TITLE: Remote Ischemic Conditioning: A Review of the Clinical Effectiveness

DATE: 7 May 2010

CONTEXT AND POLICY ISSUES:

In 1986, it was discovered that brief episodes of non-lethal ischemia applied locally could render the heart resistant to a later, more prolonged period of ischemia.1 This implied that the heart maintained a pre-conditioned phenotype (cardiac memory) even after the removal of the stimulus.1,2 In experimental models (performed in young, healthy animals), ischemic pre-conditioning was shown to reduce infarct size by as much as 80%.2 Pre-conditioning was also shown to confer other benefits, for example reducing ventricular arrhythmias.1,3

The benefits of pre-conditioning are not confined to the myocardium. Animals studies have shown that brief episodes of non-lethal ischemia applied in any peripheral site (for example kidney, bowel, or skeletal muscle) induces protection against a more prolonged and lethal ischemia that may occur anywhere in the body, hence the term remote pre-conditioning or pre-conditioning at a distance.1,3,4

Again in animal studies, applying brief intermittent ischemia was shown to provide significant protection during an evolving myocardial infarction, before cardiac reperfusion resumes (per-conditioning).4 It was also shown that the heart could be protected from reperfusion injury by giving brief episodes of ischemia during the early reperfusion period of a pronounced ischemic insult (post-conditioning).4,5

Thus, depending on the timing of the application of the stimulus, conditioning may be classified as pre-, per-, or post-conditioning.4 Clinically, a pre-conditioning intervention may be used to protect against ischemia-reperfusion injury in patients undergoing a cardiac intervention or surgery1,4 Per- and post-conditioning interventions may be given to patients experiencing a myocardial infarction.4 Types of interventions that induce ischemic conditioning include aortic cross clamping, multiple balloon inflations and deflations during cardiac catheterization, and pharmacological agents (for example dipyridamole and diazoxide).2,3 More recently, limb ischemia has been investigated in clinical studies.6
This report will review remote conditioning, induced with limb ischemia, to protect against a cardiac ischemic event or to reduce myocardial injury in a person experiencing an acute cardiac ischemic event.

RESEARCH QUESTION:

What is the clinical effectiveness of remote ischemic conditioning in patients experiencing acute ischemic events?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including OVID’s Medline and Embase, the Cochrane Library (Issue 4, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and April 7, 2010. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, observational studies, and guidelines.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, systematic reviews and meta-analyses are presented first, followed by randomized controlled trials (RCTs). The quality of the systematic review and meta-analysis was assessed using the Oxman and Guyatt scale. The quality and the adequacy of the allocation concealment of the RCTs were measured using the Jadad scale and the Schulz scale respectively. Finally, RCTs included in the systematic review and meta-analysis were not reviewed with the same level of detail as the RCTs found through our literature search.

SUMMARY OF FINDINGS:

One systematic review and meta-analysis that included four RCTs, and eight additional RCTs were found. In total, 11 RCTs met our literature search criteria (one RCT fell outside the five-year search limit). Nine were on pre-conditioning and two were on per-conditioning. There were no relevant health technology assessments, controlled clinical trials, observational studies, and guidelines retrieved.

Systematic review and meta-analysis

Pre-conditioning (applied to protect against a future cardiac ischemic event)

One systematic review and meta-analysis on remote ischemic pre-conditioning (RIPC) for the prevention of myocardial injury in patients scheduled for cardiovascular surgery was published in 2008 (Table 1). The main objective was to determine whether RIPC is beneficial in patients who undergo cardiovascular surgery.

Four RCTs met the systematic review’s inclusion criteria, three of which were identified in our literature search. The trials were conducted in different populations: children who underwent repair of congenital heart defects; adult participants who required open abdominal aortic
Remote Ischemic Conditioning

ANEURISM (AAA) repair; adult patients who underwent elective coronary artery bypass graft (CABG) surgery; and male patients who underwent coronary artery surgery. In each trial, RIPC was stimulated differently: one used clamping of the common iliac artery; one used an automated cuff inflator placed on the upper arm; one used a blood pressure cuff applied to a lower limb; and one used a tourniquet around the right upper extremity. The control groups received no RIPC or wore a blood pressure cuff with no inflation.

