Remote Ischemic Perconditioning to Reduce Reperfusion Injury During Acute ST-Segment–Elevation Myocardial Infarction: A Systematic Review and Meta-Analysis

Shelley L. McLeod, PhD(c), MSc; Alla Iansavichene, BS, MLIS; Sheldon Cheskes, MD, CCFP(EM), FCFP

Background—Remote ischemic conditioning (RIC) is a noninvasive therapeutic strategy that uses brief cycles of blood pressure cuff inflation and deflation to protect the myocardium against ischemia–reperfusion injury. The objective of this systematic review was to determine the impact of RIC on myocardial salvage index, infarct size, and major adverse cardiovascular events when initiated before catheterization.

Methods and Results—Electronic searches of Medline, Embase, and Cochrane Central Register of Controlled Trials were conducted and reference lists were hand searched. Randomized controlled trials comparing percutaneous coronary intervention (PCI) with and without RIC for patients with ST-segment–elevation myocardial infarction were included. Two reviewers independently screened abstracts, assessed quality of the studies, and extracted data. Data were pooled using random-effects models and reported as mean differences and relative risk with 95% confidence intervals. Eleven articles (9 randomized controlled trials) were included with a total of 1220 patients (RIC+PCI=643, PCI=577). Studies with no events were excluded from meta-analysis. The myocardial salvage index was higher in the RIC+PCI group compared with the PCI group (mean difference: 0.08; 95% confidence interval, 0.02–0.14). Infarct size was reduced in the RIC+PCI group compared with the PCI group (mean difference: −2.46; 95% confidence interval, −4.66 to −0.26). Major adverse cardiovascular events were lower in the RIC+PCI group (9.5%) compared with the PCI group (17.0%; relative risk: 0.57; 95% confidence interval, 0.40–0.82).

Conclusions—RIC appears to be a promising adjunctive treatment to PCI for the prevention of reperfusion injury in patients with ST-segment–elevation myocardial infarction; however, additional high-quality research is required before a change in practice can be considered. (J Am Heart Assoc. 2017;6:e005522. DOI: 10.1161/JAHA.117.005522.)

Key Words: ischemia reperfusion injury • meta-analysis • percutaneous coronary intervention • remote ischemic conditioning • ST-segment elevation myocardial infarction

More than 1.4 million patients worldwide are hospitalized each year with an acute coronary syndrome; one third of these patients will have an ST-segment–elevation myocardial infarction (STEMI).1,2 Prompt restoration of blood flow is crucial to salvage ischemic myocardium.3–5 Reperfusion strategies such as primary percutaneous coronary intervention (PCI) and thrombolysis have been shown to reduce mortality and infarct size and to improve left ventricular function; however, reperfusion itself may result in adverse events.6–11 Abrupt reperfusion therapy can lead to reversible impaired myocardial contractility (myocardial stunning), ventricular arrhythmias, and microvascular dysfunction. The pattern of injury that is inflicted on the myocardium has been termed reperfusion injury,12 and the accumulating deleterious effects result in myocyte necrosis and impaired infarct healing and contribute to postinfarction heart failure and other poor outcomes.13–16 Consequently, the prevention of reperfusion injury and minimization of postinfarction heart...
Remote ischemic conditioning (RIC) is a noninvasive therapeutic strategy that uses brief cycles of blood pressure cuff inflation and deflation to protect the myocardium against ischemia–reperfusion injury. Previous proof-of-concept clinical studies using RIC before (preconditioning) or during (perconditioning) a major ischemic event have demonstrated improvements in surrogate markers of ischemia (eg, increased myocardial salvage and reduced infarct size) in a variety of clinical scenarios including acute STEMI, elective PCI, and coronary artery bypass grafting (CABG) surgery. In addition, in patients with STEMI, RIC before PCI has been shown to reduce the incidence of contrast-induced acute kidney injury and has prevented acute kidney injury in patients undergoing cardiopulmonary bypass–assisted cardiac surgery.

