Remote ischaemic pre-conditioning does not affect clinical outcomes following coronary Artery bypass grafting. A systematic review and meta-analysis

King, N::0000-0001-6989-5760

http://hdl.handle.net/10026.1/11115

10.1016/j ctrsc.2016.03.001
Clinical Trials and Regulatory Science in Cardiology
Elsevier BV

All content in PEARL is protected by copyright law. Author manuscripts are made available in accordance with publisher policies. Please cite only the published version using the details provided on the item record or document. In the absence of an open licence (e.g. Creative Commons), permissions for further reuse of content should be sought from the publisher or author.
Remote ischaemic pre-conditioning does not affect clinical outcomes following coronary Artery bypass grafting. A systematic review and meta-analysis

Nicola King a,⁎,1, Gudrun Dieberg b,1, Neil A. Smart b,1

a School of Biomedical and Healthcare Sciences, Plymouth University Peninsula Schools of Medicine and Dentistry, University of Plymouth, Plymouth PL4 8AA, UK
b School of Science and Technology, University of New England, Armidale, NSW 2350, Australia

1. Introduction

Remote ischaemic pre-conditioning (RIPC) is a novel prophylactic treatment during which brief periods of ischaemia in a remote vascular bed provides protection against a subsequent longer bout of ischaemia in the heart. Initially demonstrated in a separate cardiovascular bed [1], it was later shown that protection could also be achieved by preconditioning in a remote organ [2] or in a remote limb [3]. Transfer of the signalling stimulus to the heart is thought to involve the somatosensory system, the spinal cord, the autonomous nervous system and humoral elements. Candidates for the humoral signal include nitric oxide, MicroRNA-144, and stromal derived factor-1α [4]. A further complex signal transduction occurs in the heart possibly involving the reperfusion injury salvage kinase (RISK) pathway [4]. Since the early animal studies [1–3], RIPC has been shown to reduce myocardial injury in patients undergoing both elective [5] and primary percutaneous interven-