The outcomes measured were the levels of cardiac biomarkers as an indicator of myocardial injury. In one study, they obtained the mean area under the concentration-time curve of serum cardiac troponin-I. In the second study, they abstracted the total serum troponin-T released 72 hours after surgery. In the third study, they abstracted the level of troponin-I at three hours post-operatively. In the last study, they abstracted the level of lactate dehydrogenase (LDH) five minutes after declamping the aorta. The pooled analysis (a total of 184 patients) showed a reduction in biomarkers with RIPC compared to the control group (standardized mean difference -0.82, [95% CI: -1.29, -0.33], p=0.001). Given that this systematic review contained limited information about the included studies, data on three of the four studies were extracted with additional results provided in the Appendix, Table 2. The fourth study was not reviewed because it fell outside of the five-year search limit.

<table>
<thead>
<tr>
<th>Search methods</th>
<th>Inclusion criteria</th>
<th>Outcome measured</th>
<th>Results</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medline, January 1996 to May 2008; manual search of secondary sources</td>
<td>prospective randomized controlled trials of remote ischemic pre-conditioning versus control in patients undergoing cardiovascular surgery</td>
<td>biomarkers of myocardial injury</td>
<td>4 RCTs (n=184) Pooled analysis: decrease in biomarkers of myocardial injury with remote ischemic pre-conditioning, standardized mean difference -0.82, [95% CI: -1.29, -0.33], p=0.001</td>
<td>3 (major flaws)*</td>
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</table>

*Using the Oxman and Guyatt Scale
CI=confidence interval; RCTs=randomized controlled trials

**Randomized controlled trials**

*Pre-conditioning (applied to protect against a future cardiac ischemic event)*

Six RCTs on RIPC stimulated by limb ischemia were found. Four studies were described as double-blinded. Details of each study are included in the Appendix, Table 3.

Iliodromitis et al. compared RIPC to no RIPC in patients with stable angina and single-vessel disease undergoing elective PCI with stent implantation. RIPC was stimulated by giving three cycles of five minutes of ischemia followed by five minutes of reperfusion of both upper arms using a blood pressure cuff inflated to 200 mm Hg (n=20). This was compared to no RIPC which consisted of placing a deflated blood pressure cuff on the upper limbs (n=21). Twelve additional participants also received RIPC without a cardiac intervention. Outcomes included levels of the
biomarkers C-reactive protein (CRP), creatine phosphokinase (CK), creatine phosphokinase cardiac isoenzymes M and B (CK-MB), and troponin-I. Twenty-four hours after baseline measures were taken, CK-MB and troponin-I levels were statistically significantly higher in the RIPC group compared to the control group. The authors concluded that RIPC exacerbates enzyme and troponin-I release from the heart after single-vessel angioplasty with a stent.11

In the CRISP Stent study,12 patients undergoing an elective PCI were randomized to receive RIPC (n=125) or no RIPC (n=117) one hour before the procedure. RIPC was induced by placing a blood pressure cuff around the non-dominant upper arm inflated to 200 mm Hg pressure for five minutes followed by five minutes of deflation and repeated twice. Patients in the control group also had a cuff placed around the upper arm, but it remained deflated. The main outcome measure was the level of troponin-I. Secondary measures included ischemic symptoms, evidence of ischemia measured with an electrocardiogram (ECG), CRP, and major adverse cardiac and cerebral events (MACCE) occurring within six months of the PCI. The median troponin-I concentration at 24 hours was statistically significantly lower in the RIPC group, with 48% of patients with no detectable levels of troponin-I compared to 29% of the control group. Participants in the RIPC group had statistically significantly less chest pain, statistically significantly fewer ischemic ECG changes during stenting, and a statistically significantly lower rate of MACCE compared to the control group. The authors concluded that RIPC improves the tolerance of the myocardium to ischemia, reduces chest discomfort during PCI, and although CRP remains unchanged, decreases the concentration of troponin-I after PCI.12

