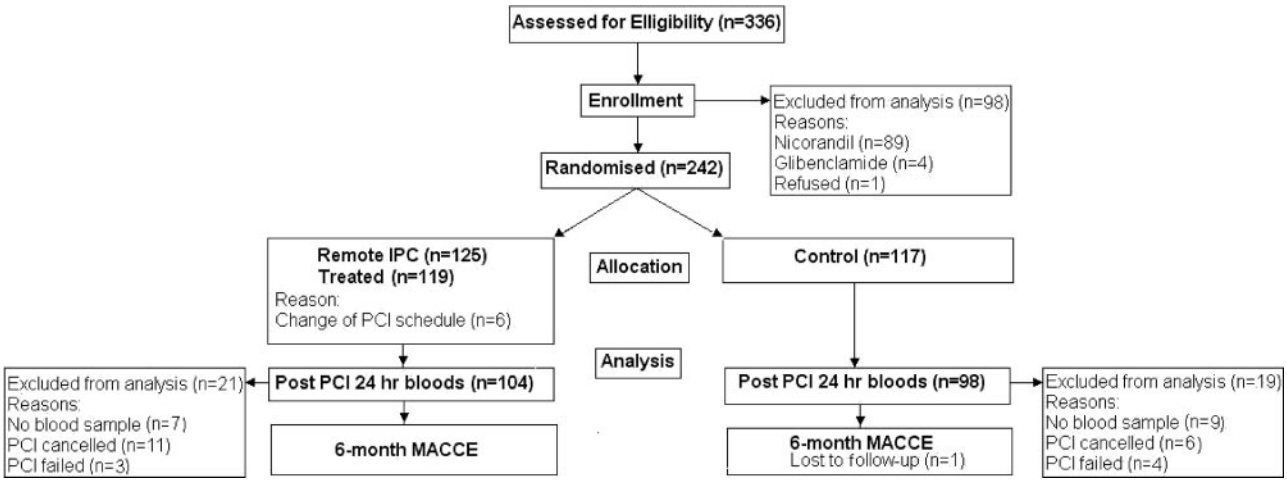

Figure 1. Flowchart of study recruitment and assessment schedule, including number of patients who received PCI and those in whom a full data set was available.

sealed envelopes marked with the study number in a separate Research and Development Unit. The process was performed by independent research staff and supervised by an independent statistician. Once a patient gave consent and was registered with Research and Development, the group allocation was released to the study coordinator.

Statistical Methods and Analysis

The trial adhered to Consolidated Standards of Reporting Trials guidelines, and analysis was by intention to treat in patients who underwent coronary stenting because the primary outcome cannot be meaningfully interpreted in the absence of stent deployment. Resulting bias is minimal because protocol violators are identified explicitly in both groups.

Although sample size was based on the assumption of normality for the distribution of mean cTnI, the extent of skewness in the distribution observed was such that means could not be assumed to have a normal distribution. Therefore, analysis was based on nonparametric analysis using the Wilcoxon rank-sum test. In addition, data were analyzed by categorizing the cTnI data into those with a defined MI and those with cTnI below the lower limit of detection of the assay.

Continuous variables were summarized as mean (SD) or median (quartiles) and compared by use of Student's *t* test or a Mann-Whitney-Wilcoxon test when appropriate. Categorical data were expressed as numbers (percentages) and compared by use of Fisher's exact test. Spearman rank correlation was used to assess the relationship between cuff-to-balloon time (CTBT) and cTnI in the remote IPC group. A value of $P<0.05$ was considered significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Study Population

Two hundred forty-two patients were recruited (Figure 1). Sixteen patients (7 remote IPC patients, 9 control subjects) did not have post-PCI blood samples taken as a result of administrative issues. Twenty-four patients were excluded from the final analysis (14 remote IPC patients, 10 control subjects) because they did not receive PCI (17 PCIs were canceled [11 medically managed, 6 referred for coronary artery bypass grafting], 7 PCIs failed [5 failures to cross the lesion, 1 failure to cross with the balloon, and 1 failure to deploy the stent]). Excluded patients were more likely to be women (43% versus 22%; $P=0.01$) and older (67 versus 63 years; $P=0.003$) with a low incidence of cTnI release (median, 0.00 versus 0.11 ng/mL; $P<0.001$). Two hundred two patients received a stent and were included in the analysis (Table 1).