A systematic review and meta-analysis by Brevoord et al included 23 clinical studies reporting the use of RIC for patients undergoing cardiac surgery, vascular surgery, or elective or acute PCI. Despite reporting significant clinical heterogeneity (eg, clinical scenarios, patient population, RIC protocol), data were pooled for meta-analysis. The authors concluded that no evidence showed that RIC reduced major adverse cardiovascular events (MACE) or mortality associated with ischemic events. RIC, however, did reduce the incidence of periprocedural myocardial infarctions and the release of troponin. More recently, Le Page et al conducted a systematic review and meta-analysis of 53 articles (44 studies) and concluded that RIC was associated with a significant reduction in cardiac biomarkers and long-term morbidity and mortality in situations presenting a risk of myocardial ischemia–reperfusion injury. The authors were unable to extend their conclusions to STEMI patients because too few studies were available at the time of publication. To date, despite multiple systematic reviews, no meta-analysis has explored the effect of RIC exclusively in STEMI patients undergoing emergent PCI, and new randomized trials specifically investigating RIC in STEMI patients have been published. The primary objective of this systematic review and meta-analysis was to determine the impact of RIC on myocardial salvage index when initiated before catheterization. Secondary outcomes included the impact of RIC on infarct size and MACE including mortality, reinfarction, stroke, and congestive heart failure.

**Clinical Perspective**

**What Is New?**

- In this systematic review and meta-analysis of the impact of remote ischemic conditioning on patients undergoing primary percutaneous coronary intervention for acute ST-segment–elevation myocardial infarction, we found a significant improvement in the primary outcome of myocardial salvage index as well as a significant reduction in myocardial infarct size and major adverse cardiovascular events.

**What Are the Clinical Implications?**

- Remote ischemic conditioning appears to be a promising adjunctive treatment to percutaneous coronary intervention for the prevention of reperfusion injury in patients with ST-segment–elevation myocardial infarction.
- Additional high-quality research focusing on patient-important, clinical outcomes is required before a change in practice can be considered.

**Methods**

**Literature Search Strategy**

The systematic literature searches were conducted in Medline (1946 to October 2016), using both Ovid and PubMed search interfaces; Embase (1947 to October 2016); the Cochrane Central Register of Controlled Trials (October 2016); and electronic bibliographic databases by a research librarian with formal training in electronic literature searching, in consultation with the review authors. A sensitive search strategy (Data S1) included a combination of subject headings and free-text terms using various spelling and endings, such as, but not limited to, the following terms: ischemic postconditioning, ischemic preconditioning, remote, RIPC (remote ischemic preconditioning), myocardial infarction, heart infarction, ST-segment–elevation myocardial infarction, STEMI, myocardial reperfusion injury, thrombolytic therapy, fibrinolytic therapy, percutaneous coronary intervention, angioplasty, ischemic preconditioning, and myocardium.

**Study Setting and Population**

Randomized controlled trials (RCTs) involving STEMI patients undergoing urgent PCI with RIC initiated before catheterization (eg, in the prehospital setting or on hospital arrival) compared with PCI alone were eligible for inclusion. Studies investigating the use of local ischemic postconditioning (inflation and deflation of the angioplasty balloon) were included only if they also used RIC before reperfusion (perconditioning). Studies comparing the use of local ischemic postconditioning versus PCI alone were excluded from the review because they did not investigate RIC. There was no age restriction. Studies that compared RIC for other ischemic conditions in isolation (eg, elective PCI, CABG, stroke, renal failure) were excluded from this review.
The searches were restricted to studies published in the English language only. An optimized hedges filter and text words were used to refine search results to RCTs and systematic reviews published on the topic. The search strategies were modified for each particular database to include specific terms, search filters, and fields. Reference lists of relevant retrieved articles and reviews were also hand searched for other relevant citations, and the regulatory website ClinicalTrials.gov was searched to identify any unpublished trials. The authors independently screened the search output to identify potentially eligible trials, the full texts of which were retrieved and assessed for inclusion (Figure 1). The extent of agreement between reviewers during final study selection was estimated using Cohen's $\kappa$ statistic and percentage agreement.

### Outcome Measures

The primary outcome was the impact of RIC on myocardial salvage index, defined as the proportion of area at risk of the left ventricle salvaged by treatment following emergent PCI for STEMI. Secondary outcomes included infarct size and MACE including mortality, reinfarction, stroke, and congestive heart failure. Studies that did not report any of these outcomes were excluded from the pooled analyses.

### Data Analysis and Risk of Bias Assessment

Using a standardized data collection form, 2 reviewers independently extracted data on patient demographics, sample size, RIC protocol used, and all outcomes data. Risk of bias for the individual trials was independently assessed using the Cochrane Collaboration's tool, and discrepancies in quality assessment scores were resolved by discussion. The following domains were assessed as having a low, unclear (uncertain), or high risk of bias: random sequence generation; allocation concealment; blinding of participants/personnel; blinding of outcome assessment; incomplete outcome data (attrition); and selective outcome reporting.

