Effects of pre-procedural remote ischaemic pre-conditioning on the outcomes of elective percutaneous coronary intervention. A systematic review and meta-analysis

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Abstract

Objectives: Trials of remote ischemic pre-conditioning (RIPC) have suggested this intervention reduces complications of percutaneous coronary intervention and coronary by-pass surgery. The aims of this work were to (i) conduct a systematic review and meta-analysis of the effects of RIPC on cardiac and renal damage in patients undertaking elective percutaneous coronary intervention (PCI); (ii) summarize the results in an evidence-based clinical context.

Methods: We conducted a systematic search of published randomized controlled trials of RIPC for elective PCI up until May 1st, 2015. Studies of peri- or post-ischemic conditioning or emergency PCI were excluded.

Results: Nine studies, totalling 1253 patients were included. Compared to control, RIPC groups exhibited reduced peri-procedural myocardial infarction (MI) Odds Ratio (OR) 0.72 (95% CI 0.54 to 0.97, p = 0.03); ST-segment deviation OR 0.42 (95% CI 0.28 to 0.63, p = 0.0001); major adverse cardiac events (MACE) OR 0.41 (95% CI 0.21 to 0.84, p = 0.01); and acute kidney injury (AKI) OR 0.47 (95% CI 0.26 to 0.86, p = 0.01), but not mortality OR 1.00 (95% CI 0.27 to 3.73, p = 1.00).

Conclusions: RIPC is likely to prevent major adverse cardiac and renal events in patients undertaking elective PCI.

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1. Introduction

Coronary artery disease (CAD) is associated with the development of atherosclerotic plaques in the coronary arteries. Percutaneous coronary intervention (PCI) is one of the major treatment options used to relieve CAD symptoms, prevent myocardial infarction and in the immediate treatment of myocardial infarction. Unfortunately re-opening of a previously partially or completely occluded coronary vessel exposes the myocardium to ischemia reperfusion injury.

Remote ischaemic pre-conditioning (RIPC) relates to short sequences of ischemia, usually 4–5 min, of repeated blood pressure cuff inflation and deflation on a limb. Short periods of ischemia trigger cellular signalling pathways that protect against a subsequent longer period of ischemia, such as during PCI. RIPC is one of the most effective techniques of protecting the heart against ischemia reperfusion injury. The RIPC process usually involves 3–4 cycles of repeated inflation-deflation lasting about 25–30 min [1]. RIPC has become increasingly attractive because it is relatively simple to administer and is non-invasive. Moreover, RIPC can be administered during natural waiting periods as patients enter the catheter lab for PCI. RIPC has been used in both upper and lower limbs and offers cardio-protection for those undergoing percutaneous coronary revascularization [2]. RIPC has also been found to reduce acute kidney injury in those exposed to contrast media [3] and infarct size by administering RIPC during transport to the medical centre prior to cardiac surgery [4]. More recent work has examined the cumulative effects of repeated RIPC treatments to manage blood pressure [5], improve endothelial function and blood flow [6].

The effects of RIPC may extend beyond the tissues exposed to cuff occlusion, with recent reports suggesting a neuroprotective effect that improved tolerance to cerebral ischemia [7]. RIPC induced neuroprotection by attenuating adenosine 5'-monophosphate-activated protein kinase [8]. RIPC may therefore improve impaired cognitive function in those with known cardiovascular or metabolic disease [9].

Despite several studies showing statistically significant reductions in surrogate measures of infarct size [10], some clinicians remain ambivalent about the clinical significance of these findings [11]. Modelling of creatine kinase [12] and tumour necrosis factor alpha [13] have been used to quantify infarct size in those with ST-elevated myocardial...
infarcts. Cardiac biomarkers are used as a cardiac risk stratification tool [14].

Recent meta-analyses examined the benefits of IPC for people under- 
taking PCI, but this work only assessed surrogate measures of myo-
cardial infarct size and acute kidney injury and the latter of these 
analyses also considered non-elective PCI [15,16]. There are many 
other relevant RIPC outcome measures that have been reported for 
which data pooling has not yet been conducted. Other analyses com-
bined data from studies of pre- and post-conditioning, but between 
study heterogeneity was high indicating data pooling of these two 
slightly different interventions may not be justified [17,18]. Despite 
these previous pooled analyses the clinical significance of RIPC 
remains in doubt as the findings have not been compared with published thresh-
olds of clinical significance [19,20]. We have therefore taken the ap-
proach of limiting our analysis to remote-preconditioning only in 
those undertaking elective percutaneous intervention in order to mini-
mize the confounding effects of varied study inclusion criteria and in the 
type of preconditioning stimulus.

