

### Remote Ischemic Conditioning for the Reduction of Ischemia-Reperfusion Injury in Acute Myocardial Infarction

#### Summary

- ✓ The autoRIC Device is a non-invasive device that provides automated delivery of remote ischemic conditioning (RIC), a temporary stop and restart of blood flow through a series of inflations and deflations of a blood pressure arm cuff. RIC is a novel adjunctive therapy for protection against ischemia-reperfusion injury in patients presenting with ST-segment elevation myocardial infarction (STEMI).
- ✓ Five randomized controlled trials (RCTs) involving 902 patients have reported short-term improvements in surrogate biomarkers of ischemia-reperfusion injury, microvascular reperfusion, left ventricular function, and contrast medium-induced acute kidney injury in STEMI patients receiving RIC as an adjunctive therapy to percutaneous coronary intervention (PCI). A substantial proportion of the original cohort was excluded from the final analysis in four of the trials, which may have introduced selection bias.
- ✓ A four-year extension study of 251 patients suggests that RIC may have persistent effects on clinical outcomes, but the study lacked adequate statistical power to detect differences in clinical end points.
- ✓ No safety issues or complications associated with RIC were observed in any of the trials.
- ✓ Two large, multi-centre RCTs are in progress to determine whether using the autoRIC Device as an adjunctive therapy to PCI can reduce the rates of cardiovascular death and hospitalization for heart failure at one year in STEMI patients. The first is a pan-European trial that will treat patients with RIC during ambulance transport to hospital. The second trial, based in the United Kingdom, will treat patients with RIC after presentation to the emergency room. The two trials will enroll an estimated 4,000 patients, with completion anticipated in 2016.

- ✓ The effects of RIC on clinical outcomes such as hospitalization, heart failure, and mortality in various patient subpopulations will need to be determined before translation into current clinical practice for STEMI. Pending confirmatory evidence to support routine use, health care practitioners interested in piloting RIC as an adjunctive treatment for STEMI patients will need to ensure that the RIC protocol does not delay the initiation of PCI, and consider possible adverse effects such as bruising and hematomas in thrombolitically treated patients.

#### Background

A myocardial infarction occurs when a thrombus forms in a coronary artery, resulting in a sudden disruption in blood flow to the heart muscle (ischemia) and the death of heart tissue.<sup>1</sup> Prompt restoration of blood flow (reperfusion) is the most effective strategy for reducing myocardial infarct size (the extent of heart tissue death), heart failure, ventricular arrhythmias, and mortality following a myocardial infarction.<sup>1</sup> However, when blood flow to cardiac cells is disrupted and then restored, this precipitates further heart damage known as ischemia-reperfusion injury.<sup>2</sup>

Despite considerable improvements in prophylaxis therapies and reperfusion strategies,<sup>3-5</sup> myocardial infarctions are a leading cause of morbidity and mortality in Canada.<sup>6</sup> Many adjuvant treatments to limit or prevent ischemia-reperfusion injury including pharmacological agents (e.g., adenosine and erythropoietin), mechanical cardioprotection (e.g., thrombus aspiration and thrombectomy), and endovascular cooling have been investigated but none have shown consistent benefit.<sup>7-10</sup> An alternative therapeutic approach to prevent ischemia-reperfusion injury is to harness innate mechanisms that condition the heart to protect itself against injury.<sup>7</sup> One strategy is to apply brief episodes of ischemia followed by reperfusion to the infarct-related coronary artery using an angioplasty balloon, known as local ischemic post-conditioning.<sup>11</sup> However, the protective effect of local ischemic post-conditioning has not been shown to be consistent in myocardial infarction patients, and there

are potential safety concerns including additional myocardial injury, deterioration of organ function, and possible thrombus microembolization.<sup>12,13</sup>

Remote ischemic conditioning (RIC) is a novel, non-invasive technique that uses brief cycles of inflation and deflation of a blood pressure cuff on a limb distant from the heart.<sup>14</sup> The mechanism through which RIC protects the myocardium from ischemic-reperfusion injury is unclear, although it has been suggested that a neurohormonal pathway conveys a cardioprotective signal to the heart from the remotely conditioned limb.<sup>15-17</sup> The stimulus can be applied before (pre-conditioning), during (per-conditioning), or immediately after (post-conditioning) the ischemic event.<sup>11</sup> Since a myocardial infarction is an unpredictable event, pre-conditioning can only be used during elective interventions associated with myocardial ischemia-reperfusion injury such as non-emergent coronary artery bypass grafting (CABG) or percutaneous coronary interventions (PCI).<sup>18</sup> Implementing RIC as an adjunct to standard-of-care in acute care settings may improve patient outcomes following myocardial infarction.

## The Technology

The autoRIC Device (CellAegis Devices, Inc., Toronto, Ontario) is a non-invasive, portable device that provides automated delivery of RIC as an alternative to manually operating a standard blood pressure cuff.<sup>19</sup> The autoRIC Device System consists of a reusable controller, battery-charging cradle, and a single-use, patient-specific cuff. Placed on the arm, the device allows for the consistent delivery of RIC as five-minute inflation and deflation cycles for a total of 40 minutes. The process is compatible with current standard-of-care treatments and can be applied in the ambulance, in a hospital, or at home, as directed by a health care professional. The automated device is expected to be easier to use and more reliable than using a standard manual blood pressure cuff,<sup>20</sup> and there is limited risk of the arm remaining occluded or non-delivery of therapy if the health care practitioner is called away.