Direct comparisons were performed using DerSimonian-Laird random-effects models to account for both within- and between-study heterogeneity and reported as relative risks (RRs) with 95% confidence intervals (CIs) using Review Manager 5.3.4 (RevMan; Nordic Cochrane Centre). Secondary outcomes of mortality, reinfarction, stroke, and congestive heart failure were reported as RRs with 95% CIs. In studies with no events in the RIC+PCI or PCI-alone groups, 0.5 was added to each cell of the contingency table (continuity correction) to allow calculation of RR. Studies with no events in both groups were excluded from the meta-analysis. RRs were computed such that a value <1 indicated that RIC+PCI was better than PCI alone for STEMI patients. Statistical significance was defined as $P<0.05$ or 95% CI of the RR that excluded unity.

Statistical heterogeneity was assessed using the $I^2$ statistic. $I^2$ describes the percentage of variability in the effect estimates that is due to underlying differences between the studies rather than occurring by chance. $I^2$ values $\geq 75\%$ indicated substantial heterogeneity. To explain possible heterogeneity, a priori subgroup analyses were planned to investigate the RIC protocol used by each study as well as the duration of outcome follow-up.

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) criteria were used to evaluate the quality of evidence by each outcome and were presented using the GRADEpro Guideline Development Tool.

### Results

The search strategy yielded 1846 potentially relevant citations. After eliminating duplicate citations and studies that did not meet eligibility criteria, 30 full-text articles were retrieved for complete review (Figure 1). Nineteen studies were subsequently excluded, leaving 11 articles (9 RCTs) included in the review with a combined total of 1220 individual patients, 643 in the RIC+PCI group and 577 in the PCI group.

Percentage agreement for final selection of included trials was 29 of 30 (96.7%) with very good interrater agreement, $\kappa=0.93$ (95% CI, 0.81–1.0).