In Hoole et al.,13 22 patients with single vessel disease awaiting elective PCI were randomized to receive RIPC induced with a blood pressure cuff placed around the upper arm and inflated to 200 mm Hg for five minutes, followed by five minutes of deflation for a total of three cycles between the first and second balloon occlusions (n=11) or no RIPC (n=11). Outcomes included angiographic measurements to determine if there were improvements in coronary blood flow or in microvascular resistance. RIPC did not improve microvascular function, nor did it augment blood flow. The authors concluded that the cardioprotection conferred by RIPC is not explained by changes in microvascular resistance or in augmentation of coronary blood flow.13

Venogupal et al.14 induced RIPC (n=23) or no RIPC (n=22) in patients undergoing elective coronary artery bypass graft (CABG) with cold-blood cardioplegia. RIPC consisted of applying three 5-minutes cycles of limb ischemia using a blood pressure cuff placed on the upper arm and inflated to 200 mm Hg, intervened with five minutes of reperfusion during which time the cuff was deflated. The control group had a deflated cuff placed on the upper arm for 30 minutes. The primary end-point of interest was the concentration of troponin-T as a marker for myocardial injury, with measurements taken pre-operatively and six, 12, 24, 48, and 72 hours after surgery. The total troponin-T released over 72 hours was statistically significantly reduced by 42.4% with RIPC compared to no RIPC. The authors concluded that RIPC can reduce myocardial injury in elective patients undergoing CABG with cold-blood cardioplegia.14

Walsh et al.15 had 40 patients receive RIPC (n=18) or no RIPC (n=22) immediately before elective endovascular aneurysm repair (EVAR). RIPC consisted of two sequential periods of lower limb ischemia using an inflatable tourniquet placed around the thigh. The cuff was inflated for 10 minutes then deflated. The procedure was repeated on the other leg. Various biomarkers were measured to assess the renal and cardiac impact of RIPC, including urinary levels of retinol binding protein, urinary albumin:creatinine ratio, serum creatinine, estimated glomerular
filtration rate, and serum troponin-I. The rate of major adverse cardiac events was also recorded. The investigators found no statistically significant differences between the two groups for any of these outcomes. One patient in the RIPC group had a myocardial infarction post-operatively on the second day and suffered a fatal cardiac arrest on the seventh day. The authors concluded that RIPC reduced urinary biomarkers in patients undergoing elective EVAR. However, this conclusion was based on within group comparisons, and not comparisons between the RIPC and the control group.

Wenwu et al. used RIPC in infants undergoing ventricular septal defect repair. RIPC (n=30) was applied using a blood pressure cuff wrapped around the left upper arm and inflated to 240 mm Hg pressure for five minutes, followed by five minutes deflation and repeated for two additional cycles, 24 hours and one hour pre-operatively for each infant in the treated group. The control group (n=30) was not pre-treated with RIPC. Various physiological parameters were obtained to assess lung and heart function. These included static lung compliance (Cs), dynamic lung compliance (Cd), respiratory index (RI), left ventricular fractional shortening (LVFS), left ventricular ejection fraction (LVEF), inotropic score, interleukin (IL)-6, -8, -10, tumour necrosis factor-alpha (TNF-α), LDH, CK, CK-MB, troponin-I, heat shock protein (HSP) 70 content, malondialdehyde (MDA), and superoxide dismutase (SOD). Patients with RIPC had statistically significantly higher Cs, Cd, SOD, IL-10, and HSP 70 protein, and statistically significantly lower RI, inotropic score, MDA, IL-6, IL-8, TNF-α, LDH, CK, CK-MB, and troponin-I compared to control group. There was no statistically significant difference in LVEF and LVFS between groups. The investigators concluded that limb RIPC can attenuate systemic inflammatory response syndrome, and can increase systemic tolerance to ischemia-reperfusion injury.