The aims of this work were to; (i) examine the effects of RIPC on a 
range of major adverse cardiac events (MACE) and markers of myo-
cardial and renal damage in patients undertaking elective PCI; (ii) relate 
these findings to established thresholds of clinical significance and pro-
vide an evidence based context for RIPC use.

2. Materials & methods

2.1. Search strategy

To identify potential studies systematic searches were carried out 
using the following databases: EMBASE, PubMed, Web of Science and 
the Cochrane Central Registry of Controlled Trials (CENTRAL). The 
search was supplemented by scanning the reference lists of eligible 
papers. The search strategy included the key concepts of “remote ischemic 
preconditioning” AND “percutaneous coronary intervention” (see supplementary Fig. S1). All identified papers were assessed indepen-
dently by two reviewers. A third reviewer was consulted to resolve dis-
putes. Searches of published papers were conducted up until May 1st, 
2015.

2.2. Types of studies to be included

Only randomized controlled trials (RCTs) of RIPC in patients under-
going elective PCI were included. There were no language restrictions. 
Animal studies, review papers and non-randomized controlled trials 
were excluded. Studies that do not have any of the desired outcome 
measures or participants who were treated by other surgical modalities 
such as coronary artery bypass grafting were excluded. Incomplete data, 
or data from an already included study, were excluded. Studies that in-
cluded interventions other than RIPC were excluded.

2.3. Participants/population

This meta-analysis analysed RCTs of both male and female adult 
(≥18 years) patients with coronary artery disease who were undergoing 
elective, but not emergency, PCI. Other treatment modalities and inter-
ventions for coronary artery disease such as RIPC in coronary artery by-
pass grafting were excluded.

2.4. Intervention(s), exposure(s)

This meta-analysis considered all RCTs where patients with stable 
angina or acute coronary syndrome being treated with PCI were ex-
posed to RIPC. More specifically all RCTs where the intervention of 
expanding a blood pressure cuff or applying a medical tourniquet in a 
remote limb was carried out before PCI.

2.5. Comparator(s)/control

The meta-analysis utilised RCT’s that compare RIPC during percuta-
neous coronary intervention with a usual care control group receiving 
sham or no RIPC during percutaneous coronary intervention.

2.6. Search Results

Our initial search found 486 articles. Of these 441 were excluded 
based upon title and abstract. Nineteen studies were excluded as they 
were not RCTs. Nine studies were excluded because they were trials of 
post-conditioning, one study was excluded because it was peri-condi-
tioning and 7 studies were excluded because they were studies of emergen-
cy PCI (see supplementary Fig. S2). Nine studies [2,21–26,28,29] 
were included in our analysis.

2.7. Outcome(s)

The primary outcomes analysed were:

1. Peri-procedural myocardial infarction (MI)
   (This was defined differently in the different trials. Ahmed et al. [21] 
   and Xu et al. [22] defined MI as an increase in cTnT as greater than 
   three times the 99th percentile URL, whilst Hoole et al. [23] used 
   the same parameters for cTnI. Ghaemian et al. [24] and Prasad et al. 
   [25] considered MI as cTnT > 0.03 ng/ml. Liu et al. [2] and Prasad et al. 
   [25] did not report how they defined MI. Luo et al. [26] defined MI as 
   cTnI > 0.2 mg/ml).
2. ST segment deviation
   (This was defined as either an elevation or depression of the ST seg-
   ment on an ECG of > 1 mm).
3. Incidence of post-PCI major adverse cardiac events (MACE) at 
   3 months
   (Ghaemian et al. [24] defined this as hospitalization for acute coro-
   nary syndrome, MI, or death due to MI. Hoole et al. [23] defined this 
   as hospital admissions with unstable angina/acute coronary syn-
   drome, MI, heart failure, and stroke/transient ischemic attack. Liu et 
   al. [2] defined this as cardiac death, hospital admissions with unsta-
   ble angina/acute coronary syndrome, MI, heart failure and stroke/ 
   transient ischemic attack.)
4. Mortality
5. Acute kidney injury
   (Defined as an increase in serum creatinine of ≥25% above baseline).
6. C-reactive protein
7. Troponin T
   (Measured at 16 h post PCI in Ahmed et al. [21]. Ghaemian et al. [24] 
   measured this at 12 h and 24 h post PCI with the 24 h measurement 
   used in this study. Prasad et al. [25] measured this at 8, 16 and 24 h 
   post PCI with the 24 h measurement used in this study.)