Remote IPC

Remote IPC was successfully administered to 119 patients without complication. Remote IPC was not administered to 6 patients because of unforeseen alterations to the catheter

Table 1. Preprocedure Demographic and Clinical Data of Patients Randomized to Remote IPC and Control Subjects

Variable	Control (n=98)	Remote IPC (n=104)	*P*
Demographics			
Age, y	61.8 (10.3)	63.2 (10.1)	0.33
Male sex, n (%)	74 (76)	84 (81)	0.46
Risk factors			
Diabetes mellitus, n (%)	20 (20)	24 (23)	0.77
Total cholesterol, mmol/L	4.4 (1.2)	4.2 (1.0)	0.46
Active or ex-smoker, n (%)	69 (70)	74 (71)	0.97
BMI, kg/m^2	27.8 (4.5)	27.8 (4.5)	0.97
Hypertension, n (%)	51 (52)	53 (51)	0.89
Clinical details			
LVEF, %	49.8 (9.2)	50.5 (10.4)	0.42
Previous MI, n (%)	52 (53)	60 (58)	0.57
NYHA class III/IV, n (%)	27 (28)	28 (27)	1.00
CCS grade III/IV, n (%)	24 (24)	22 (21)	0.62
Medications, n (%)			
Statins	95 (97)	97 (93)	0.33
β-Blockers	78 (80)	82 (79)	1.0
ACEI/ARB	69 (70)	80 (77)	0.34

BMI indicates body mass index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; CCS, Canadian Cardiology Society; ACEI, angiotensin-converting enzyme inhibitor; and ARB, angiotensin II receptor blocker. Data are mean (SD) when appropriate.

laboratory schedule, although these patients were included in the remote IPC group for intention-to-treat analysis.

PCI Procedure

There were no major procedure-related complications in either group (death or urgent revascularization within the first 24 hours). Angiographic parameters were similar in both groups, and any difference in cTnI release after remote IPC was not due to lower risk (Table 2). Collateral grade assessed by modified Rentrop score to the target vessel was poor in both groups. Angiographic parameters and complication rates were similar in both groups.

Primary Outcome

Subjects were eligible for the study if the baseline cTnI was below the lower limit of detection for the assay (<0.04 ng/mL). After PCI, the median cTnI concentration at 24 hours was lower in the remote IPC group: 0.06 versus 0.16 ng/mL ($P=0.04$; Figure 2 and Table 3). In addition, more patients who received remote IPC had no detectable cTnI release (56 versus 31 patients [48% versus 29%]; $P<0.005$), and there was a trend to less PCI-related MI. Renal function was similar in both groups.

The time between the last blood pressure cuff deflation and stent balloon inflation (cuff-to-balloon time) was 66±30 minutes. There was a weak correlation between cuff-to-balloon time and cTnI concentration at 24 hours ($r=0.28$, $P=0.006$) and a suggestion of a trend for remote IPC to confer less benefit in the elderly (cTnI in those <65 years: median, 0.05 ng/mL [interquartile range (IQR), 0 to 0.37 ng/mL]; in those ≥65 years of age: median, 0.14 ng/mL; [IQR, 0.02 to 1.70 ng/mL]; $P=0.09$) and in patients with a history of MI (median, 0.14 ng/mL [IQR, 0.02 to 1.27 ng/mL] versus 0.04 ng/mL [IQR, 0.02 to 0.42 ng/mL]; $P=0.08$). A history of hypertension or diabetes did not influence the effect of remote IPC (median cTnI, 0.06 ng/mL [IQR, 0.02 to 0.65 ng/mL] versus 0.09 ng/mL [IQR, 0 to 0.46 ng/mL]; $P=0.76$; and 0.04 ng/mL [IQR, 0.02 to 0.48 ng/mL] versus 0.07 ng/mL [IQR, 0 to 0.58 ng/mL]; $P=0.93$, respectively).