© 2016 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Table 1  
Characteristics of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>RIPO protocol</th>
<th>Comparator</th>
<th>N RIPO (control)</th>
<th>Population</th>
<th>Age RIPO (control)</th>
<th>Male % RIPO (control)</th>
<th>All outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmad et al., 2014 [17]</td>
<td>Upper limb 3 × 5 min &amp; 5 min reperfusion</td>
<td>Sham (Cuff deflated)</td>
<td>35 (32)</td>
<td>Triple vessel CABG</td>
<td>54.46 ± 8.83 (55.16 ± 10.95)</td>
<td>77 (78)</td>
<td>CK-MB Creatinine</td>
</tr>
<tr>
<td>Pakistan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IABP Inotropic support</td>
</tr>
<tr>
<td>Alien et al., 2010 [23]</td>
<td>Upper limb 3 × 5 min &amp; 5 min reperfusion</td>
<td>Sham (Cuff deflated)</td>
<td>50 (50)</td>
<td>Double/triple vessel CABG</td>
<td>56.02 ± 8.24 (51.6 ± 9.58)</td>
<td>94 (84)</td>
<td>CK-MB IABP Inotropic support</td>
</tr>
<tr>
<td>Pakistan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AF</td>
</tr>
<tr>
<td>Candidio et al., 2015 [7]</td>
<td>Upper and lower limb 3 × 5 min &amp; 5 min reperfusion</td>
<td>Sham (Cuff deflated)</td>
<td>89 (89)</td>
<td>Single-quadruple vessel CABG and/or valve surgery</td>
<td>65 ± 10 (66 ± 10)</td>
<td>81 (75)</td>
<td>Creatinine hsTnT</td>
</tr>
<tr>
<td>UK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ICU stay Inotropic support</td>
</tr>
<tr>
<td>Candidio et al., 2015 [7]</td>
<td>Upper and lower limb 3 × 5 min &amp; 5 min reperfusion</td>
<td>Sham (Cuff deflated)</td>
<td>89 (89)</td>
<td>Single-quadruple vessel CABG and/or valve surgery</td>
<td>65 ± 10 (66 ± 10)</td>
<td>81 (75)</td>
<td>Creatinine hsTnT</td>
</tr>
<tr>
<td>UK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ICU stay Inotropic support</td>
</tr>
<tr>
<td>Gedik et al., 2014 [18]</td>
<td>Upper limb 3 × 5 min &amp; 5 min reperfusion</td>
<td>Sham (Cuff deflated)</td>
<td>10 (10)</td>
<td>Double/triple vessel CABG</td>
<td>62.6 ± 3.4 (65.5 ± 4.2)</td>
<td>90 (80)</td>
<td>Autophagy markers</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cTnI</td>
</tr>
<tr>
<td>Hauenloy et al., 2007 [24]</td>
<td>Upper limb 3 × 5 min &amp; 5 min reperfusion</td>
<td>Sham (Cuff deflated)</td>
<td>27 (30)</td>
<td>Single-quadruple vessel CABG</td>
<td>67 ± 11.8 (67 ± 9.4)</td>
<td>78 (80)</td>
<td>AKF</td>
</tr>
<tr>
<td>UK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute kidney injury</td>
</tr>
<tr>
<td>Hauenloy et al., 2015 [21]</td>
<td>Upper limb 4 × 5 min &amp; 5 min reperfusion</td>
<td>Sham (Cuff deflated)</td>
<td>801 (811)</td>
<td>CABG and valve surgery</td>
<td>76.1 ± 6.1 (76.3 ± 7)</td>
<td>70.4 (72.7)</td>
<td>MACE</td>
</tr>
<tr>
<td>UK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mortality Autophagy markers</td>
</tr>
<tr>
<td>Holmberg et al., 2014 [19]</td>
<td>Upper limb 3 × 5 min &amp; 5 min reperfusion</td>
<td>No RIPC</td>
<td>20 (21)</td>
<td>CABG and valve surgery</td>
<td>68 ± 11 (72 ± 9)</td>
<td>75 (67)</td>
<td>cTnI</td>
</tr>
<tr>
<td>Denmark</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inotropic support</td>
</tr>
<tr>
<td>Karuppaasamy et al., 2011 [25]</td>
<td>Upper limb 3 × 5 min &amp; 5 min reperfusion</td>
<td>Sham (Cuff deflated)</td>
<td>27 (27)</td>
<td>Double-quintuple vessel CABG</td>
<td>66.9 ± 11.2 (67.3 ± 10.3)</td>
<td>81 (85)</td>
<td>MACE</td>
</tr>
<tr>
<td>UK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mortality AKF  BNP cTnI</td>
</tr>
<tr>
<td>Kottenberg et al., 2012 [26]</td>
<td>Isoflurane anaesthetic</td>
<td>No RIPC</td>
<td>20 (19)</td>
<td>Triple vessel CABG</td>
<td>64 ± 9 (65 ± 9)</td>
<td>95 (84)</td>
<td>Inotropic support</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cTnI</td>
</tr>
<tr>
<td>Kottenberg et al., 2012 [26]</td>
<td>Isoflurane anaesthetic</td>
<td>No RIPC</td>
<td>14 (19)</td>
<td>Triple vessel CABG</td>
<td>65 ± 15 (64 ± 12)</td>
<td>64 (84)</td>
<td>cTnI</td>
</tr>
<tr>
<td>Propofol anaesthetic</td>
<td>Upper limb 3 × 5 min &amp; 5 min reperfusion</td>
<td>No RIPC</td>
<td>40 (40)</td>
<td>Mean 2.7 vessel CABG</td>
<td>56.5 ± 8.7 (58.1 ± 6.4)</td>
<td>90 (93)</td>
<td>cTnI</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CK-MB IABP ICU stay Inotropic support</td>
</tr>
<tr>
<td>Limonovrotov et al., 2012 [27]</td>
<td>Upper limb 3 × 5 min &amp; 5 min reperfusion</td>
<td>Sham (Cuff deflated)</td>
<td>27 (28)</td>
<td>Mean 3.6 vessel CABG</td>
<td>59 ± 7 (62 ± 10)</td>
<td>96 (86)</td>
<td>cTnI</td>
</tr>
<tr>
<td>Russia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Creatinine</td>
</tr>
<tr>
<td>Lucchinietti et al., 2012 [28]</td>
<td>Lower limb 4 × 5 min &amp; 5 min reperfusion</td>
<td>Sham (Cuff deflated)</td>
<td>27 (28)</td>
<td>Mean 3.6 vessel CABG</td>
<td>59 ± 7 (62 ± 10)</td>
<td>96 (86)</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Canada</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hsCRP</td>
</tr>
<tr>
<td>Meybohm et al., 2013 [29]</td>
<td>Upper limb 4 × 5 min &amp; 5 min reperfusion</td>
<td>Sham (Cuff inflated to 20 mm Hg)</td>
<td>90 (90)</td>
<td>CABG and valve surgery</td>
<td>70 (68)</td>
<td>77 (86)</td>
<td>NT-proBNP S100</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AF cTnI</td>
</tr>
<tr>
<td>Meybohm et al., 2015 [22]</td>
<td>Upper limb 4 × 5 min &amp; 5 min reperfusion</td>
<td>Sham (Dummy arm)</td>
<td>692 (693)</td>
<td>CABG and valve surgery</td>
<td>65.8 ± 10.7 (66 ± 10)</td>
<td>73.4 (75)</td>
<td>AF cTnI</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AKF</td>
</tr>
<tr>
<td>Rahman et al., 2010 [30]</td>
<td>Upper limb 3 × 5 min &amp; 5 min reperfusion</td>
<td>No RIPC</td>
<td>80 (82)</td>
<td>Triple to quadruple vessel CABG</td>
<td>63 (65)</td>
<td>89 (88)</td>
<td>AF cTnI</td>
</tr>
<tr>
<td>Pakistan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mortality MI Stroke</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AF cTnI</td>
</tr>
</tbody>
</table>