A summary of the characteristics of the included trials can be viewed in Table 1. All 9 RCTs included in this review were conducted outside of North America; 7 (77.8%) were...
### Table 1. Characteristics of Included Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Inclusion Criteria</th>
<th>RIC Protocol</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bøtker20 (2010), Denmark</td>
<td>STEMI, symptom onset &lt;12 h, ≥18 y</td>
<td>4 × 5-min cycles of RIC (200 mm Hg) in ambulance</td>
<td>Mean (SD) myocardial salvage index at 30 d&lt;br&gt;RIC-PCI (n = 73): 0.69 (0.27)&lt;br&gt;PCI (n = 69): 0.57 (0.26)&lt;br&gt;Mean (SD) infarct size at 30 d&lt;br&gt;RIC-PCI (n = 109): 8 (10)&lt;br&gt;PCI (n = 110): 12 (13)</td>
</tr>
<tr>
<td>Eitel38 (2015), Germany</td>
<td>STEMI, symptom onset &lt;12 h</td>
<td>3 × 5-min cycles of RIC (200 mm Hg) on arrival (RIC) followed by 4 × 30-s cycles after stent deployment (post-IC)</td>
<td>Mean (SD) myocardial salvage index at 3 d&lt;br&gt;RIC-PCI + post-IC (n = 158): 0.51 (0.28)&lt;br&gt;PCI (n = 160): 0.43 (0.29)&lt;br&gt;Mean (SD) infarct size at 3 d&lt;br&gt;RIC-PCI + post-IC (n = 166): 18 (12)&lt;br&gt;PCI (n = 168): 20 (14)</td>
</tr>
<tr>
<td>Liu39 (2016), Mongolia</td>
<td>STEMI, symptom onset &lt;12 h, ≥18 y</td>
<td>4 × 5-min cycles of RIC (200 mm Hg) in ambulance</td>
<td>Mean (SD) infarct size at 3 d&lt;br&gt;RIC-PCI (n = 59): 14.2 (6.1)&lt;br&gt;PCI (n = 60): 16.6 (6.7)</td>
</tr>
<tr>
<td>Manchurov40 (2014), Russia</td>
<td>Acute myocardial infarction (45 STEMI, 3 NSTEMI)</td>
<td>4 × 5-min cycles of RIC (200 mm Hg) before PCI</td>
<td>Brachial artery flow-mediated dilation at 7 d&lt;br&gt;RIC-PCI (n = 23): 12.3%&lt;br&gt;PCI (n = 25): 7.4%</td>
</tr>
<tr>
<td>Munk41 (2010), Denmark</td>
<td>STEMI, symptom onset &lt;12 h, ≥18 y</td>
<td>4 × 5-min cycles of RIC (200 mm Hg) in ambulance</td>
<td>Mean (SD) LVEF at 30 d&lt;br&gt;RIC-PCI (n = 103): 0.54 (0.08)&lt;br&gt;PCI (n = 103): 0.53 (0.10)</td>
</tr>
<tr>
<td>Prunier42 (2014), France</td>
<td>STEMI, symptom onset &lt;6 h, ≥18 y</td>
<td>3 × 5-min cycles of RIC (200 mm Hg) on arrival to hospital</td>
<td>Mean (SD) CK-MB at 72 h&lt;br&gt;RIC-PCI (n = 18): 5038 (3187)&lt;br&gt;RIC-PCI + post-IC (n = 20): 5156 (2799)&lt;br&gt;PCI (n = 17): 7222 (2021)</td>
</tr>
<tr>
<td>Rentoukas43 (2010), Greece</td>
<td>STEMI, symptom onset &lt;6 h, 35–75 y</td>
<td>3 × 4-min cycles of RIC (20 mm Hg above systolic arterial pressure) on arrival to hospital</td>
<td>ST-segment resolution ≥80% at 30 min&lt;br&gt;RIC-PCI (n = 33): 73%&lt;br&gt;PCI (n = 30): 53%&lt;br&gt;Mean (SD) reduction of ST-segment deviation score&lt;br&gt;RIC-PCI (n = 33): 69.9% (29.1)&lt;br&gt;PCI (n = 30): 53.2% (35.2)&lt;br&gt;Mean (SD) peak troponin I levels (ng/mL)&lt;br&gt;RIC-PCI (n = 33): 166.0 (160.8)&lt;br&gt;PCI (n = 30): 255.5 (194.5)</td>
</tr>
<tr>
<td>Sloth44 (2014), Denmark</td>
<td>STEMI, symptom onset &lt;12 h, ≥18 y</td>
<td>4 × 5-min cycles of RIC (200 mm Hg) in ambulance</td>
<td>Composite end point MACCE at 3.8 y&lt;br&gt;RIC-PCI (n = 126): 19 (15.1%)&lt;br&gt;PCI (n = 125): 37 (29.6%)&lt;br&gt;All-cause mortality at 3.8 y&lt;br&gt;RIC-PCI (n = 126): 5 (4.0%)&lt;br&gt;PCI (n = 125): 15 (12.0%)</td>
</tr>
<tr>
<td>Verouhis45 (2016), Sweden</td>
<td>STEMI, symptom onset &lt;6 h, ≥18 y</td>
<td>≥1 × 5-min cycles of RIC (200 mm Hg) on arrival followed by 4 × 5 min cycles of RIC (200 mm Hg) after reperfusion</td>
<td>Mean (SD) myocardial salvage index at d 4–7&lt;br&gt;RIC-PCI + post-IC (n = 47): 0.49 (0.22)&lt;br&gt;PCI (n = 46): 0.49 (0.12)&lt;br&gt;Mean (SD) infarct size at d 4–7&lt;br&gt;RIC-PCI + post-IC (n = 47): 20.6 (13.0)&lt;br&gt;PCI (n = 46): 17.9 (8.6)</td>
</tr>
</tbody>
</table>

Continued
Risk of Bias

Risk of bias was assessed for all 11 articles.\textsuperscript{20,21,27,38–45} With respect to random sequence generation, 8 studies (72.7%) were judged to have low risk of bias, and risk was unclear in 3 studies (27.3%; Table 2). Allocation was adequately concealed in 9 (81.2%) and unclear in 2 (18.2%) of the included studies. Because of the application of the blood pressure cuff, blinding of patients and personnel had high risk of bias in all but 1 study. In the trial by Rentoukas et al, it was unclear if patients in the PCI group were blinded to their treatment because they had a manometer cuff placed on their upper arm that was inflated to 20 mm Hg below their diastolic pressure to mimic RIC. Blinding of outcome assessment was judged to be low risk in 9 (81.2%) and unclear in 2 (18.2%) of the included studies. Attrition bias was judged to be high in 8 (72.3%) of the included studies, as many of the enrolled randomized patients did not complete follow-up imaging investigations required to assess the primary outcome or were subsequently excluded from the final analysis, which may have introduced selection bias. Selective reporting of outcomes was judged to have low risk of bias in all included trials.