Secondary Outcomes

Subjects receiving remote IPC had significantly less chest pain and ischemic ECG changes during stent implantation (Table 2). Mean CRP was elevated after PCI compared with baseline (mean±SD CRP, 3.6±5.0 versus 5.5±7.3 mg/mL after PCI; $P<0.001$), but the mean change in CRP was similar in both groups (Table 3).

Of the 242 patients, 1 patient was lost to follow-up at 6 months. There were 17 adverse events (7.1%) at 6 months after PCI (median cTnI at 24 hours, 0.26 ng/mL [IQR, 0 to 2.2 ng/mL] compared with 0.09 ng/mL [IQR, 0 to 0.8 ng/mL] for those without events; $P=0.55$). In those patients who received remote IPC before elective PCI, the MACCE rate at 6 months was lower (4 hospital admissions with an acute coronary syndrome versus 13 events in the control group: 11 acute coronary syndromes, 1 acute left ventricular failure, 1 death), with a hazard ratio of 0.28 (95% CI, 0.12 to 0.82; $P=0.018$; Figure 3).

Table 2. Angiographic and Periprocedure Data of Patients Randomized to Remote IPC and Control Subjects

Variable	Control (n=98)	Remote IPC (n=104)	P
Angiographic parameters			
Target vessel, n (%)			
LCx	14 (14)	18 (17)	0.84
LAD	43 (44)	42 (40)	
RCA	26 (27)	25 (24)	
Combined/other	15 (15)	19 (18)	
Modified jeopardy score, n (%)			
<6	91 (93)	91 (88)	0.24
≥6	7 (7)	13 (12)	
Modified Rentrop score, n (%)			
0	66 (67)	76 (73)	0.60
1	18 (18)	15 (14)	
2/3	14 (14)	12 (12)	
Lesion type (AHA/ACC), n (%)			
A	33 (34)	29 (28)	0.33
B	36 (37)	34 (33)	
C	29 (29)	41 (39)	
Stenosis severity, %	86.8 (12.7)	87.2 (12.1)	0.84
Side branch >2 mm, n (%)	33 (34)	41 (39)	0.47
Acute gain, mm	2.29 (0.79)	2.21 (0.77)	0.51
Stent length, mm	34.8 (18.4)	32.3 (15.7)	0.30
Drug-eluting stent, n (%)	66 (67.3)	80 (76.9)	0.16
Screen time, min	10.1 (5.6)	11.3 (8.0)	0.20
Radiation dose, cGy/cm^2	69.4 (41.9)	72.7 (44.5)	0.59
Contrast, mL	187.5 (74.2)	196.7 (80.1)	0.40
Predilatation time, s	35.8 (29.0)	39.0 (29.6)	0.43
Postdilatation time, s	24.4 (29.5)	20.4 (26.7)	0.31
Clinical state during stent implantation			
SBP, mm Hg	138.6 (24.0)	138.4 (24.6)	0.95
DBP, mm Hg	70.4 (10.8)	69.1 (11.2)	0.38
HR, bpm	66.4 (12.5)	63.4 (11.7)	0.08
Chest pain score >1, n (%)	76 (78)	56 (54)	0.0006
ECG ST deviation >1 mm, n (%)	55 (56)	37 (36)	0.005
Complications, n (%)			
Dissection	5 (5)	7 (7)	0.77
Jailed side branch (TIMI 0/1)	3 (3)	4 (4)	1.0
Complication (total)	9 (9)	11 (11)	0.82
After the procedure, n (%)			
TMBG			
0–2	8 (8)	4 (4)	0.32
3	90 (92)	100 (96)	
TIMI flow score			
0–2	7 (7)	6 (6)	0.91
3	91 (93)	98 (94)	

LCx indicates left circumflex artery; LAD, left anterior descending artery; RCA, right coronary artery; ACC, American College of Cardiology; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TIMI, Thrombolysis in Myocardial Infarction; and TMBG, TIMI myocardial blush grade. Data are mean (SD) when appropriate.

