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). Prompt restoration of blood flow is crucial to salvage ischemic myocardium. 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. 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, and the accumulating deleterious effects result in myocyte necrosis and impaired infarct healing and contribute to postinfarction heart failure and other poor outcomes. Consequently, the prevention of reperfusion injury and minimization of postinfarction heart
Remote ischemic conditioning appears to be a promising adjunctive treatment to percutaneous coronary intervention for the prevention of reperfusion injury in patients with STEMI. Additional high-quality research focusing on patient-important, clinical outcomes is required before a change in practice can be considered.

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 STEMI patients.
- 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 (postconditioning). 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.

failure are considered pivotal goals for improving outcomes in STEMI patients.

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 periocedural 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.
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.

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, $k = 0.93$ (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
| Trial                                      | Inclusion Criteria                  | RIC Protocol                                                                 | Main Findings                                                                                                                                 |
|-------------------------------------------|-------------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Bøtker (2010), Denmark                    | STEMI, symptom onset <12 h, ≥18 y   | 4 × 5-min cycles of RIC (200 mm Hg) in ambulance                            | Mean (SD) myocardial salvage index at 30 d RIC-PCI (n=73): 0.69 (0.27) PCI (n=69): 0.57 (0.26) Mean (SD) infarct size at 30 d RIC-PCI (n=109): 8 (10) PCI (n=110): 12 (13) |
| Eitel (2015), Germany                     | STEMI, symptom onset <12 h          | 3 × 5-min cycles of RIC (200 mm Hg) on arrival (RIC) followed by 4×30-s cycles after stent deployment (post-IC) | Mean (SD) myocardial salvage index at 3 d RIC-PCI+post-IC (n=158): 0.51 (0.28) PCI (n=160): 0.43 (0.29) Mean (SD) infarct size at 3 d RIC-PCI+post-IC (n=166): 18 (12) PCI (n=168): 20 (14) |
| Liu (2016), Mongolia                      | STEMI, symptom onset <12 h, ≥18 y   | 4 × 5-min cycles of RIC (200 mm Hg) in ambulance                            | Mean (SD) infarct size at 3 d RIC-PCI (n=59): 14.2 (6.1) PCI (n=60): 16.6 (6.7) Mean (SD) LVEF at 5 d RIC-PCI (n=59): 0.48 (0.07) PCI (n=60): 0.45 (0.07) MACCE at 1 y RIC-PCI (n=59): 3 (5.1%) PCI (n=60): 8 (13.3%) |
| Munk (2010), Denmark                      | STEMI, symptom onset <12 h, ≥18 y   | 4 × 5-min cycles of RIC (200 mm Hg) in ambulance                            | Mean (SD) LVEF at 30 d RIC-PCI (n=103): 0.54 (0.08) PCI (n=103): 0.53 (0.10)                                                          |
| Prunier (2014), France                    | STEMI, symptom onset <6 h, ≥18 y    | 3 × 5-min cycles of RIC (200 mm Hg) on arrival to hospital                 | Mean (SD) CK-MB at 72 h RIC-PCI (n=18): 5038 (3187) RIC-PCI+post-IC (n=20): 5156 (2799) PCI (n=17): 7222 (2021) |
| Rentoukas (2010), Greece                  | STEMI, symptom onset <6 h, 35–75 y  | 3 × 4-min cycles of RIC (20 mm Hg above systolic arterial pressure) on arrival to hospital | ST-segment resolution ≥80% at 30 min RIC-PCI (n=33): 73% PCI (n=30): 53% Mean (SD) reduction of ST-segment deviation score RIC-PCI (n=33): 69.9% (29.1) PCI (n=30): 53.2% (35.2) Mean (SD) peak troponin I levels (ng/mL) RIC-PCI (n=33): 166.0 (160.8) PCI (n=30): 255.5 (194.5) |
| Sleth (2014), Denmark                     | STEMI, symptom onset <12 h, ≥18 y   | 4 × 5-min cycles of RIC (200 mm Hg) in ambulance                            | Composite endpoint MACCE at 3.8 y RIC-PCI (n=126): 19 (15.1%) PCI (n=125): 37 (29.6%) All-cause mortality at 3.8 y RIC-PCI (n=126): 5 (4.0%) PCI (n=125): 15 (12.0%) |
| Verouhis (2016), Sweden                   | STEMI, symptom onset <6 h, ≥18 y    | ≥1 × 5-min cycles of RIC (200 mm Hg) on arrival followed by 4×5 min cycles of RIC (200 mm Hg) after reperfusion | Mean (SD) myocardial salvage index at d 4–7 RIC-PCI+post-IC (n=47): 0.49 (0.22) PCI (n=46): 0.49 (0.12) Mean (SD) infarct size at d 4–7 RIC-PCI+post-IC (n=47): 20.6 (13.0) PCI (n=46): 17.9 (8.6) |

