Remote Ischemic Postconditioning During Percutaneous Coronary Interventions

Remote Ischemic Postconditioning—Percutaneous Coronary Intervention Randomized Trial

Shahar Lavi, MD; Sabrina D’Alfonso, MSc; Pantelis Diamantouros, MD; Anthony Camuglia, MD; Pallav Garg, MD; Patrick Teefy, MD; George Jablonsky, MD; Kumar Sridhar, MD; Ronit Lavi, MD

Background—Remote ischemic preconditioning may result in reduction in infarct size during percutaneous coronary intervention (PCI). It is unclear whether remote ischemic postconditioning (RIPost) will reduce the incidence of myocardial injury after PCI, and whether ischemic conditioning of a larger remote organ (thigh versus arm) would provide further myocardial protection.

Methods and Results—We randomized 360 patients presenting with stable or unstable angina (28% of patients) and negative Troponin T at baseline to 3 groups: 2 groups received RIPost (induced by ischemia to upper or lower limb), and a third was the control group. RIPost was applied during PCI immediately after stent deployment, by three 5-minute cycles of blood pressure cuff inflation to >200 mm Hg in the arm or thigh (20 mm Hg in the control) with 5-minute breaks between each cycle. The primary end-point was the proportion of patients with Troponin T levels >3×ULN postprocedure (at 6 or 18–24 hours), where ULN stands for upper limit of normal. A total of 120 patients were randomized to each group. There were no differences in baseline characteristics between the 3 groups. The primary outcome occurred in 30%, 35%, and 35% of the arm, thigh, and control groups, respectively (P=0.64). There were no differences in creatine kinase or high sensitivity C-reactive protein levels after PCI or in the incidence of acute kidney injury between the groups.

Conclusions—RIPost during PCI did not reduce the incidence of periprocedural myocardial injury. Similar effect was obtained when remote ischemia was induced to the upper or lower limb.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00970827.


Key Words: angioplasty ■ reperfusion injury

Percutaneous coronary intervention (PCI) is associated with a risk of myocardial injury during the procedure, which may lead to a temporary or permanent decrease in myocardial function. This injury, known as periprocedural myocardial injury (PMI), is thought to be caused by a combination of factors including distal embolization, side branch occlusions, and reperfusion. The mechanism of injury during PCI involves distal embolization and side branch occlusions, mainly during stent deployment or balloon postdilatation, followed by spontaneous lysis and reperfusion. Thus, it is possible that myocardial injury after PCI can be used as a model for assessment of interventions that reduce ischemia-reperfusion injury. Using such a model is important considering the difficulty in the translation of cardioprotective interventions to clinical practice.

A potential method to reduce myocardial injury is ischemic conditioning. Remote ischemic preconditioning applied to a coronary artery in an animal model was effective as local ischemic conditioning. In humans, remote ischemia preconditioning (RIPre), induced by prolonged blood pressure cuff inflation on the arm, has been associated with a decrease in periprocedural myocardial injury, and subsequent decreases in cardiac events. Ischemic postconditioning was found to be as effective as preconditioning in an animal models, and to reduce myocardial injury in animals, as well as in patients with acute myocardial infarction (MI) who were treated with PCI. However, several recent studies did not demonstrate clinical benefit of ischemic conditioning.

Remote ischemic postconditioning (RIPost) has potential advantages compared with RIPre. By definition, in the...
WHAT IS KNOWN

- Ischemic preconditioning has been shown to reduce myocardial injury after PCI and improve outcome.
- Ischemic postconditioning during STEMI may be beneficial.
- The preferred method of applying ischemic conditioning is unknown.

WHAT THE STUDY ADDS

- Remote ischemic postconditioning during PCI did not reduce the incidence of myocardial injury in patients with negative troponin at baseline.
- There was no difference in effect when remote ischemic conditioning was applied to a larger organ (thigh) or a smaller organ (arm).

setting of acute myocardial infarction (MI), only RIPost could be applied. In >80% of cases, PCIs is performed ad hoc, immediately after diagnostic coronary angiography. In this situation, the time interval is not sufficient for preconditioning.

There is uncertainty regarding the most effective method for application of ischemic conditioning. In animal models, remote conditioning applied to a larger organ or induction of simultaneous interventions was more effective compared with applying ischemia to a smaller organ or using a single intervention. In healthy humans, when ischemia-reperfusion injury was induced, lower limb RIPost was associated with better preservation of systemic endothelial function compared with that of upper limb RIPost.