Data Synthesis

Four of the included trials reported myocardial salvage index with a total of 636 patients (RIC+PCI, n=321; PCI, n=315).\textsuperscript{20,21,38,45} The myocardial salvage index was higher in the RIC+PCI group compared with the PCI-alone group (mean difference [MD]: 0.08; 95% CI, 0.02–0.26; Figure 2). Five of the included studies reported infarct size with a total of 848 patients (RIC+PCI, n=424; PCI, n=424).\textsuperscript{20,21,38,39,45} Infarct size was reduced in the RIC+PCI group compared with the PCI-alone group (MD: −0.14; 95% CI, −0.26 to −0.02), with moderate statistical heterogeneity among the studies (Figure 3). Four of the included studies reported MACE (Figure 4) with a total of 928 patients (RIC+PCI, n=464; PCI, n=464).\textsuperscript{20,21,38,39,44} MACE was lower in the RIC+PCI group (9.5%) compared with the PCI-alone group (17.0%; RR: 0.57; 95% CI, 0.40–0.82). When the individual components of MACE were considered, there was no statistical difference with respect to mortality, reinfarction, or stroke (Figure 5); however, there was a statistically significant reduction in heart
failure with RIC+PCI (RR: 0.41; 95% CI, 0.20–0.84). All outcomes were judged to be of moderate quality of evidence using GRADE criteria, downgraded for imprecision due to small number of events (Table 3).

### Discussion

In this systematic review and meta-analysis of the impact of RIC on patients undergoing primary PCI for acute STEMI, we found a significant improvement in the primary outcome of myocardial salvage index as well as a significant reduction in myocardial infarct size and MACE. Previous systematic reviews have reported the use of RIC for patients undergoing a variety of clinical scenarios including cardiac surgery, vascular surgery, and elective and acute PCI. In the review by Yetgin et al, 1448 patients with coronary heart disease undergoing elective PCI, emergent PCI, or CABG were randomized to RIC or control. RIC induced by transient limb ischemia was associated with a significant decrease in myocardial injury biomarkers (creatine kinase–myocardial band and troponin) for patients undergoing CABG (standardized MD: −0.34; 95% CI, −0.59 to −0.08) and a nonsignificant reduction for patients undergoing both emergent and elective PCI (standardized MD: −0.21; 95% CI, −0.66 to 0.24). However, when the authors restricted their analysis to the 2 primary PCI studies, they reported a significant positive effect of RIC on myocardial injury (standardized MD: −0.55; 95% CI, −0.77 to −0.32). No data related to myocardial infarct size or clinical outcomes were presented.

RIC before cardiac surgery has been shown to improve biomarkers of ischemic and reperfusion injury in patients undergoing cardiac surgery, but uncertainty about clinical outcomes remains. Meybohm et al conducted a prospective, blinded, multicenter RCT involving adults who were scheduled for elective cardiac surgery requiring cardiopulmonary bypass under anesthesia with intravenous

### Table 2. Risk of Bias Summary for Included Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Random Sequence Generation</th>
<th>Allocation Concealment</th>
<th>Blinding of Patients/Personnel</th>
<th>Blinding of Outcome Assessment</th>
<th>Attrition (%)</th>
<th>Selective Outcome Reporting</th>
<th>Other Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bøtker20 (2010), Denmark</td>
<td>Low</td>
<td>Low</td>
<td>High*</td>
<td>Low</td>
<td>333 Randomized, 219 included (34.2% attrition)</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Eitel38 (2015), Germany</td>
<td>Low</td>
<td>Low</td>
<td>High*</td>
<td>Low</td>
<td>464 Randomized, 318 included (31.5% attrition)</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Liu39 (2016), Mongolia</td>
<td>Low</td>
<td>Low</td>
<td>High*</td>
<td>Low</td>
<td>141 Randomized, 119 included (15.6% attrition)</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Manchurow40 (2014), Russia</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High*</td>
<td>Unclear</td>
<td>48 Randomized, 48 included (0% attrition)</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Munk41 (2010), Denmark</td>
<td>Low</td>
<td>Low</td>
<td>High*</td>
<td>Low</td>
<td>333 Randomized, 206 included (38.1% attrition)</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Prunier42 (2014), France</td>
<td>Unclear</td>
<td>Low</td>
<td>High*</td>
<td>Low</td>
<td>151 Randomized, 55 included (63.5% attrition)</td>
<td>Low</td>
<td>High†</td>
</tr>
<tr>
<td>Rentoukas43 (2010), Greece</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>63 Randomized, 63 included (0% attrition)</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Sloth44 (2014), Denmark</td>
<td>Low</td>
<td>Low</td>
<td>High*</td>
<td>Low</td>
<td>333 Randomized, 251 included (24.6% attrition)</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Verouhis45 (2016), Sweden</td>
<td>Low</td>
<td>Low</td>
<td>High*</td>
<td>Low</td>
<td>150 Randomized, 93 included (38.0% attrition)</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>White21 (2015), UK</td>
<td>Low</td>
<td>Low</td>
<td>High*</td>
<td>Low</td>
<td>323 Randomized, 83 included (74.3% attrition)</td>
<td>Low</td>
<td>High†</td>
</tr>
<tr>
<td>Yamanaka27 (2015), Japan</td>
<td>Low</td>
<td>Low</td>
<td>High*</td>
<td>Low</td>
<td>125 Randomized, 94 included (24.8% attrition)</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Summary score</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
<td>High risk of bias</td>
<td>Low risk of bias</td>
<td>High risk of bias</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
</tr>
</tbody>
</table>