Per-conditioning (applied during a cardiac ischemic event, before reperfusion)

Two RCTs on remote ischemia per-conditioning were found. In Bøtker et al., 333 patients with chest pain and a first episode of ST-elevation acute myocardial infarction (STEMI) were randomized to receive a primary PCI alone (n=167) or PCI with remote conditioning (n=166). Remote conditioning was induced by four cycles of alternating five-minute inflation and five-minute deflation of a blood pressure cuff to 200 mm Hg started during ambulance transport. The primary end-point was a myocardial salvage index measured 30 days after PCI. Secondary end-points included final infarct size 30 days after PCI, troponin-T concentration, markers of reperfusion, death, reinfarction, hospital admission for heart failure within 30 days of PCI, left ventricular ejection fraction, and the New York Heart Association (NYHA) class of disease at 30 days. Although 82 patients were excluded upon arrival at the hospital because they did not meet the inclusion criteria, an intention-to-treat (ITT) analysis was provided. With the ITT analysis, no statistically significant differences were found for any of the end-points measured. A per-protocol analysis of myocardial salvage index was performed for 69 patients in the control group and 73 patients in the conditioning group because perfusion imaging availability was not possible for every patient. The per-protocol analysis showed that the myocardial salvage index was statistically significantly higher in the remote conditioning group than the control. The authors concluded that remote ischemic conditioning before hospital admission increases myocardial salvage, but this conclusion is based on the per-protocol analysis.

Rentoukas et al. randomized 96 patients with acute STEMI and symptom onset no more than six hours before receiving primary PCI to three groups. Group A (n=33) received remote
conditioning by placing a blood pressure cuff on the upper arm and inflated to 20 mm Hg above the systolic blood pressure for four minutes, then deflated for four minutes, and repeated for two additional cycles, 10 minutes before first balloon inflation. Group B (n=33) also received remote conditioning and were also administered morphine sulfate 5 mg by slow intravenous infusion five minutes before first balloon inflation. Group C (n=30), the control group, had a BP cuff inflated to 20 mm Hg below diastolic pressure and received an infusion of normal saline. The primary end-point was the number of patients achieving full ST-segment resolution, and secondary end-points included the percent reduction of ST-segment deviation score and the peak level of troponin-I. A statistically significantly higher proportion of patients in groups A (73%) and B (82%) achieved full ST-segment resolution 30 minutes after PCI than those in Group C (53%). Similarly, the difference in the percent reduction of ST-segment deviation score before and 30 minutes after PCI was in favour of Group B: ST-segment deviation score was statistically significantly reduced by 87.3±2.7% in Group B compared with 69.9 ±5.1% in Group A and 53.2± 6.4% in Group C. The troponin-I level was statistically significantly lower in patients in Group B. The investigators concluded that remote conditioning with or without morphine in acute STEMI demonstrates a cardioprotective effect.21

Limitations

Systematic review and meta-analysis

Based on the Oxman and Guyatt Scale7, the quality of the systematic review and meta-analysis by Takagi et al.10 is rated as 3 (major flaws) because the search methods used were not comprehensive; the authors did not specify how bias was avoided in selecting the studies; the quality of the included studies was not assessed; and the methods used to pool the data were only partially described. Furthermore, the pooling of different cardiac biomarkers, in a patient population with different types of RIPC, may not be clinically appropriate.

Randomized controlled trials

A quality assessment of each trial is provided in the Appendix, Table 3. The RCTs were well-designed, although most studies were reported as double-blinded when it was impossible to blind patients and physicians because the control group wore a deflated blood pressure cuff. Surrogate outcomes that measured myocardial injury were used. Whether or not the results translate into improved patient outcomes such as mortality or health-related quality of life is unknown.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

One systematic review and meta-analysis that included four RCTs, and eight additional RCTs that met the inclusion criteria were identified. Remote conditioning has been studied mostly in a pre-operative setting when the risk of experiencing an ischemic event is high. Only two studies were found that applied remote conditioning induced with limb ischemia in patients experiencing an acute myocardial infarction.

Mostly surrogate outcomes were measured. In the pre-conditioning studies, only two studies reported morbidity outcomes. The CRISP stent study12 showed that RIPC patients had statistically significantly less chest pain during stenting, and that the rate of major adverse
cardiac and cerebral events were statistically significant lower at six months. The study by Walsh et al.\textsuperscript{15} showed no statistically significant differences in cardiac outcomes between groups. Similarly, one per-conditioning study\textsuperscript{20} reported no statistically significant differences in cardiac outcomes between groups.