N. King et al. / Clinical Trials and Regulatory Science in Cardiology 17 (2016) 1–8
2. 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 studies. The search strategy included the key concepts of “remote ischaemic preconditioning” and “coronary artery bypass grafting”. All identified papers were assessed independently by two reviewers. A third reviewer was consulted to resolve disputes. Searches of published papers were conducted up until November 1st, 2015.

![Fig. 1. Post discharge mortality.](image-url)
2.2. Types of studies to be included

Only randomized controlled trials (RCTs) of RIPC in patients undergoing coronary artery bypass grafting with/without valve surgery 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 modalities such as percutaneous coronary intervention were excluded. Authors were contacted to provide missing data or to clarify if data was duplicated in multiple publications. Incomplete data, or data from an already included study, were excluded. Studies that included 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 coronary artery bypass grafting with/without valve surgery. Other treatment modalities and interventions for coronary artery disease such as RIPC in percutaneous coronary intervention 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 coronary artery bypass grafting with/without valve surgery were exposed 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 coronary artery bypass grafting.

2.5. Comparator(s)/control

The meta-analysis utilised RCTs that compare RIPC during coronary artery bypass grafting with/without valve surgery with a usual care control group receiving sham or no RIPC during coronary artery bypass grafting with/without valve surgery.

2.6. Search results

Our initial search found 74 articles. Of these 7 studies were excluded on the basis of title and abstract. Forty two studies were excluded as they were not RCTs. Of these RCTs we excluded 7 studies: 2 studies included post-conditioning; 2 studies concentrated on STAT5; 1 study each concentrated on kinin receptor expression in neutrophils, on glycolysis, or on nitric oxide synthetase respectively (see supplementary Table S1). Eighteen studies were included in our analysis [7,17–33].

2.7. Outcome(s)

The primary outcomes analysed were:

1. Mortality.
2. Hospital stay.
3. ICU stay.
4. Inotrope usage.
5. New onset atrial fibrillation.
6. Cardiac troponins (cTnT and cTnl. Area under the curve).
7. Serum creatinine.

2.8. Risk of bias (quality) assessment

The JADAD scale was used to assess study quality and reporting [34].

2.9. Strategy for data synthesis

Odds ratios were calculated for dichotomous data. Mean differences were calculated for continuous data. Meta-analyses were completed for continuous data by calculating the mean difference between intervention and control groups from post-intervention data only. It is an accepted practice to 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. 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 [33]. We used a 5% level of significance and 95% confidence intervals; figures were produced using Revman 5.3.

3. Results

The eighteen studies included in the analyses had an aggregate of 4551 participants, 2267 of which received RIPC and 2283 were control/sham group participants. Table 1 summarizes the characteristics of the included studies. Supplementary Table S1 lists the excluded RCTs and reasons for exclusion. Fifteen studies used a sham control group, as opposed to usual care. Only two studies 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. Long term postoperative outcomes

Eight studies reported post discharge mortality. The odds ratio (OR) for the pooled analysis was 1.27 (95% confidence interval [CI] 0.87 to 1.86, p = 0.22), see Fig. 1.
3.2. Short term postoperative outcomes — length of hospital and ICU stay (days)

Six studies reported the length of hospital stay in days. The MD for the pooled analysis was 0.18 (95% CI −0.30 to 0.66, p = 0.47) (see Fig. 2). Seven studies reported the length of ICU stay in days. The MD for the pooled analysis was −0.02 (95% CI −0.12 to 0.07, p = 0.61) (see Fig. 3).