*Personnel performing remote conditioning and percutaneous coronary intervention were not masked to treatment assignment.
†The extensive exclusion criteria may have introduced selection bias.
‡The authors selected only patients with ST-segment–elevation myocardial infarction and complete occlusion in the infarct-related artery (pre-percutaneous coronary intervention TIMI [Thrombolysis in Myocardial Infarction] flow grade 0), as these patients were less likely to have spontaneously reperfused and therefore most likely to benefit from remote ischemic conditioning.
propofol. The primary end point was a composite measure of death, myocardial infarction, stroke, or acute renal failure up to the time of hospital discharge. There was no difference in the composite primary end point in the RIC group (14.3%) compared with the sham-RIC group (14.6%) and no difference reported for any of the individual component outcomes.48 Similarly, Walsh et al performed an RCT to evaluate the effect of RIC on markers of heart and kidney injury after cardiac surgery. RIC did not reduce myocardial injury (absolute MD in creatine kinase–myocardial band: 0.15; 95% CI, 0.07 to 0.36) or kidney injury (absolute MD in creatinine: 0.06; 95% CI, 0.10 to 0.23) during cardiac surgery. When 6-month clinical outcomes were assessed, there was no difference between the RIC and sham groups for myocardial infarction (RR: 1.35; 95% CI, 0.85–2.17), acute kidney injury (RR: 1.10; 95% CI, 0.68–1.78), stroke (RR: 1.02; 95% CI, 0.34–3.07), or mortality (RR: 1.47; 95% CI, 0.65–3.31), although the number of events was noted to be small. The authors concluded RIC is unlikely to substantially improve patient-important outcomes in cardiac surgery.49 Both studies are consistent with the most recent meta-analysis by the Remote Preconditioning Trialists’ Group, which included 23 trials of RIC involving a total of 2200 patients undergoing cardiovascular surgery. In that meta-analysis, RIC did not have a significant effect on clinical end points, including death, myocardial infarction, acute renal failure, stroke, or mesenteric ischemia.50

These findings are difficult to extrapolate to and compare with acute STEMI, which represents an entirely different clinical condition. Propofol, a sedative-hypnotic agent that binds neurotransmitter γ-aminobutyric acid receptors, has been shown to attenuate the efficacy of RIC by affecting mitochondrial permeability and adenosine triphosphate synthesis.51 Consequently, propofol should be used cautiously, if at all, in any conditions associated with reperfusion injury. Many of the RIC trials in CABG used propofol anesthesia, potentially mitigating the impact of RIC. In addition, the degree of myocardial ischemia during elective cardiac surgery while the heart is under cardioplegia cannot be assumed to be similar to that occurring during STEMI. It is clear from RCTs involving STEMI that the maximal benefit from RIC appears to occur in patients with the greatest degree of cardiac ischemia (eg, TIMI [Thrombolysis in Myocardial Infarction] 0–1 flow), which is not comparable to the flow state to the myocardium during elective cardiac surgery.20,38 Although underpowered, Sloth et al were able to demonstrate significant improvements in STEMI patients treated with RIC for rates of MACE (hazard ratio: 0.49; 95% CI, 0.27–0.89) and all-cause mortality (hazard ratio: 0.32; 95% CI, 0.12–0.88).44 The majority of benefits from RIC on clinical outcomes such as MACE and all-cause mortality appear to occur after 1 year of follow-up, suggesting that, at least in STEMI, the assessment of the benefit of RIC pertaining to clinical outcomes may require a
longer period of follow-up than noted in the aforementioned cardiac surgery RCTs.