More studies measuring short-term and long-term morbidity and mortality are required to determine the clinical effectiveness of remote conditioning in any clinical setting.

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REFERENCES:


## Appendix: Randomized controlled trials on remote conditioning

### Table 2: RCTs* included in the meta-analysis by Takagi\textsuperscript{10}

<table>
<thead>
<tr>
<th>First author, source of funding</th>
<th>Blinding, quality</th>
<th>Interventions, population</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheung, 2006\textsuperscript{17}</td>
<td>DB (patients and data analysts)</td>
<td>RIPC (4 x 5 min cycles of lower limb ischemia and 5 min reperfusion using a BP cuff inflated to 15 mm Hg greater than systolic arterial pressure) vs. no RIPC (BP cuff without inflation) in children undergoing repair of congenital heart defects n=37</td>
<td>lung function, cytokines (IL-6, IL-8, IL-10, and TNF), troponin-I, total body water</td>
<td>RIPC group had lower airway resistance at 6 h post-op (p=0.009); post-op inotropic requirement higher in control group at 3 h (p=0.04) and 6 h (p=0.03); mean levels of cytokines not statistically significantly different between the 2 groups; levels of troponin-I higher in control group (p=0.04); no statistically significant difference in total body water between the 2 groups</td>
</tr>
<tr>
<td>Ali, 2007\textsuperscript{18}</td>
<td>DB (patients and data analysts)</td>
<td>RIPC (2 cycles of intermittent cross-clamping of the common iliac artery with 10 min of ischemia followed by 10 min of reperfusion) vs. no RIPC in elective open AAA repair n=82</td>
<td>primary: myocardial injury (increase in serum cardiac troponin &gt;0.40 ng/mL) secondary: MI, renal impairment, death</td>
<td>absolute risk of myocardial injury reduced by 27% (p=0.005), and MI by 22%, (p=0.006) in RIPC group absolute risk of renal impairment reduced by 23% (p=0.009) in the RIPC group no statistically significant difference in mortality</td>
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\textsuperscript{*RCTs: Randomized controlled trials
<table>
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<tr>
<th>Study</th>
<th>Allocation</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
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<tbody>
<tr>
<td>Hausenloy, 2007</td>
<td>DB (patients and surgeons)</td>
<td>RIPC before surgery (3 x 5 min cycles of right upper limb ischemia induced by an automated cuff-inflator placed on the upper arm to 200 mm Hg, with an intervening 5 min of reperfusion during which the cuff was deflated) vs. no RIPC in elective CABG using cross-clamp fibrillation or cardioplagia</td>
<td>troponin-T concentration in RIPC group was reduced at 6 h (p=0.039), 12 h (p=0.02), 24 h (p=0.003), and 48 h (p=0.036) after surgery, but not at 72 h</td>
<td>43% reduction in total serum troponin-T released over 72 h (mean difference between RIPC and control group: 15.55±5.32 sd, 95%CI: 4.88, 36.21, p=0.005)</td>
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</table>

*The fourth trial (Güdnaydin B et al. Pharmacol Res 2000;41:493-96) is not reviewed because it falls outside of our five-year search limit.

AAA=abdominal aortic aneurysm; CABG=coronary artery bypass graft; CI=confidence interval; DB=double blind; h=hour; IL=interleukin; MI=myocardial infarction; min=minutes; POSSUM=physiological operative severity score for the enumeration of mortality and morbidity; RCT=randomized controlled trial; RIPC=remote ischemic pre-conditioning; sd=standard deviation; TNF=tumour necrosis factor.
## Table 3: RCTs on remote conditioning induced using limb ischemia