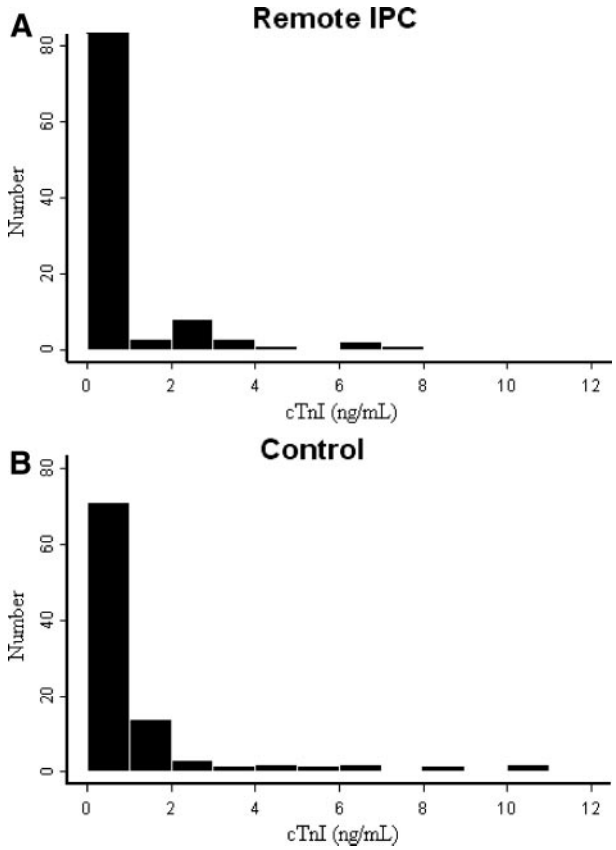

Figure 2. Distribution of 24-hour cTnI in patients after PCI in those who received remote IPC (A) and control patients (B; 1 outlier in each group is excluded from the histograms but was included in the analysis).

Discussion

The present study demonstrates that remote IPC, administered by transient upper-limb ischemia, attenuates PCI-related troponin release in patients undergoing elective PCI. The use of remote IPC shortly before PCI appears to confer improved clinical outcome at 6 months.

Several studies have shown that PCI-related cTnI release is associated with a worse prognosis, especially in those patients with the most marked elevation in cTnI concentration.[5–7,9] A postprocedure increase in cTnI concentration of >5-fold baseline levels is an independent predictor of a composite of death, MI, and revascularization at 1 year (hazard ratio, 2.39; 95% CI, 1.09 to 5.26).[7] Gadolinium late enhancement with cardiac magnetic resonance has demonstrated that procedural cTnI release is due to MI both downstream of the stented lesion and adjacent to the implanted stent.[3,25] Microembolization of plaque debris and side-branch occlusion have been proposed as the most likely mechanisms of cTnI release. A Doppler flow-wire study reported that the number of microembolic high-intensity signals during PCI correlated with cTnI release.[4] The highest frequency of high-intensity signals is seen during stent deployment, although the background signal is increased throughout PCI. Several parameters, including stent length, acute gain in vessel diameter, case complexity, and immediate complications, have been shown to be related to PCI-associated cTnI release.[3,5,25] The recent redefinition of MI specifically identifies PCI as a cause of MI (MI 4a) when the postprocedure cTnI concentration has risen to 3 times the baseline value.[18] Although the magnetic resonance studies suggest that myocardial injury sustained during PCI is the result of more distal and peri-stent microcirculatory obstruction and/or side-branch occlusion, myocyte damage and troponin release also may be associated with a form of ischemia/reperfusion injury during stent deployment.

Birnbaum and colleagues[26] described the ability of remote IPC to reduce infarct size in animal models. They found that a partial reduction in rabbit hind-limb blood flow combined with electric gastrocnemius muscle stimulation before coronary occlusion and reperfusion reduced infarct size by ≈60% compared with control animals. Kharbanda and colleagues[27] demonstrated that transient upper-limb ischemia, induced by a blood pressure cuff inflated around the upper arm for three 5-minute cycles, with intervening periods of reperfusion ameliorated contralateral forearm ischemia/reperfusion endothelial dysfunction in human volunteers. Subsequent studies in adult patients have shown that transient upper- or lower-limb ischemia has the potential to attenuate myocardial