Continued
Table 1. Continued

| Trial | Inclusion Criteria | RIC Protocol | Main Findings |
|-------|-------------------|--------------|---------------|
| White21 (2015), UK | STEMI, symptom onset <12 h, 18–80 y | 4×5-min cycles of RIC (200 mm Hg) on arrival to hospital | Mean (SD) myocardial salvage index at d 3–6 RIC-PCI (n=43): 0.42 (0.29) PCI (n=40): 0.28 (0.29) Mean (SD) infarct size at d 3–6 RIC-PCI (n=43): 18.0 (10) PCI (n=40): 24.5 (12.0) |
| Yamanaka27 (2015), Japan | STEMI, symptom onset <24 h, ≥20 y | 3×5-min cycles of RIC (200 mm Hg) on arrival to hospital | CI-AKI at 48–72 h RIC-PCI (n=47): 5 (10.6%) PCI (n=47): 17 (36.2%) Mean (SD) serum creatinine levels at 48–72 h RIC-PCI (n=47): 0.81 (0.21) PCI (n=47): 1.03 (0.61) VF/VT within 24 h RIC-PCI (n=47): 1 (2%) PCI (n=47): 7 (14%) |

CI-AKI indicates contrast-induced acute kidney injury; CK-MB, creatine kinase–MB isoenzyme release; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; post-IC, local ischemic postconditioning; RIC, remote ischemic conditioning; STEMI, ST-segment elevation myocardial infarction; VT/VT, ventricular fibrillation/ventricular tachycardia.

Conducted in Europe,20,21,38,40,42,43,45 1 trial was performed in Mongolia,29 and 1 trial was performed in Japan.27 The primary outcomes varied among the studies and included surrogate biomarkers of myocardial reperfusion injury, microvascular reperfusion, left ventricular function, and acute kidney injury in STEMI patients. Seven trials (77.8%) used a standard manual, upper arm, blood pressure cuff and a stopwatch for the delivery of RIC before PCI.20,21,38–40,42,43 The trial by Verouhis et al used a blood pressure cuff around the left thigh connected to an automated device (PeriVasc Cuff Unit; EBIDA) programmed to inflate to 200 mm Hg (or 20 mm Hg above systolic blood pressure if systolic blood pressure was >180 mm Hg) for 5 minutes followed by deflation for 5 minutes in repeated cycles.45 Yamanaka et al also used an automated continuous blood pressure device (FB-270; Fakuda Denshi) connected to the upper arm that was modified to perform 3 cycles of inflation and deflation automatically.27 RIC was started by ambulance personnel in 2 (22.2%) of the included studies20,39 and initiated on arrival at the hospital (before PCI) for the remaining included trials.

Risk of Bias

Risk of bias was assessed for all 11 articles.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).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, 0.02–0.14; Figure 2). Five of the included studies reported infarct size with a total of 848 patients (RIC+PCI, n=424; PCI, n=424).20,21,38,39,45 Infarct size was reduced in the RIC+PCI group compared with the PCI-alone group (MD: −2.46; 95% CI, −4.66 to −0.26), 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).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.  