As noted in the perspective by Rosello and Yellon, many cardioprotective therapies aimed at reducing myocardial reperfusion injury that have been successfully examined in the preclinical setting have not demonstrated a reduction in infarct size at the bedside or demonstrated clinical benefits. The authors suggest that the failure to translate cardioprotective therapies into the clinical setting may be attributed to many factors, such as patient comorbidities (eg, diabetes

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RIC</th>
<th>RIC+PCI</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1.1 Within 7 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White 2015</td>
<td>18</td>
<td>10</td>
<td>43 24.5 12 40 13.5% -0.60 [-1.27, 1.7]</td>
<td></td>
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<tr>
<td>Vetricchia 2016</td>
<td>20.6</td>
<td>13</td>
<td>47 17.9 8.6 46 14.7% 2.70 [1.77, 7.17]</td>
<td></td>
</tr>
<tr>
<td>Ellei 2015</td>
<td>18</td>
<td>12</td>
<td>56 16.6 24 16.6% 2.00 [0.88, 4.80]</td>
<td></td>
</tr>
<tr>
<td>Liu 2015</td>
<td>14.2</td>
<td>6.1</td>
<td>7.5 16.6 6.7 60 26.6% -2.40 [0.70, 0.11]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>315</td>
<td>314</td>
<td>78.3% -2.03 [-4.75, 0.69]</td>
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</tr>
<tr>
<td>Heterogeneity: Ta = 4.54, Ch2 = 7.77, df = 3 (P = 0.05); I2 = 61%</td>
<td></td>
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</tr>
</tbody>
</table>

Test for overall effect Z = 1.46 (P = 0.14)

2.1.2 30 days

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RIC</th>
<th>RIC+PCI</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Risk of Bias</th>
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<tbody>
<tr>
<td>Bokker 2010</td>
<td>8</td>
<td>10</td>
<td>89 22 12 110 21.7% -1.00 [0.70, 0.31]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>109</td>
<td>110</td>
<td>110 21.7% -1.00 [0.70, 0.31]</td>
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<tr>
<td>Heterogeneity: Not applicable</td>
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</table>

Test for overall effect Z = 2.59 (P = 0.01)

Total (95% CI) 424 424 100.0% -2.46 [-4.66, -0.26] |

Heterogeneity: Ta = 3.34, Ch2 = 8.04, df = 4 (P = 0.05); I2 = 55% |

Test for overall effect Z = 2.19 (P = 0.03)

Test for subgroup differences: Ch2 = 0.89, df = 1 (P = 0.35), I2 = 0%

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 4. Major adverse cardiac events with and without RIC before primary PCI for patients with ST-segment–elevation myocardial infarction. CI indicates confidence interval; M-H, Mantel–Haenszel method; PCI, percutaneous coronary intervention; random, random-effects model; RIC, remote ischemic conditioning.

Figure 3. Infarct size as a percentage of left ventricle with and without RIC before primary PCI for patients with ST-segment–elevation myocardial infarction. CI indicates confidence interval; IV, inverse variance method; PCI, percutaneous coronary intervention; random, random-effects model; RIC, remote ischemic conditioning.

DOI: 10.1161/JAHA.117.005522  Journal of the American Heart Association 8
mellitus, advanced age) and medications (eg, β-blockers, anticoagulants) that may limit the proposed benefit of RIC. These factors have not been addressed or adequately controlled for in any of the RCTs to date. Future studies should attempt to address these issues in the study design.

Limitations
Our systematic review and meta-analysis has several limitations. Only RCTs in English were evaluated for inclusion. The majority of the included studies were small and focused on the effect of RIC on biomarker release and other surrogate indicators of organ injury as opposed to clinical outcomes. For the included trials that did report clinical outcomes, only 2 studies extended the assessment beyond 6 months, and the number of reported events was small. Patient follow-up of <1 year may be too short to detect long-term benefit for patients undergoing RIC as an adjunct to primary PCI.

Attrition bias was judged to be high in 8 (72.7%) of the included studies because many of the randomized patients did not complete imaging investigations required to assess the primary outcome (eg, myocardial infarct size) or were subsequently excluded from the final analysis, which may have introduced selection bias. These missing patient outcome data present a threat to the internal and external validity of the individual trial and our summary findings.

![Breakdown of major adverse cardiac events with and without RIC before primary PCI for patients with ST-segment-elevation myocardial infarction.](image-url)

**Figure 5.** Breakdown of major adverse cardiac events with and without RIC before primary PCI for patients with ST-segment-elevation myocardial infarction. *0.5 added to each cell of 2×2 contingency table because no events were found in one of the comparison groups. CI indicates confidence interval; M-H, Mantel–Haenszel method; PCI, percutaneous coronary intervention; random, random-effects model; RIC, remote ischemic conditioning.
Remote Ischemic Perconditioning in STEMI  McLeod et al

Table 3. The GRADE Criteria Were Used to Evaluate the Certainty of Evidence by Each Outcome

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Effect</th>
<th>Design</th>
<th>Myocardial salvage index (better indicated by lower values)</th>
<th>Infarct size (better indicated by lower values)</th>
<th>Major adverse cardiac events</th>
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</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>No. of studies</td>
<td>Myocardial salvage index (better indicated by lower values)</td>
<td>Infarct size (better indicated by lower values)</td>
<td>Major adverse cardiac events</td>
<td></td>
</tr>
<tr>
<td>MD 0.08 higher (95% CI 0.02–0.14)</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
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<tr>
<td>MD 2.46 lower (4.86–2.65 lower)</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MD, mean difference; PCI, percutaneous coronary intervention; RIC, remote ischemic conditioning.