Table 3. Plasma cTnI, Creatinine, and CRP Concentrations at 24 Hours After PCI

Variable	Control (n=98)	Remote IPC (n=104)	*P*
Post-PCI cTnI			
cTnI, median (IQR), ng/mL	0.16 (0.04–1.04)	0.06 (0.02–0.56)	0.04
cTnI <0.04 ng/mL, n (%)	24 (24)	44 (42)	0.01
Incidence of MI, n (%)			
No MI (<0.12 ng/mL)	45 (46)	57 (55)	0.23
MI 4a (0.12–<0.78 ng/mL)	22 (22)	25 (24)	0.82
WHO-defined MI (≥0.78 ng/mL)	31 (32)	22 (21)	0.075
Renal function			
eGFR, median (IQR), mL · min^{-1} · 0.1.73 m^{-2}	75.5 (65.3–89.8)	72.0 (55.8–86.0)	0.15
Serum creatinine >25% increase, n (%)	10 (10)	6 (6)	0.30
Inflammatory response			
ΔCRP, mg/mL	2.13 (6.81)	1.97 (5.27)	0.88

WHO indicates World Health Organization; eGFR, estimated glomerular filtration rate.

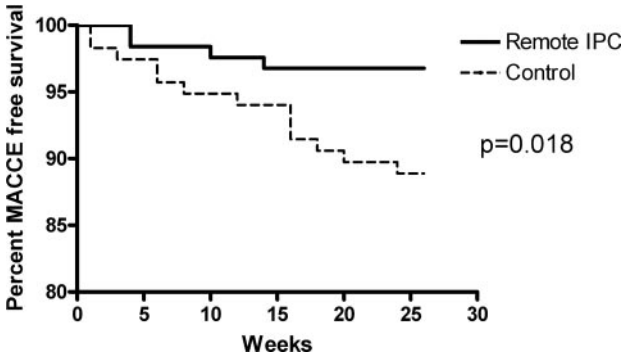

Figure 3. Kaplan-Meier graph of the MACCE rate at 6 months after PCI in the 201 patients with complete data (104 in the IPC group, 97 in the control group).

injury, indicated by troponin release, in a number of clinical situations, including coronary artery surgery[13] and noncardiac surgery.[16] In children, transient leg ischemia reduced myocardial injury during surgery to correct congenital heart defects.[15] Remote IPC has a biphasic pattern of myocardial protection. An early classic phase is believed to act within a few minutes to 2 hours after the preconditioning stimulus and is mediated through opening of mitochondrial ATP-sensitive potassium channels.[28–30] A delayed second window of protection occurs at 24 to 72 hours and probably is the result of modified gene expression that suppresses the proinflammatory response to the ischemia/reperfusion injury.[31]

The use of remote IPC to protect the heart from ischemia associated with a therapeutic procedure is clearly attractive, particularly for elective intervention. Porto and colleagues[1] reported that no myocardial protection was conferred by remote IPC induced by three 5-minute cycles of bilateral upper-limb ischemia in the catheterization laboratory immediately before PCI. In contrast, they observed that remote IPC exacerbated cTnI 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 larger prospective randomized controlled study, we found that remote IPC applied to a broad case mix ≈1 hour before PCI 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. Chest discomfort and ECG ST-segment deviation during first coronary balloon occlusion were both significantly improved after remote IPC.

We undertook telephone follow-up at 6 months to assess whether there was a difference in hospitalization between those patients who received remote IPC before PCI and the control subjects. This was undertaken without knowledge of the treatment allocation, and analysis was deferred until the end of the study. Patients who received remote IPC exhibited a lower MACCE rate (predominantly because of a reduction in acute coronary syndromes), which concurs with the data that the magnitude of cTnI release after PCI offers prognostic information. The mechanism for this effect is unknown. Preconditioning has a beneficial platelet inhibitory and antithrombotic effect,[32] which might stabilize vulnerable plaques, improve endothelial function, and reduce inflammation.[1,31] Furthermore, the effector signal-mediating myocardial protection after limb ischemia through remote IPC is not defined and appears to depend on both humoral and neuronal integrity. The ganglion blocker trimetaphan abolishes the protective effect of remote IPC on forearm ischemia-induced endothelial dysfunction in humans.[33] However intact innervation is not essential; Konstantinov and colleagues[28] noted a reduction in the extent of MI after remote IPC in a porcine transplanted heart, in agreement with the original work on IPC that argued for a circulating humoral mediator.[34]

Clinical Implications

We have demonstrated that the simple, cheap, safe, and well-tolerated application of remote IPC in a busy PCI center is feasible and reduces the prevalence of PCI-related cTnI release. Remote IPC also appears to enhance myocyte tolerance to ischemia and to reduce patient discomfort during PCI. The reduction in PCI-related cTnI release may offer prognostic benefit. The ability of remote IPC to reduce MACCE after PCI should be investigated in a large trial.