<table>
<thead>
<tr>
<th>First author</th>
<th>Blinding, quality</th>
<th>Interventions, population</th>
<th>Outcomes</th>
<th>Results</th>
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<tr>
<td>Pre-conditioning (used to protect against an ischemic event)</td>
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<tr>
<td>Hoole, 2009(^{12}) (CRISP Stent study)</td>
<td>DB (patients and interventionist)</td>
<td>RIPC (BP cuff around upper arm and inflated to 200 mm Hg for 5 min, followed by 5 min deflation one hour before procedure) vs. no RIPC (cuff without inflation) in elective PCI</td>
<td>primary: troponin-I; secondary: ischemic symptoms, ECG evidence of ischemia, CRP, major adverse cardiac and cerebral events (MACCE) at 6 months</td>
<td>median troponin-I concentration at 24 h lower with RIPC, p=0.04; 48% of patients with no detectable levels of troponin-I in RIPC group vs. 29% of controls, p&lt;0.005 during stenting: RIPC patients had less chest pain (p=0.0006) and ischemic ECG changes (p=0.005); at 24 h: mean change in CRP, incidence of MI, and renal function similar in both groups; at 6 months: MACCE rate lower in RIPC groups, HR=0.28 (95%CI: 0.12, 0.82), p=0.018</td>
</tr>
<tr>
<td>Hoole, 2009(^{13})</td>
<td>no blinding</td>
<td>RIPC (BP cuff around upper arm and inflated to 200 mm Hg for 5 min, followed by 5 min deflation for a total of 3 times between 1(^{st}) and 2(^{nd}) balloon occlusions) vs. no RIPC in patients with single vessel disease receiving elective PCI</td>
<td>lesion severity (assessed with coronary angiography)</td>
<td>no statistically significant difference between the 2 groups; no improvement in coronary blood flow or in microvascular resistance</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Intervention</td>
<td>Outcome</td>
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<td>Iliodromitis, 2006&lt;sup&gt;11&lt;/sup&gt;</td>
<td>DB (patients and data analysts)</td>
<td>RIPC (3 cycles of 5 min ischemia-reperfusion of both upper limbs using a BP cuff to 200 mm Hg) vs. no RIPC (cuff without inflation) in patients with stable angina and single-vessel disease undergoing elective PCI with stent implantation</td>
<td>levels of CRP, CK, CK-MB, troponin-I</td>
<td>no statistically significant difference in CRP between groups; no statistically significant difference between groups in CK levels at 48 h; CK-MB levels higher after RIPC compared to control group (p&lt;0.05) at 24 h; troponin-I higher in RIPC group (p&lt;0.05) compared to control at 24 h patients with RIPC but without a coronary intervention had unchanged levels of CRP, CK, CK-MB, and troponin-I compared to baseline</td>
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<tr>
<td>Venugopal, 2009&lt;sup&gt;14&lt;/sup&gt;</td>
<td>DB (patients and surgeons)</td>
<td>RIPC before surgery (3 x 5 min cycles of right forearm ischemia induced by inflating a BP cuff on the upper arm to 200 mm Hg, with an intervening 5 min reperfusion) vs. no RIPC (cuff without inflation) in elective CABG with or without concomitant aortic valve replacement using cold-blood cardioplegia</td>
<td>myocardial injury (troponin-T concentration ≥0.10 µg/L)</td>
<td>42% reduction in the total serum troponin-T released over 72 h (mean difference between RIPC and control group: 13.37 µg/L, 95%CI 2.41, 24.33 µg/L, p=0.019)</td>
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<tr>
<td>Study (Year)</td>
<td>Design</td>
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<td>Primary Outcomes</td>
<td>Secondary Outcomes</td>
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<td>Walsh, 2009</td>
<td>n=45</td>
<td>no difference in baseline characteristics</td>
<td>primary: urinary levels of RBP and urinary ACR; number of patients in each group with a post-operative serum troponin-I level ≥0.15 mg/dL</td>
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<td></td>
<td>Allocation concealment: adequate</td>
<td>renal: no statistically significant difference in urinary RBP, ACR, RBP:creatinine ratio, eGFR, serum creatinine levels, or renal function deterioration between the 2 groups</td>
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<td>Jadad score: 3</td>
<td>cardiac: no statistically significant difference in cardiac outcomes between the 2 groups</td>
<td>1 death reported in the RIPC group (MI on the 2nd day post-op with cardiac arrest on 7th day)</td>
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<td>Wenwu, 2010</td>
<td>DB (staff involved in clinical care and data analysts)</td>
<td>n=60</td>
<td>lung function (Cs, Cd, RI), heart function (LVFS, LVEF, inotropic score), inflammatory mediators and enzymes (IL-6, IL-8, IL-10, TNF-α, LDH, CK, CK-MB, troponin-I), HSP 70 content, MDA, and SOD</td>
<td>higher Cs, higher Cd, lower RI, lower inotropic score, lower MDA, higher SOD, higher IL-10, higher expression of HSP 70 protein; lower concentration of IL-6, IL-8, TNF-α, LDH, CK, CK-MB, and troponin-I in RIPC group</td>
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<td>Study</td>
<td>Assignment</td>
<td>Allocation concealment</td>
<td>Intervention</td>
<td>Outcomes</td>
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<td>Bøtker, 2010&lt;sup&gt;20&lt;/sup&gt;</td>
<td>SB</td>
<td>Adequate</td>
<td>Remote conditioning (4 cycles of 5 min inflation and 5 min deflation of BP cuff to 200 mm Hg) started during ambulance transport + primary PCI at hospital vs. primary PCI at hospital, without remote conditioning</td>
<td>Primary: myocardial salvage index at 30 days after PCI measured by perfusion imaging. Secondary: final infarct size at 30 days after PCI, troponin-T concentration, death, markers of reperfusion, reinfarction, hospital admission within 30 days, LVEF, NYHA class of disease at 30 days.</td>
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<td>Rentoukas, 2010&lt;sup&gt;21&lt;/sup&gt;</td>
<td>DB</td>
<td>4</td>
<td>Group A: remote conditioning (BP cuff on upper arm)</td>
<td>Primary: number of patients achieving full ST-</td>
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Allocation concealment: unclear