2.8. Risk of bias (quality) assessment

The PEDro scale was used to assess study quality and reporting [27].

2.9. Strategy for data synthesis

Odds ratios will be calculated for dichotomous data. Meta-analyses 
will be completed for continuous data by calculating the mean differ-
ence between intervention and control groups from post-intervention 
data only. It is an accepted practice to only use post-intervention data 
for meta-analysis, but this method assumes that random allocation of 
participants always creates intervention groups matched at baseline 
for age, disease severity. In the case of elective PCI this will be true as 
negligible levels of creatine kinase etc. would be expected at baseline 
prior to elective PCI, hence we have excluded emergency PCI studies. 
All analyses were conducted using Revman 5.0 (Nordic Cochrane Centre 
Denmark). A fixed effects inverse variance model was used unless
heterogeneity was >75%, then a random effects model was used. Heterogeneity was quantified using the Cochrane Q test. We used a 5% level of significance and 95% confidence intervals; figures were produced using Revman 5.3.

3. Results

The nine studies [2,21–26,28,29] included in the analyses had an aggregate of 1253 participants, 630 of which received RIPC and 623 were control/sham group participants. Table 1 summarizes the characteristics of the included studies. Table S1 lists the excluded RCTs and reasons for exclusion. Seven studies used a sham control group, as opposed to usual care. Only one study utilized the lower limb for RIPC. The RIPC protocols were very similar in terms of periods of cuff occlusion and periods of reperfusion.

### 3.1. Peri-procedural myocardial infarction and ST-segment deviation

Seven studies reported the incidence of peri-procedural myocardial infarction (MI), the odds ratio for the pooled analysis of RIPC versus control group was 0.72 (95% CI 0.54 to 0.97, \(p = 0.03\)) suggesting a 28% reduced risk of MI in patients receiving RIPC (see Fig. 1). These findings were supported by reductions in ST-segment deviation, as the odds ratio for the pooled analysis of RIPC versus control group was OR 0.42 (95% CI 0.28 to 0.63, \(p < 0.0001\)) suggesting a 58% reduction in prevalence of ST-segment deviation in patients receiving RIPC (see Fig. 2).

### 3.2. Major adverse coronary events at 6 months

Three studies reported the incidence of major adverse cardiac events (MACE), the odds ratio for the pooled analysis of RIPC versus control