Yamanaka 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**

| Trial                                      | Random Sequence Generation | Allocation Concealment | Blinding of Patients/Personnel | Blinding of Outcome Assessment | Attrition (%) | Selective Outcome Reporting | Other Bias |
|-------------------------------------------|----------------------------|------------------------|-------------------------------|-------------------------------|---------------|-----------------------------|------------|
| Bøtker20 (2010), Denmark                   | Low                        | Low                    | High*                         | Low                           | 333 Randomized, 219 included (34.2% attrition) | Low          | Low                        |
| Eitel38 (2015), Germany                   | Low                        | Low                    | High*                         | Low                           | 464 Randomized, 318 included (31.5% attrition) | Low          | Low                        |
| Liu39 (2016), Mongolia                     | Low                        | Low                    | High*                         | Low                           | 141 Randomized, 119 included (15.6% attrition) | Low          | Low                        |
| Manchurow40 (2014), Russia                | Unclear                    | Unclear                | High*                         | Unclear                       | 48 Randomized, 48 included (0% attrition)        | Low          | Low                        |
| Munk41 (2010), Denmark                    | Low                        | Low                    | High*                         | Low                           | 333 Randomized, 206 included (38.1% attrition)   | Low          | Low                        |
| Prunier42 (2014), France                  | Unclear                    | Low                    | High*                         | Low                           | 151 Randomized, 55 included (63.5% attrition)    | Low          | High†                      |
| Rentoukas43 (2010), Greece                | Unclear                    | Unclear                | Unclear                       | Unclear                       | 63 Randomized, 63 included (0% attrition)         | Low          | Low                        |
| Sloth44 (2014), Denmark                   | Low                        | Low                    | High*                         | Low                           | 333 Randomized, 251 included (24.6% attrition)    | Low          | Low                        |
| Verouhis45 (2016), Sweden                 | Low                        | Low                    | High*                         | Low                           | 150 Randomized, 93 included (38.0% attrition)     | Low          | Low                        |
| White46 (2015), UK                       | Low                        | Low                    | High*                         | Low                           | 323 Randomized, 83 included (74.3% attrition)     | Low          | High‡                      |
| Yamanaka47 (2015), Japan                  | Low                        | Low                    | High*                         | Low                           | 125 Randomized, 94 included (24.8% attrition)     | Low          | Low                        |
| Summary score                             | Low risk of bias           | Low risk of bias       | High risk of bias             | Low risk of bias              | High risk of bias                                | Low          | Low                        |

*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

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...
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.39,44 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.

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.