Study Limitations

The cTnI concentration was measured in a single blood sample obtained 24 hours after PCI rather than defining the cTnI release profile every 4 to 6 hours. The resultant value may not be the maximum plasma concentration, although it is generally accepted that the maximum concentration occurs between 12 and 24 hours after myocyte necrosis.[35]

During coronary intervention, we recorded ischemic time (duration of coronary balloon occlusion), heart rate, and systolic blood pressure (to derive rate-pressure product); we could not define the area of myocardium at risk during PCI, which is an important determinant of infarct size. However, the surrogate measures to ascertain the extent of myocardium subtended by the vessel undergoing intervention did not differ between the 2 groups.

The protective effect observed was modest but apparent despite the inclusion of elderly patients and patients with conditions such as diabetes mellitus, hypertension, and previous MI, which have previously been shown to blunt the protective effect of preconditioning.[36–38] There was also judicious use of intracoronary glyceryl trinitrate, a preconditioning-mimetic substance, in both groups.[39] A direct preconditioning effect from coronary balloon inflation was probably below the reported threshold for protection,[40] and the effect of antecedent angina was minimized by instructing participants to avoid overexertion. However, we cannot exclude the possibility that the control group received additional protection by these mechanisms. Our study reports the ability of remote IPC to confer benefit in a "real-life" clinical application of this technique in which patients are preconditioned before entering the catheter laboratory and inevitably will be affected by delays. It is possible that if the cuff-to-balloon time had been shorter, the protective effect observed would have been magnified.

Conclusions

Remote IPC increases the tolerance of the myocardium to ischemia, reduces ischemic chest discomfort during coronary balloon occlusion, and reduces the prevalence of cTnI release after elective PCI. The mechanism of benefit

remains unclear and was not associated with a change in plasma CRP concentration. The observed cardioprotection appears to confer sustained benefit, and a larger study to assess the ability of remote IPC to reduce MACCE after PCI should be undertaken.

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Disclosures

None.

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CLINICAL PERSPECTIVE

A transient sublethal episode of ischemia before a prolonged ischemia/reperfusion injury (ischemic preconditioning) offers a powerful endogenous protective strategy to reduce infarct size. Although readily demonstrable in animal models, the translation from bench to bedside has been slow. Clinical application of ischemic preconditioning is limited by restricted access to tissues requiring protection, safety issues, and the temporality of the therapeutic effect. However, protection can spread to distant tissues through remote ischemic preconditioning. Preemptive remote ischemic preconditioning of ischemia-resistant skeletal tissue to protect distant myocardium before potential coronary stent-induced infarction (4a myocardial infarction) circumvents some of the limitations that potentially impede the demonstration of clinical benefit. The novel results of the present randomized control study in 242 patients undergoing elective percutaneous coronary intervention (PCI) demonstrate that remote IPC (induced by three 5-minute inflations of a blood pressure cuff to 200 mm Hg around the upper arm, followed by 5-minute intervals of reperfusion, ≈1 hour before PCI) reduced median troponin I release at 24 hours after the procedure (0.06 versus 0.16 ng/mL; $P=0.04$), chest pain, and ST deviation during the procedure ($P<0.005$) and major adverse cardiac and cerebral event rate at 6 months (4 versus 13 events; $P=0.04$). Protection was time dependent, with the greatest benefit observed in those with shorter cuff-to-balloon times. The implication of this real-world study is that remote ischemic preconditioning has therapeutic benefit to reduce ischemic chest discomfort and subsequent myocardial infarction after elective PCI and that this simple, safe, and cheap procedure has the potential to affect the prognosis of patients with stable coronary disease treated with coronary stent implantation.