### Table 1

Characteristics of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>RIPC protocol</th>
<th>Comparator</th>
<th>N RIPC (control)</th>
<th>Population</th>
<th>Age RIPC (control)</th>
<th>Male % RIPC (control)</th>
<th>All outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmed et al. 2013</td>
<td>Upper limb 3 × 5 min &amp; 5 min</td>
<td>Sham RIPC (deflated cuff)</td>
<td>77 (72)</td>
<td>Elective</td>
<td>54.6 ± 7.8 (53.5 ± 8.8)</td>
<td>87 (86)</td>
<td>CK-MB, Troponin T</td>
</tr>
<tr>
<td>Egypt</td>
<td>reperfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CRP, Procedural MI</td>
</tr>
<tr>
<td>Er et al. 2012</td>
<td>Upper limb 4 × 5 min &amp; 5 min</td>
<td>Sham RIPC (10 mm Hg)</td>
<td>50 (50)</td>
<td>Elective</td>
<td>73.2 ± 9.1 (72.7 ± 11.4)</td>
<td>68 (74)</td>
<td>Acute kidney injury,</td>
</tr>
<tr>
<td>Germany</td>
<td>reperfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Creatinine, Cystatin C</td>
</tr>
<tr>
<td>Ghaemian et al. 2012</td>
<td>Lower limb 2 × 5 min &amp; 5 min</td>
<td>Sham RIPC (deflated cuff)</td>
<td>40 (40)</td>
<td>Elective</td>
<td>58.8 ± 9.8 (61 ± 9.8)</td>
<td>40 (55)</td>
<td>Urinary NGAL, Mortality,</td>
</tr>
<tr>
<td>Iran</td>
<td>reperfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Procedural MI, Intra-procedural</td>
</tr>
<tr>
<td>Hoole et al. 2009</td>
<td>Upper limb 3 × 5min &amp; 5 min</td>
<td>Sham RIPC (deflated cuff)</td>
<td>104 (98)</td>
<td>Elective</td>
<td>63.2 (61.8)</td>
<td>81 (76)</td>
<td>Mortality, ST-segment deviation,</td>
</tr>
<tr>
<td>UK</td>
<td>reperfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MACE</td>
</tr>
<tr>
<td>Iliodromitis et al. 2006</td>
<td>Upper limb 3 × 5min &amp; 5 min</td>
<td>Sham RIPC (deflated cuff)</td>
<td>20 (21)</td>
<td>Elective</td>
<td>61 ± 10 (62 ± 8)</td>
<td>Not given</td>
<td>CK, CK-MB, Troponin I</td>
</tr>
<tr>
<td>Greece</td>
<td>reperfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CRP</td>
</tr>
<tr>
<td>Liu et al. 2014</td>
<td>Upper limb 3 × 5 min &amp; 5 min</td>
<td>Sham RIPC (deflated cuff)</td>
<td>98 (102)</td>
<td>Elective</td>
<td>59.9 ± 16.2 (56.3 ± 14.3)</td>
<td>48 (61)</td>
<td>CK, CRP, Troponin I,</td>
</tr>
<tr>
<td>China</td>
<td>reperfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intra-procedural</td>
</tr>
<tr>
<td>Luo et al. 2013</td>
<td>Upper limb 3 × 5min &amp; 5 min</td>
<td>No RIPC</td>
<td>101 (104)</td>
<td>Elective</td>
<td>59.2 ± 10.3 (59.3 ± 9.5)</td>
<td>77 (75)</td>
<td>Mortality, ST-segment deviation,</td>
</tr>
<tr>
<td>China</td>
<td>reperfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MACE, Procedural MI,</td>
</tr>
<tr>
<td>Prasad et al. 2013</td>
<td>Upper limb 3 × 3 min &amp; 3 min</td>
<td>Sham RIPC (10 mm Hg)</td>
<td>47 (48)</td>
<td>Elective</td>
<td>67.2 ± 11.4 (65.1 ± 11)</td>
<td>91 (75)</td>
<td>Creatinine, GFR</td>
</tr>
<tr>
<td>USA</td>
<td>reperfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Troponin T, CK-MB,</td>
</tr>
<tr>
<td>Xu et al. 2014</td>
<td>Upper limb 3 × 5 min &amp; 5 min</td>
<td>No RIPC</td>
<td>102 (98)</td>
<td>Elective</td>
<td>69.1 ± 3.8 (68.9 ± 2.9)</td>
<td>66 (70)</td>
<td>Mortality, Troponin I,</td>
</tr>
<tr>
<td>China</td>
<td>reperfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CRP, GFR, Procedural MI</td>
</tr>
</tbody>
</table>

CK – creatine kinase; CRP – C-reactive protein; EPC – endothelial progenitor cells; GFR – glomerular filtration rate; MACE – major adverse coronary events; MI – myocardial infarction; PCI – percutaneous coronary intervention; RIPC – remote ischaemic pre-conditioning; Urinary NGAL – urinary neutrophil gelatinase-associated lipocalin.

CK – creatine kinase; CRP – C-reactive protein; EPC – endothelial progenitor cells; GFR – glomerular filtration rate; MACE – major adverse coronary events; MI – myocardial infarction; PCI – percutaneous coronary intervention; RIPC – remote ischaemic pre-conditioning; Urinary NGAL – urinary neutrophil gelatinase-associated lipocalin.
group was OR 0.41 (95% CI 0.21 to 0.84, \( p = 0.01 \)) suggesting a 59% reduced risk of MACE in patients receiving RIPC (see Fig. 3).

### 3.3. Mortality

Five studies reported the mortality incidence, the odds ratio for the pooled analysis of RIPC versus control group was 1.00 (95% CI 0.27 to 3.73, \( p = 1.00 \)) suggesting no significantly reduced risk of mortality in patients receiving RIPC (see Fig. 4).