| Study or Subgroup | RIC | PCI | RIC | PCI | Risk Ratio | Risk Ratio | Risk of Bias |
|-------------------|-----|-----|-----|-----|------------|------------|--------------|
|                  | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI | A | B | C | D | E | F | G |
| 3.1.2 Death       |      |     |      |     |         |            |              |    |    |    |  |  |  |  |
| Yamamoto 2015     | 0    | 47  | 3    | 47  | 8.2%   | 0.14 [0.01, 2.60] |              |    |    |    |  |  |  |  |
| Liu 2018          | 1    | 59  | 4    | 60  | 13.5%  | 0.25 [0.03, 2.21] |              |    |    |    |  |  |  |  |
| Solo (sub-task of Bobor) 2014  | 5   | 126 | 15   | 125 | 34.8%  | 0.33 [0.12, 0.88] |              |    |    |    |  |  |  |  |
| Ettel 2015        | 15   | 232 | 14   | 232 | 43.4%  | 1.07 [0.53, 2.17] |              |    |    |    |  |  |  |  |
| Subtotal (95% CI) | 464  | 464 | 100.0% |       | 0.50 [0.20, 1.23] |              |    |    |    |  |  |  |  |
| Total events      | 21   |     | 26   |     |         |            |              |    |    |    |  |  |  |  |
| Heterogeneity Taq = 0.38, Ch = 6.57, df = 3 (P = 0.19), P = 69% | | | | | | | | | | | | |
| Test for overall effect Z = 1.62 (P = 0.13) | | | | | | | | | | | | |
| 3.1.3 Re-infarction |      |     |      |     |         |            |              |    |    |    |  |  |  |  |
| Yamamoto 2015     | 0    | 47  | 0    | 47  | Not estimable |              |    |    |    |  |  |  |  |
| Liu 2018          | 1    | 59  | 1    | 60  | 8.2%   | 1.02 [0.07, 16.88] |              |    |    |    |  |  |  |  |
| Ettel 2015        | 2    | 232 | 1    | 232 | 19.9%  | 2.00 [0.18, 21.50] |              |    |    |    |  |  |  |  |
| Solo (sub-task of Bobor) 2014  | 0   | 125 | 1    | 125 | 93.6%  | 0.72 [0.30, 1.72] |              |    |    |    |  |  |  |  |
| Subtotal (95% CI) | 464  | 464 | 100.0% |       | 0.93 [0.38, 2.32] |              |    |    |    |  |  |  |  |
| Total events      | 11   |     | 13   |     |         |            |              |    |    |    |  |  |  |  |
| Heterogeneity Taq = 0.00, Ch = 0.64, df = 2 (P = 0.73), P = 69% | | | | | | | | | | | | |
| Test for overall effect Z = 0.47 (P = 0.64) | | | | | | | | | | | | |
| 3.4.1 Heart failure |      |     |      |     |         |            |              |    |    |    |  |  |  |  |
| Yamamoto 2015     | 1    | 59  | 0    | 60  | 9.4%   | 0.51 [0.05, 5.48] |              |    |    |    |  |  |  |  |
| Solo (sub-task of Bobor) 2014  | 1   | 126 | 1    | 125 | 39.8%  | 0.57 [0.17, 1.89] |              |    |    |    |  |  |  |  |
| Ettel 2015        | 2    | 232 | 1    | 232 | 43.3%  | 0.31 [0.10, 1.03] |              |    |    |    |  |  |  |  |
| Subtotal (95% CI) | 464  | 464 | 100.0% |       | 0.41 [0.20, 0.84] |              |    |    |    |  |  |  |  |
| Total events      | 10   |     | 25   |     |         |            |              |    |    |    |  |  |  |  |
| Heterogeneity Taq = 0.00, Ch = 0.69, df = 3 (P = 0.60), P = 69% | | | | | | | | | | | | |
| Test for overall effect Z = 2.42 (P = 0.02) | | | | | | | | | | | | |
| 3.1.5 Stroke      |      |     |      |     |         |            |              |    |    |    |  |  |  |  |
| Yamamoto 2015     | 0    | 47  | 1    | 47  | 21.6%  | 0.33 [0.01, 1.79] |              |    |    |    |  |  |  |  |
| Solo (sub-task of Bobor) 2014  | 2   | 176 | 4    | 125 | 39.8%  | 0.60 [0.04, 2.66] |              |    |    |    |  |  |  |  |
| Subtotal (95% CI) | 173  | 172 | 100.0% |       | 0.46 [0.10, 2.04] |              |    |    |    |  |  |  |  |
| Total events      | 2    |     | 5    |     |         |            |              |    |    |    |  |  |  |  |
| Heterogeneity Taq = 0.00, Ch = 0.05, df = 1 (P = 0.63), P = 69% | | | | | | | | | | | | |
| Test for overall effect Z = 1.04 (P = 0.30) | | | | | | | | | | | | |

Test for subgroup differences: Ch = 1.60, df = 3 (P = 0.81), P = 69%
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 (selection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Favours RIC Favours PCI

DOI: 10.1161/JAHA.117.005522
Journal of the American Heart Association

9
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 PCI. 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 as hospitalization, heart failure, and mortality.

Disclosures

None.