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<td>Allocation concealment: unclear</td>
<td>inflated to 20 mm Hg above systolic pressure for 4 min, then deflated for 4 min and repeated for 2 additional cycles, 10 min before time of first balloon inflation) vs. Group B: remote conditioning (same as above) with morphine 5 mg slow iv infusion 5 min before time of first balloon inflation vs. Group C: no remote conditioning (BP cuff inflated to 20 mm Hg below diastolic pressure) and no morphine (similar infusion of normal saline) in patients with acute STEMI undergoing primary PCI, with symptom onset not more than 6 h before presentation</td>
<td>segment resolution secondary: % reduction of ST-segment deviation score, peak troponin-I levels and B (82%) achieving full resolution than Group C (53%), p=0.045 ST-segment deviation score reduced by 87.3±2.7% in Group B compared with 69.9 ±5.1% in Group A and 53.2± 6.4% in Group C, p=0.00002 troponin-I level lower in Group B, p=0.006</td>
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<tr>
<td>n=96</td>
<td>no difference in baseline characteristics</td>
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ACR=albumin:creatinine ratio; BP=blood pressure; CABG=coronary artery bypass graft; CI=confidence interval; CK=creatine phosphokinase; CK-MB=creatine phosphokinase cardiac isoenzyme; CRP=C-reactive protein; Cd= dynamic lung compliance; Cs= static lung compliance; DB=double blind; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; EVAR=endovascular aneurysm repair; h=hour; HR=hazard ratio; HSP=heat shock protein; IL=interleukin; ITT=intention-to-treat; iv=intravenous; LDH=lactose dehydrogenase; LVEF=left ventricular ejection fraction; LVFS=left ventricular fractional shortening; MACCE= major adverse cardiac and cerebral events; MI=myocardial infarction; MDA=malondialdehyde; min=minute; NYHA=New York Heart Association; PCI=percutaneous coronary intervention; RCT=randomized controlled trial; RBP=retinol binding protein; RI= respiratory index; RIPC=remote ischemic pre-conditioning; SB=single-blind; SOD=superoxide dismutase; STEMI=ST-segment elevation in myocardial infarction; TNF-α=tumour necrosis factor alpha; VSD=ventricular septal defect