### 3.4. Acute kidney injury

Four studies reported the incidence of acute kidney injury, the odds ratio for the pooled analysis of RIPC versus control group was 0.47 (95% CI 0.26 to 0.86, \( p = 0.01 \)) suggesting a 53% reduced risk of acute kidney injury in patients receiving RIPC. (See Fig. 5.)

### 3.5. Biomarkers of cardiovascular damage and inflammation

Troponin-T and C-reactive protein were not significantly different between RIPC and control groups (supplementary Figs. S3 and S4, respectively).

### 3.6. Assessment of study quality

We utilised the Physiotherapy Evidence database (PEDro) scale to evaluate study quality. Median PEDro score was 7 with 1 study scoring 9, 4 studies scoring 7, 3 studies scored 6 and 1 study scored 5 (Supplementary Table S2).

### 3.7. Publication bias and study heterogeneity

We assessed publication bias by Egger Plots. There was minimal evidence of bias. Study heterogeneity was assessed by Cochrane Q test, and was low in all cases except MACE, where it was moderate (51%).

### 4. Discussion

Our meta-analysis is the first to examine the benefits of remote ischemic pre-conditioning (RIPC) for people undertaking elective percutaneous coronary intervention for outcome measures other than myocardial infarct size and acute kidney injury. We found RIPC significantly reduced the risk of peri-procedural infarct, ST-segment deviation, major adverse cardiac events (MACE) and acute kidney injury. These
findings provide evidence of a wider scope of benefits from RIPC than had been reported previously.

One of the dilemmas faced by patients confronted with the decision to undergo non-emergency (elective) PCI is to weigh up the potential risks of PCI against the likely stabilising benefits. Our work has shown that RIPC provides a likely mitigating effect for a variety of complications to elective PCI. Recent work has shown that PCI does not reduce post-intervention mortality risk as much as cardiac by-pass grafting (CABG), even after adjusting for confounders [30]. Risk of myocardial infarction (MI) during PCI has been estimated using cardiac biomarkers as about 8.6% (95% confidence intervals: 5.8% to 12.2%), with symptomatic ischemia in about 25% of MI patients [31]. Taking an evidence-based approach, our analyses suggest that the risk of MI could be reduced by 28% from 8.6% to 6.2%. These data imply that the number of patients needed to be treated to prevent 1 MI is \( \approx 4 \). Prevalence data for MACE suggested 12% during PCI [32]. Our analyses suggest RIPC could reduce MACE during PCI by 59% to 71%.

While our analyses did not suggest a significantly reduced risk of mortality in patients receiving elective RIPC, this may be due to the small number of deaths reported in the included studies. In the RIPC groups 5 deaths were recorded, while in the sham/control groups 9 deaths were recorded. Intuitively, we are able to deduce two things from these data: First, the number of published deaths are too few currently for analyses to provide statistical significance. Second, the number of deaths in the non-intervention groups is almost twice that of the RIPC groups, this could be considered clinically significant even if it is not statistically significant.

Incidence of acute kidney injury (AKI) during PCI ranges from 6 to 26%, but depends on haemoglobin levels [33]. Using the reported conservative prevalence estimate of 6%, our analyses suggest RIPC could reduce AKI during PCI by 53% to 3.2%.

RIPC is inexpensive, not time-consuming and easily administered by staff with minimal training. In addition to the utilization of RIPC for PCI or CABG, several works have recently reported the use of repeated sessions of RIPC over 1–8 week periods, in order to manage blood pressure and improve blood flow [5,6]. We now await results of further trials that are in progress.

The primary limitation of this work is that relatively few adverse events exist in randomized, controlled trials reported in the published literature. A secondary limitation is that studies have used marginal techniques to establish if myocardial injury has occurred, rather than established techniques like cardiac MRI or repeated Troponins, or combinations of two or more methods.

5. Conclusions

Remote ischemic pre-conditioning (RIPC) provides clinically meaningful reductions in major adverse cardiac and renal events for people undertaking elective percutaneous coronary intervention. These findings provide evidence that only a small number of patients (< 5) are required to prevent one adverse event, RIPC is therefore probably under-utilized.

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None.

Conflicts of interest

None.

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References


Fig. 5. Acute kidney injury.