References

1. Tu JV, Austin PC, Filate WA, Johansen HL, Brien SE, Pilote L, Alter DA; Canadian Cardiovascular Outcomes Research Team. Outcomes of acute myocardial infarction in Canada. Can J Cardiol. 2003;19:893–901.
2. Tu JV, Donovan LR, Austin PC, Ko DT, Wang JT, Newman AM. Quality of cardiac care in Ontario—Phase 1. Report 1. Toronto: Institute for Clinical Evaluative Sciences; 2004.
3. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators, Van De Werf F, Agey J, Ardissino D, Armstrong PW, Aylward P, Barbash G, Betriu A, Binbrek AS, Califf R, Diaz R, Fanebust R, Fox K, Granger C, Heikkilä J, Husted S, Jansky P, Langer A, Lupi E, Maseri A, Meyer J, Milczoch J, Mocetti D, Myburgh D, Oto A, Paolasso E, Peitheron K, Seabra-Gomes R, Soares-Pereira L, Sugrue D, Tendler M, Topol E, Toutouzas P, Vahanian A, Verheugt F, Wallentin L, White H. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomized trial. Lancet. 1999;354:716–722.
4. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO Investigators. N Engl J Med. 1993;329:673–682.
5. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK; American College of Cardiology; American Heart Association Task Force on Practice Guidelines;
Remote Ischemic Perconditioning in STEMI

McLeod et al

Canadian Cardiovascular Society. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation. 2004;110:e82–e92.

6. Heusch G, Gersh B. The pathophysiology of acute myocardial infarction and strategies of protection beyond reperfusion: a continual challenge. Eur Heart J. 2017;38:774–784.

7. Cannon CP, Gibson CM, Lambrech CT, Shoults DA, Levy D, French WJ, Gore JM, Weaver WD, Rogers WJ. Tienfenbrunn AJ. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. JAMA. 2000;283:2941–2947.

8. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation. 2004;109:1223–1225.

9. Effectiveness of intravenous thrombolysis treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico (GISSI). Lancet. 1986;1:397–402.

10. Armstrong PW, Collen D, Antman E. Fibrinolysis for acute myocardial infarction: the future is here and now. Circulation. 2003;107:2533–2537.

11. De Luca G, Suryapranata H, Zijlstra F, Jukema JW, de Boer MJ. Remote Ischemic Infarction Study Group. Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. J Am Coll Cardiol. 2003;42:991–997.

12. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. N Engl J Med. 2009;358:1112–1135.

13. Bolli R. Mechanism of myocardial “stunning”. Circulation. 1990;82:723–738.

14. Frangogiannis NG, Smith CW, Entman ML. The inflammatory response in myocardial infarction. Cardiovasc Res. 2002;53:31–47.

15. Braunwald E, Kloner RA. Myocardial reperfusion injury. Circulation. 1985;76:1713–1719.

16. Schmidt MR, Smerup M, Konstantinov IE, Shimizu M, Li J, Cheung M, White PA, Kristiansen SB, Sorensen K, Dzavik V, Redington AN, Kharbanda RK. Intermittent peripheral tissue ischemia during coronary ischemia reduces myocardial infarction through a KATP-dependent mechanism: first demonstration of remote ischemic preconditioning. Am J Physiol Heart Circ Physiol. 2007;292:H1883–H1890.

17. Heusch G, Betker HE, Przyklenk K, Redington A, Yellon D. Remote ischemic conditioning: J Am Coll Cardiol. 2015;65:177–195.

18. Ovize M, Thibault H, Przyklenk K. Myocardial conditioning: opportunities for clinical translation. Circ Res. 2013;113:439–450.

19. Schmidt MR, Py dys K, Betker HE. Novel adjunctive treatments of myocardial infarction. Circulation. 2014;130:434–440.

20. Betker HE, Kharbanda R, Schmidt MR, Betckett M, Koltak OA, Jerkelis CJ, Munk K, Andersen NH, Hansen TM, Trautner S, Lassen JF, Christiansen EH, Krusell LR, Kristensen SD, Thuesen L, Nielsen SS, Rehling M, Sørensen HT, Nielsen TT, Poulsen SH. Remote ischemic conditioning reduces myocardial infarct size and edema in patients with ST-segment elevation myocardial infarction. JACC Cardiovasc Interv. 2015;8:178–188.

21. White SK, Frohlich GM, Sado DM, Maestri V, Fontana M, Treibel TA, Tehrani S, Flett AS, Peier P, Aritei C, Davies JR, Moon JC, Yellon DM, Hausenloy DJ. Remote ischemic conditioning reduces myocardial infarct size and edema in patients with ST-segment elevation myocardial infarction. JACC Cardiovasc Interv. 2015;8:178–188.