It is possible that at least in certain populations, such as the elderly, a larger conditioning stimulus may be needed to obtain a clinical effect.

The purpose of the present study was to test the hypothesis that RIPost at the time of PCI will decrease myocardial necrosis compared with standard care, and that ischemia of a larger organ (thigh versus arm) for RIPost is associated with additional myocardial protection during PCI.

Methods

This was a single center, randomized, controlled trial. The Research Ethics Board of Western University approved the study. All patients provided written informed consent before enrollment. The study is registered at http://www.clinicaltrials.gov; identifier NCT00970827.

Study Population

Ejective patients with stable angina or admitted patients with unstable angina, undergoing cardiac catheterization or PCI, were enrolled in the study. Patients were excluded if they had elevation of cardiac Troponin before PCI, MI, or coronary bypass surgery during the past 4 weeks; heart failure (NYHA III or IV); chronic inflammatory disease (eg, lupus, rheumatoid arthritis); severe renal impairment (estimated glomerular filtration rate <30 mL/min); symptomatic peripheral vascular disease; and patients on glibenclamide (an ATP potassium channel blocker, that blocks the ischemic conditioning effect) at the time of the intervention.

Protocol

Blood samples for Troponin T/ high sensitivity (hs) Troponin T, creatine kinase, and creatinine were obtained immediately before cardiac catheterization. If troponin levels were above the upper limit of normal (ULN), the patients were excluded. Serial blood samples were obtained before PCI from patients with unstable angina to ensure negative troponin. A fourth-generation cardiac Troponin T assay (Roche, Basel, Switzerland) was used for the first 233 patients, and the hs Troponin T assay (Roche, Basel, Switzerland) was used for the remaining 127 patients. Postprocedure blood samples were taken after 6 hours and after 18 to 24 hours.

PCI was performed via the femoral or radial approach using standard techniques at the discretion of the operator. Procedure-related decisions such as type of stents used and adjunctive medications were made before randomization.

Randomization and Postconditioning Protocol

Randomization envelopes containing the study group (arm RIPost, thigh RIPost or control) were prepared following a computer-generated randomization sequence. The randomization sequence was 1:1:1 and set in random blocks of 12, 15, and 18. This size of blocks was used to decrease prediction of allocation in case of unmasking.

A blood pressure cuff was placed on the left arm and thigh of each patient, before draping. Randomization envelopes were opened, and cuff inflation cycles began simultaneously with the deployment of the first stent. If rotational atherectomy was used, cuff inflation began at the time of the atherectomy. The nurse who inflated the cuff was not blinded to the patient randomization, but an effort was made to keep the operators blinded. To keep the patients comfortable and blinded as much as possible, all patients received 1 mg of midazolam and 25 mcg of fentanyl. In the active groups, the cuff was inflated 3 times to ≥200 mm Hg (recommended 300 mm Hg in the thigh group to ensure complete compression of the arteries), and >50 mm Hg above systolic blood pressure, for 5 minutes (ischemia), followed by a 5-minute deflation (reperfusion). A pulse-oximeter on the finger or toe of the occluded limb was used to verify that the cuff was adequately occlusive. In the control group, the arm cuff was cycled in the same fashion but inflated to a low pressure of 20 mm Hg, which would not cause ischemia.

End Points

The primary end point was the proportion of patients with Troponin T levels >3×ULN (0.03 μg/L for the fourth-generation Troponin T). Troponin was measured at 6 hours and 18 to 24 hours postprocedure, and the highest level was used for outcome assessment. This cutoff was chosen according to the universal definition of periprocedural MI when the study began. The comparable hs Troponin cutoff used was >0.053 μg/L. Secondary end-points included any elevation of cardiac troponin above the 99th percentile (0.01 μg/L for fourth-generation Troponin T, or 0.014 μg/L for hs Troponin T) as an indication of a procedure-related myocardial injury at 6 hours or 18 to 24 hours after PCI, creatine kinase >ULN, creatinine levels 18 to 24 hours after PCI, incidence of acute kidney injury (AKI), and high sensitivity C-reactive protein at 18 to 24 hours. PCI-related AKI was defined as a relative increase in serum creatinine of ≥25%, compared with baseline, or an absolute increase in serum creatinine of >44 μmol/L. Because of the recent modification in the universal definition of periprocedural MI, we also assessed the proportion of patients with cardiac troponin >5×99th percentile as an indication of MI range injury. All laboratory tests were performed by the hospital laboratory, blinded to patient characteristics or the randomization group.