To be included in our systematic review, studies investigating the use of RIC initiated after catheterization were included only if they also used RIC before balloon inflation. This, along with variation in cycles of RIC before PCI, may have introduced an element of heterogeneity into the treatment protocols. Studies comparing the use of local ischemic conditioning after catheterization versus PCI alone were excluded from the review. In addition, for all included studies, the RIC protocol had to be initiated before reperfusion (perconditioning); therefore, randomization occurred before PCI and before a definitive decision could be made as to whether the patient had met specific inclusion criteria. It is unknown how many cycles of RIC were completed before PCI for the included studies and whether that affects the effect of RIC for acute STEMI patients. Finally, all studies included in our review excluded patients who presented with cardiogenic shock or who underwent PCI following STEMI complicated by cardiac arrest, a subgroup of patients who may gain maximal benefit from the RIC technique.

Conclusions

This systematic review and meta-analysis suggests that RIC is emerging as a promising adjunctive treatment to PCI for the prevention of reperfusion injury in STEMI patients; however, additional high-quality research is required before a change in practice can be considered. Ongoing multicenter clinical trials should help elucidate the effect of RIC on clinical outcomes such a hospitalization, heart failure, and mortality.

Disclosures

None.

References


Remote Ischemic Perconditioning in STEMI

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SUPPLEMENTAL MATERIAL
Data S1. Search strategy.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present (October, 2016)

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<td>7347</td>
<td>Advanced</td>
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<td>2</td>
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<td>11571</td>
<td>Advanced</td>
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<tr>
<td>3</td>
<td>or/1-2</td>
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<td>remote$.mp.</td>
<td>54497</td>
<td>Advanced</td>
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<td>1333</td>
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<tr>
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<td>(3 and 4) or 5</td>
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<td>16</td>
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<td>Advanced</td>
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urokinase or reteplase or clexane or drotrecogin).tw.
124965 Advanced

or/16-17 239943 Advanced

6 and 18 27 Advanced

exp percutaneous coronary intervention/ 39914 Advanced

(percutaneous adj3 coronar$ adj3 (angioplast$ or intervention$ or revascularization$)).tw.
28091 Advanced

((primary or percutaneous or coronary) and (PCI or PPCI or PTCA)).tw.
18621 Advanced

angioplast$.tw. 38275 Advanced

or/20-23 73628 Advanced

6 and 24 82 Advanced

exp Myocardium/ or myocardi$.mp. 498663 Advanced

6 and 26 508 Advanced

Ischemic Preconditioning, Myocardial/ 3570 Advanced

28 and (4 or 5) 260 Advanced

11 or 15 or 19 or 25 or 27 or 29 530 Advanced

random$.tw. or randomized controlled trial/ 916900 Advanced

30 30 and 31 195 Advanced

30 and (4 or 5) 260 Advanced

limit 30 to "therapy (best balance of sensitivity and specificity)"

162 Advanced

32 32 or 33 198 Advanced

systematic review/ or meta analysis.mp,pt. or MEDLINE.tw. or systematic review.tw.
172397 Advanced

36 30 and 35 27 Advanced

34 or 36 202 Advanced

37 34 or 36 202 Advanced

38 37 not (exp Animals/ not (Human/ and exp Animals/)) 158 Advanced

39 38 not (mice or rat or rats or cat$1 or cattle$1 or dog$1 or goat$1 or horse$1 or rabbit$1 or sheep$1 or swine$1 or pig$1 or canine$1 or feline$1 or porcine$ or calf or murine).ti.

155 Advanced
39 not ("20387183" or "22108640" or "25306677" or "25512268" or "26027222").an. [5 non-English citations]
Remote Ischemic Perconditioning to Reduce Reperfusion Injury During Acute ST–Segment–Elevation Myocardial Infarction: A Systematic Review and Meta–Analysis
Shelley L. McLeod, Alla Iansavichene and Sheldon Cheskes

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