3.3. Immediate postoperative outcomes — inotrope usage and dysrhythmia

Six studies reported the use of inotropes to support patients, the OR for the pooled analysis was 1.27 (95% CI 0.84 to 1.91, p = 0.25) (see Fig. 4). Eight studies reported the incidence of new onset atrial fibrillation. The OR for the pooled analysis was 0.82 (95% CI 0.67 to 1.01, p = 0.06), see Fig. 5.

3.4. Biomarkers — troponin release and serum creatinine

Nine studies reported the area under the curve for troponin release after surgery. The MD for the pooled analysis was −3.72 (95% CI −3.92 to −3.53, p < 0.00001) (see Fig. 6). Five studies (six intervention groups) reported the serum creatinine concentration, the MD for the pooled analysis was 0.00 (95% CI −0.07 to 0.07, p = 0.97) (see Fig. 7).

4. Discussion

Our meta-analysis is the first to include the results of two large scale multi-centre trials investigating the role of RIPC in CABG with/without valve surgery. It is also the first to investigate longer term outcomes such as post discharge mortality. The results showed that troponin release is significantly reduced by RIPC, which is in agreement with other meta-analyses in this field [12–15]. Perhaps more pertinently, indicators of clinical outcome such as mortality, ICU and hospital stay, inotropic usage and new onset atrial fibrillation were unaltered by RIPC. This suggests that whilst RIPC does no harm it does not offer additional cardioprotective effects above and beyond that already provided by cardioplegia and volatile anaesthetics.

Our results showed that RIPC reduced troponin release as indicated by the area under the curve. Earlier studies that only concentrated on biomarker release also showed that RIPC reduced biomarker release [11,13–15]. Like the current study, when data from several studies was pooled in these earlier works, high heterogeneity was present [11,15]. In spite of this we considered this to be justified as repeated troponins may be a more accurate method than evaluating biomarkers at a single time point. Our work is also consistent with that of Deng et al. [16].

Our results also show that the incidence of postoperative atrial fibrillation was not reduced with RIPC. Femi et al. [36] investigated the risk of 1 year mortality, myocardial infarction (MI) and stroke in patients receiving CABG at The Cleveland Clinic. They found that there was a 3.7% increased risk of death (Hazard Ratio [HR] 1.89, 95% CI 1.42–2.53, p < 0.001) following postoperative atrial fibrillation [36]. Risk of MI and stroke were unaffected. One of the studies investigated here determined death at one year [32]. In that study RIPC reduced the incidence of one year mortality from 6.9% in control to 1.9% (HR 0.27, 95% CI 0.08–0.98, p = 0.046) [30].

Our work expands on that of Deng et al. [16]. We have also investigated the important clinical outcome of inotrope use, although there was no significant difference between the control and RIPC groups. Where our work is consistent with Deng et al. [16], is the findings that neither ICU nor hospital stay were shortened by RIPC.

Acute kidney injury is a known complication of revascularisation, with a recent study reporting a 2–3 times higher odds ratio for CABG compared to percutaneous coronary intervention [35]. We however found no differences in the serum creatinine between the control and RIPC groups. Unfortunately parameters such as urine volume and glomerular filtration rate were not measured in the studies. This prevented us from calculating the important parameter of creatinine clearance. Notwithstanding this, our work does support the meta-analysis by Deng et al. [16] who also found the incidence of acute kidney injury to be no different between control and RIPC groups.

4.1. Study limitations

RIPC did not affect post discharge mortality. However one limitation of the current study was the different reporting periods used. In one study where mortality was measured at 30 days, there was no difference [31]. However as the reporting time increased so did the mortality of the patients in the control group. Thus when mortality was measured at 6 weeks, five control patients had died compared to none in the RIPC group [7]. Then when mortality was measured at one year 3 patients in the RIPC group had died compared to 11 patients in the control group [32]. This suggests that more studies using a uniform reporting period are required.

5. Conclusions

Remote ischaemic preconditioning prior to CABG with/without valve surgery causes no harm but does not improve clinical outcomes.
References


**Glossary**

- **CABG**: coronary artery bypass grafting
- **CI**: confidence interval
- **HR**: hazard ratio
- **ICU**: intensive care unit
- **MD**: mean difference
- **MI**: myocardial infarction
- **MRI**: magnetic resonance imaging
- **OR**: odds ratio
- **RCT**: randomised controlled trial
- **RIPC**: remote ischaemic pre-conditioning