Sample Size

We estimated that 40% of patients in the control group would have Troponin T levels >0.03 μg/L on the day after the procedure. In the Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP) study, RIPre was associated with 19% absolute difference in positive troponin. To allow for 3 pairwise between-group comparisons and to maintain an overall 2-sided type 1 (α) level of 0.05, a Bonferroni correction was made. A total of 360 subjects (120 per
group) were required to detect an absolute reduction from 40% to 21% at the experimentwise type 1 error rate of 5% with 80% power. Because the primary outcome was a blood test measured during admission, and the randomization performed toward the end of PCI, we did not expect dropout or missing values. Therefore, the total number of participants remained 360.

### Statistical Analysis

Baseline variables are summarized by mean and standard deviation or median and Q1-Q3 (continuous variables) and counts/percentages (categorical variables). Comparisons between continuous variables were performed using ANOVA or Wilcoxon rank-sum test where appropriate. Categorical variables were compared with the Pearson $\chi^2$ test.

### Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Arm (n=120)</th>
<th>Thigh (n=120)</th>
<th>Control (n=120)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63.6±10.3</td>
<td>64.9±9.6</td>
<td>63.7±9.7</td>
<td>0.54</td>
</tr>
<tr>
<td>Females</td>
<td>35 (29%)</td>
<td>32 (27%)</td>
<td>30 (25%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Body mass index</td>
<td>30.4±5.6</td>
<td>29.5±4.9</td>
<td>29.6±5</td>
<td>0.32</td>
</tr>
<tr>
<td>Hypertension</td>
<td>88 (73%)</td>
<td>88 (73%)</td>
<td>80 (67%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Dystlipidemia</td>
<td>78 (66%)</td>
<td>74 (62%)</td>
<td>81 (68%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>41 (34%)</td>
<td>34 (28%)</td>
<td>37 (31%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>47 (39%)</td>
<td>48 (40%)</td>
<td>56 (47%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Previous CVA/TIA</td>
<td>11 (9%)</td>
<td>4/119 (3%)</td>
<td>6/118 (5%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>42 (35%)</td>
<td>52 (43%)</td>
<td>49 (41%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>22 (18%)</td>
<td>20 (17%)</td>
<td>24 (20%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>29/114 (25%)</td>
<td>35/116 (30%)</td>
<td>31/113 (27%)</td>
<td>0.72</td>
</tr>
<tr>
<td>LV grade 3–4</td>
<td>5/104 (5%)</td>
<td>6/102 (6%)</td>
<td>5/101 (5%)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft; CVA, cerebrovascular accident; LV, left ventricle; PCI, percutaneous coronary intervention; and TIA, transient ischemia attack.
Single-predictor (the primary analysis) and multivariable logistic regression models were used to calculate the effect of RIPost on the primary outcome. Variables found to show marginal association with the primary outcome in the single-predictor analysis (P<0.20) were used in the multivariable model. 

P values are 2-tailed, and statistical significance was defined as P<0.05 for all statistical comparisons.

Results

Patients and Procedures

A total of 360 patients were enrolled, 120 patients into each of the 3 groups. The flow diagram of the study is shown in the Figure. Baseline characteristics were similar in all groups (Table 1); 27% were women and 31% had a history of diabetes mellitus; 42% had a previous MI; 28% presented with unstable angina without elevation in cardiac markers. Procedural characteristics are presented in Table 2. The majority of the procedures were performed via the femoral approach. Bivalirudin was used as the anticoagulant in 58% of patients; Glycoprotein IIb/IIIa inhibitors were used in conjunction with unfractionated heparin in 25%; the remainder received unfractionated heparin alone. Rotational atherectomy was used less frequently in the patients who were randomized to the thigh group. All other procedural characteristics, including the proportion of bifurcation procedures, the number and specific arteries that were intervened, and stents diameter and length, were comparable among the three groups.