22. Ahmed RM, Mohamed M-HA, Ashraf M, Maitihi S, Nabil F, Rami R, Mohamed TI. Effect of remote ischemic preconditioning on serum troponin T level following elective percutaneous coronary intervention. Catheter Cardiovasc Interv. 2013;82:E647–E653.

23. Luo SJ, Zhou YJ, Shi DM, Ge HL, Wang JG, Liu RF. Remote ischemic preconditioning reduces myocardial infarct size in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial. Lancet. 2013;382:597–604.

24. Thielmann M, Kottenberg E, Kleinbongard P, Wendt D, Gedik N, Pasa S, Price CR, Shpektor A. Remote Ischemic Preconditioning and Endothelial Function in Acute Myocardial Infarction Treated by Primary Angioplasty. Circ Res. 2012;107:421–429.
45. Verouhis D, Sörensson P, Gourine A, Henareh L, Persson J, Saleh N, Settergren M, Sundqvist M, Torvall P, Witt N, Böm F, Pernow J. Effect of remote ischemic conditioning on infarct size in patients with anterior ST-elevation myocardial infarction. *Am Heart J*. 2016;181:66–73.

46. D’Ascenzo F, Cavaliero E, Moretti C, Omedè P, Sciuto F, Rahman IA, Bonser RS, Yunseok J, Wagner R, Freiberger T, Kunst G, Marber MS, Thielmann M, Ji B, Amr YM, Modena MG, Zoccai GB, Sheibani I, Gaita F. Remote ischaemic preconditioning in coronary artery bypass surgery: a meta-analysis. *Heart*. 2012;98:1267–1271.

47. Yetgin T, Manintveld OC, Boersma E, Kappetein AP, van Geuns RJ, Zijlstra F, Duncker DJ, van der Giessen WJ. Remote ischemic conditioning in percutaneous coronary intervention and coronary artery bypass grafting. *Circ J*. 2012;76:2392–2404.

48. Meybohm P, Bein B, Brosteanu O, Cremer J, Gruenewald M, Stoppe C, Coburn M, Schaeite G, Böning A, Niemann B, Roesner J, Kletzin F, Strouhal U, Reyher C, Laufenberg-Feldmann R, Ferner M, Brandes IF, Bauer M, Stehr SN, Kortgen A, Wittmann M, Baumgarten G, Meyer-Treschan T, Kienbaum P, Heringlake M, Schön J, Sander M, Treskatsch S, Smul T, Wolwender E, Schilling T, Fuernau G, Hasenclever D, Zacharowski K; RIPHeart Study Collaborators. A multicenter trial of remote ischemic preconditioning for heart surgery. *N Engl J Med*. 2015;373:1397–1407.

49. Walsh M, Whitlock R, Garg AX, Légaré JF, Duncan AE, Zimmerman R, Miller S, Femes S, Kieser T, Kharthikyan G, Chan M, Ho A, Nasr V, Vincent J, Ali I, Lavi R, Sessler DI, Kramer R, Gardner J, Syed S, VanHelder T, Guyatt G, Rao-Melacini P, Thabane L, Devereaux PJ; Remote IMPACT Investigators. Effects of remote ischemic preconditioning in high-risk patients undergoing cardiac surgery (Remote IMPACT): a randomized controlled trial. *CMAJ*. 2016;188:329–336.

50. Remote Preconditioning Trialists’ Group, Healy DA, Khan WA, Wong CS, Moloney MC, Grace PA, Coffey JC, Dunne C, Walsh SR, Sadat U, Gaunt ME, Chen S, Tehrani S, Hausenloy DJ, Yellon DM, Kramer RS, Zimmerman RF, Lomivorotov VV, Shmyrev VA, Ponomarev DN, Rahman IA, Mascaro JG, Bonser RS, Jeon Y, Hong DM, Wagner R, Thielmann M, Heusch G, Zacharowski K, Meybohm P, Bein B, Tang Y. Remote preconditioning and major clinical complications following adult cardiovascular surgery: systematic review and meta-analysis. *Int J Cardiol*. 2014;176:20–31.