Table 3. Study Outcomes and Laboratory Results

<table>
<thead>
<tr>
<th></th>
<th>Arm (n=120)</th>
<th>Thigh (n=120)</th>
<th>Control (n=120)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>36 (30%)</td>
<td>42 (35%)</td>
<td>42 (35%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Troponin T&gt;ULN</td>
<td>70 (58%)</td>
<td>74 (62%)</td>
<td>72 (60%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Troponin&gt;5×ULN</td>
<td>26 (22%)</td>
<td>29 (24%)</td>
<td>30 (25%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Absolute troponin levels</td>
<td>0.03 (0.019, 0.237)</td>
<td>0.037 (0.02, 0.07)</td>
<td>0.03 (0.018, 0.097)</td>
<td>0.92</td>
</tr>
<tr>
<td>CK&gt;ULN (190 U/L)</td>
<td>10 (9%)</td>
<td>6 (5%)</td>
<td>7 (6%)</td>
<td>0.53</td>
</tr>
<tr>
<td>hsCRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.2±5.6</td>
<td>3.5±4.6</td>
<td>3.6±4.6</td>
<td>0.46</td>
</tr>
<tr>
<td>18–24 h</td>
<td>5.7±7.4</td>
<td>4.8±5.3</td>
<td>4.7±5.3</td>
<td>0.40</td>
</tr>
<tr>
<td>Creatinine 24 h (μmol/L)</td>
<td>79.3±20.6</td>
<td>82.3±24.9</td>
<td>79.3±22.2</td>
<td>0.52</td>
</tr>
<tr>
<td>AKI within 24 h</td>
<td>5/114 (4%)</td>
<td>9/114 (8%)</td>
<td>7/109 (6%)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Primary end point: proportion of patients with elevated troponin >0.03 μg/L for fourth-generation Troponin T, or 0.053 μg/L for hs Trop T; upper limit of normal (ULN) is 99th percentile for the Troponin assays (0.01 μg/L for fourth-generation Troponin T, or 0.014 μg/L for hs Troponin T); Troponin T>5×ULN is a myocardial infarction (MI) range level according to the third universal definition of MI. AKI indicates acute kidney injury; CK, creatine kinase; and hsCRP, high sensitivity C-reactive protein. P values are univariable; the Bonferroni-adjusted pairwise P values for the primary end point were all >0.40.
Outcomes
Troponin levels after the procedure were elevated above the ULN in 60% of patients. The primary outcome (Troponin elevation >3×ULN) occurred in 33%, and MI range elevation of troponin (≥5×ULN) was found in 24% (Table 3). There were no differences between the groups in the incidence of positive troponin, regardless of the cutoff level that was used. There was no difference in the incidence of elevated creatine kinase levels above ULN between groups. The Bonferroni-adjusted pairwise P values for the primary end-point were all >0.40.

After the PCI, there was an increase in hsCRP compared with baseline, with no differences between the groups.

The incidence of AKI within 24 h was not significantly different between the groups.

Medical therapy was similar in all groups.

In a subanalysis of patients 65 years or younger (196 patients), the primary end-point occurred in 15 patients (21%) in the arm group, 18 patients (32%) in the thigh group, and 25 patient (36%) in the control group, P=0.13. There was a trend toward difference between the arm and the control subgroups (P=0.04).

The primary end-point occurred in 34.7% of the patients with unstable angina and 33.5% of the patients with stable angina, with no differences between groups. There was no statistical evidence that the effect of treatment varies across the 2 age groups (P for interaction=0.11), according to sex (P=0.11), or according to presence of unstable angina (P=0.94).

Adjustments were made for the following variables, which were found important in the single-predictor models: age, body mass index, contrast volume, stent length, use of rotational atherectomy, and history of dyslipidemia, diabetes mellitus, or previous MI. After adjustment in the multivariable model, use of rotational atherectomy, and history of dyslipidemia, diabetes mellitus, or previous MI were found important in the single-predictor models: age, and in fact higher compared with the CRISP stent study. However, angina in this group of patients may have induced ischemic conditioning. We did not find an interaction between the presence of unstable angina and the effect of RIPost. In the CRISP stent study, all patients received unfractionated heparin without glycoprotein IIb/IIIa inhibitors. We used more effective anticoagulants including bivalirudin and glycoprotein IIb/IIIa inhibitors, in accord with contemporary practice. More efficacious anticoagulant and antiplatelet therapy is important especially in the setting of PCI for unstable angina. A more effective anticoagulant may decrease troponin release after PCI and reduce differences between groups. However, the incidence of elevated troponin > ULN in our study was still high, and in fact higher compared with the CRISP stent study.

Our study extends the recent observation that applying RIPost 5 minutes after completion of PCI does not reduce the incidence of myocardial injury.20 However, it has been proposed that to achieve a protective effect, ischemic postconditioning needs to be initiated at the time of reperfusion.37 Therefore, in our study we applied RIPost at an earlier stage, when ischemia-reperfusion...
It is possible that the effect of postconditioning is different in this population. Potentially, RIPost reduces infarct size but does not eliminate PCI related myocardial injury or infarct, which was the outcome of our study. This is supported by the observation that postconditioning was more effective in patients with larger infarcts. However, in the CRISP stent study, the incidence of positive troponin was reduced as well. A few STEMI studies, including the recent Effects of Postconditioning on Myocardial Reperfusion in Patients With ST-Segment Elevation Myocardial Infarction (POST) trial, failed to demonstrate an effect of postconditioning. Taken together with the results of our study, the clinical value of ischemic conditioning should be revisited. RIPost has recently been reported to reduce PCI-related AKI in a randomized study of 225 patients. In that study, the mode of RIPost was cyclic inflations of the stent balloon, after stent deployment, to nominal pressures for 30 seconds. The investigators demonstrated a significant reduction in PCI-related AKI, using the same definition as used in the current study. The mechanisms behind this result remain obscure and our findings are in contradistinction to this, despite occlusion of arterial flow to a larger volume of metabolically active tissue in the current study. Similar to our findings, RIPre had no effect on kidney function during the first 24 hours after PCI in the CRISP stent study.

An inflammatory response is frequently observed after cardiac catheterization and PCI, and has been implicated in the pathogenesis of subsequent cardiovascular events. In an animal model, ischemic conditioning blunted the increase in CRP, induced by myocardial infarction, and was related to the degree of ischemia-reperfusion injury. In a small randomized study, ischemic conditioning induced during PCI for myocardial infarction was associated with reduction in hsCRP as well as a reduction in infarct size. In the current study, we observed an elevation in hsCRP after PCI, with no effect of RIPost on hsCRP or myocardial injury, whether applied to the thigh or the arm. Experimental evidence suggests that ischemic conditioning involves molecules that are released from cells during ischemia, an intracellular cascade of enzymes, mostly protein kinase and effectors such as the mitochondria or cytoskeleton. The interaction between the different signaling steps is important, as direct activation of a single step by a medication such as adenosine was not effective. Although it is thought that the effect of local and remote conditioning is similar, and that RIPre and RIPost exert a similar effect, the precise molecular mechanism behind each of these interventions remains to be established.

It has been suggested that ischemic conditioning is less effective in the elderly. Indeed, in our study, in patients <65 years, the incidence of the primary end-point was lower in the RIPost groups compared with the control group, with a trend toward differences between the arm and the control groups. It is possible that despite the requirement in our study of inflating the cuff to high pressure with no waveform on a pulse-oximeter on the occluded limb, the cuff pressure applied to the thigh was not sufficient to cause enough ischemia. This finding in a subgroup should be interpreted with caution.

In our experience, the inflation of the cuff on the thigh was more uncomfortable, compared with inflation of the cuff on the arm. With no difference in the primary outcome between the groups, and possibly even more effect in the arm group, it may be preferable to use the arm when inflation of the cuff is performed in future remote conditioning studies.

**Limitations**

This is a single center study. Although we tried to keep both patients and physicians blinded to the randomization, patients could become aware of their randomization once the blood pressure cuff was inflated. We tried to minimize patients’ awareness using sedation and analgesia, and by inflating the cuff in the control group to low pressure. We made an effort to keep the operator blinded by inflating the cuff under the drapes. Because randomization envelopes were opened toward the end of the procedure, all decisions such as the use of anticoagulation and glycoprotein IIb/IIIa inhibitors were made before opening of envelopes and were not affected by the randomization. All laboratory tests, including those used for the primary outcome, were analyzed in a blinded fashion.

The use of fentanyl potentially could have a cardioprotective effect and thus decrease intergroup differences. However, sedation was required to keep the patients comfortable during the prolonged blood pressure cuff inflations and was given in a low dose. Furthermore, use of sedation is common during cardiac procedures and, therefore, if remote conditioning is found to be effective, it should be applied in addition to the simple administration of low dose fentanyl.

When we began the study we used the fourth-generation Troponin T assay. During the course of the study, the hs Troponin T assay became the standard in our center. Therefore, we used accepted conversion cutoffs between the 2 assays.

The pathophysiology of ischemic injury during PCI and the clinical impact of a myocardial protection intervention are different compared with those that occur during STEMI. Therefore, our results do not exclude the possibility of a beneficial effect of RIPost in the STEMI population.

**Conclusions**

RIPost applied to the arm or thigh during nonurgent PCI did not reduce the incidence of periprocedural myocardial injury. The preferred mode of applying ischemic conditioning, number of cycles, and timing should be further explored.

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**Disclosures**

None.
References


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