51. Madathil RJ, Hira RS, Stoeckl M, Sterz F, Elrod JB, Nichol G. Ischemia reperfusion injury as a modifiable therapeutic target for cardioprotection or neuroprotection in patients undergoing cardiopulmonary resuscitation. *Resuscitation*. 2016;105:85–91.

52. Rossello X, Yellon DM. Cardioprotection: the disconnect between bench and bedside. *Circulation*. 2016;134:574–575.
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)

| #  | Searches                                                                 | Results | Search Type |
|----|--------------------------------------------------------------------------|---------|-------------|
| 1  | ischemic postconditioning/ or exp ischemic preconditioning/              | 7347    | Advanced    |
| 2  | ((ischemi$ or ischaemi$) and (conditioning$ or postconditioning$ or preconditioning$ or perconditioning$ or post-conditioning$ or pre-conditioning$ or per-conditioning$)).mp. | 11571   | Advanced    |
| 3  | or/1-2                                                                   | 11571   | Advanced    |
| 4  | remote$.mp.                                                              | 54497   | Advanced    |
| 5  | (RIPC or RPC).tw.                                                        | 1333    | Advanced    |
| 6  | (3 and 4) or 5                                                           | 1990    | Advanced    |
| 7  | exp Myocardial Infarction/ or (myocardial$ adj3 infarct$).mp.            | 212232  | Advanced    |
| 8  | (((myocardial$ or cardiac$ or heart$ or cardial$) adj3 infarct$) or (heart adj3 attack$)).mp. | 211201  | Advanced    |
| 9  | (STEMI or ((((ST-segment$ or ST segment$) adj4 elevat$) or (ST adj3 elevat$) or (non-ST adj3 elevat$) or (ST-elevation$ or non-ST-elevation$))).tw. | 20246   | Advanced    |
| 10 | or/7-9                                                                   | 220643  | Advanced    |
| 11 | 6 and 10                                                                 | 271     | Advanced    |
| 12 | Myocardial Reperfusion Injury/                                           | 12203   | Advanced    |
| 13 | (myocardi$ adj3 injur$).mp.                                              | 20516   | Advanced    |
| 14 | or/12-13                                                                 | 20516   | Advanced    |
| 15 | 6 and 14                                                                 | 266     | Advanced    |
| 16 | exp Thrombolytic Therapy/ or exp Fibrinolytic Agents/ or Mechanical Thrombolysis/ | 162766  | Advanced    |
| 17 | (thrombolys$ or thrombolytic$ or fibrinolytic or fibrolytic$ or alteplase or antifibrinolytic$ or enoxaparin or fibrinogen or fibrinolysis or plasminogen or streptokinase or tenecteplase or |
urokinase or reteplase or clexane or drotrecogin).tw.  
124965 Advanced

18 or/16-17 239943 Advanced
19 6 and 18 27 Advanced
20 exp percutaneous coronary intervention/ 39914 Advanced
21 (percutaneous adj3 coronary$ adj3 (angioplast$ or intervention$ or revascularization$)).tw. 28091 Advanced
22 ((primary or percutaneous or coronary) and (PCI or PPCI or PTCA)).tw. 18621 Advanced
23 angioplast$.tw. 38275 Advanced
24 or/20-23 73628 Advanced
25 6 and 24 82 Advanced
26 exp Myocardium/ or myocardi$.mp. 498663 Advanced
27 6 and 26 508 Advanced
28 Ischemic Preconditioning, Myocardial/ 3570 Advanced
29 28 and (4 or 5) 260 Advanced
30 11 or 15 or 19 or 25 or 27 or 29 530 Advanced
31 random$.tw. or randomized controlled trial/ 916900 Advanced
32 30 and 31 195 Advanced
33 limit 30 to "therapy (best balance of sensitivity and specificity)"
34 32 or 33 198 Advanced
35 systematic review/ or meta analysis.mp,pt. or MEDLINE.tw. or systematic review.tw. 172397 Advanced
36 30 and 35 27 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]