## Regulatory Status

Health Canada granted a Class III licence to CellAegis for the autoRIC Device in February 2013.<sup>21</sup> This is the first device on the market to provide automated RIC. It is approved for adults over the age of 18 experiencing acute myocardial infarction and for those undergoing cardiothoracic surgery or interventional cardiothoracic

procedures. The autoRIC Device received CE Mark certification in July 2012 for use in Europe but is not available for sale in the United States.<sup>19,22</sup>

## Patient Group

The Heart and Stroke Foundation estimates that 70,000 acute myocardial infarctions occur each year in Canada.<sup>23</sup> In 2009, there were 51,847 hospitalizations due to acute myocardial infarction in Canada, with an average cost of \$8,984.<sup>24</sup> The number of hospitalizations is expected to increase as Canada's population ages. The additional cost for the projected increase in hospitalizations to 2020 has been estimated at \$54 million.<sup>24</sup> In 2009, 15,111 deaths occurred in Canada due to myocardial infarctions.<sup>6</sup>

## Current Practice

Treatment for acute myocardial infarction focuses on restoring blood flow to the heart by removing blockages in the coronary artery within 12 hours of symptom onset.<sup>1,25,26</sup> This is achieved through emergent PCI or thrombolysis with clot-dissolving drugs. PCI is a non-surgical procedure performed in a cardiac catheterization laboratory. An angioplasty balloon is used to open up the blocked coronary artery and a stent is placed to keep the artery open. Current guidelines recommend PCI as first-line therapy for acute myocardial infarction when a catheterization laboratory is available within 90 minutes after contact with pre-hospital care providers in a PCI-capable hospital or within 120 minutes for patients transported to a PCI-capable hospital.<sup>1,25,26</sup> Thrombolysis is typically initiated within 30 minutes of hospital arrival by a physician in the emergency department when PCI cannot be performed within the specific time parameters or there are vascular access difficulties. CABG is a surgical procedure for bypassing blockages in the coronary artery but is less commonly performed because it is more invasive than PCI, with a longer recovery time. CABG is typically performed in patients with left main coronary artery disease, diabetics with multi-vessel disease, or patients who are not amenable to PCI.<sup>26</sup>

Almost 30% of Canadians aged 40 years and older do not have access to a PCI facility within the 90-minute recommended time frame.<sup>27</sup> First Nations patients in particular are less likely to undergo PCI and have a higher mortality rate from acute myocardial infarction than non-Aboriginal Canadians.<sup>28</sup> The optimization of pre-hospital strategies that reduce the transfer time

between the ambulance and a PCI centre can improve clinical outcomes and reduce mortality.<sup>29</sup> However, these pre-hospital strategies are currently underused in Canada.<sup>30</sup>

## Methods

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and The Cochrane Library (2014, Issue 8). Grey literature was identified by searching relevant sections of the *Grey Matters* checklist (<http://www.cadth.ca/resources/grey-matters>). No methodological filters were applied. The search was limited to English language documents published between January 1, 2009 and September 12, 2014. Regular alerts were established to update the search until December 2014. Peer-reviewed published studies evaluating the clinical efficacy and safety of RIC prior to reperfusion in acute myocardial infarction were considered for inclusion in the evidence section of this bulletin. Unpublished data obtained from conference presentations for the selected published studies were also included. All other unpublished data, case reports, editorials, letters, and literature reviews were excluded.

## The Evidence

Clinical data to support the use of RIC for the reduction of ischemia-reperfusion injury after acute myocardial infarction have been reported in five randomized controlled trials (RCTs). (See Table 1.)<sup>31-36</sup> All of the trials assessed efficacy using surrogate biomarkers of myocardial reperfusion injury, microvascular reperfusion, left ventricular function, and acute kidney injury as primary study end points in patients with ST-segment elevation myocardial infarction (STEMI). As the RIC protocol had to be initiated before reperfusion, randomization had to occur prior to PCI and before a definitive decision could be made as to whether the patient had met specific inclusion criteria. In addition, many of the enrolled patients did complete follow-up with the imaging data required to assess the primary end point. Therefore, between 30.8% and 74.3% of randomized patients were later excluded from the final analysis in four of the trials,<sup>31,34-36</sup> which may have introduced selection bias. An extension of one of these trials<sup>31</sup> has reported data regarding long-term clinical outcomes.<sup>37</sup> However, it was not adequately powered to detect differences in clinical end points. Four of the trials used a standard manual, upper arm blood pressure cuff, and stopwatch for the delivery of

RIC prior to reperfusion with PCI.<sup>31-35</sup> One trial used a blood pressure device (FB-270, Fakuda Denshi, Tokyo, Japan) that was modified to perform three cycles of inflation and deflation automatically.<sup>36</sup> (See Table 1.)

Bøtker et al. assessed if RIC administered in the ambulance during transport to the hospital before PCI would be beneficial for patients experiencing their first STEMI.<sup>31</sup> Patients were randomly assigned to PCI with (n = 166) or without RIC (n = 167). The myocardial area at risk (the area of heart muscle in the left ventricle at risk of damage due to coronary artery occlusion) at day 1 and the final infarct size (the proportion of dead muscle in the left ventricle following STEMI) at day 30 were quantified using single-photon emission computed tomography (SPECT). The primary end point was the myocardial salvage index, measured using the proportion of the area at risk of the left ventricle salvaged by treatment 30 days following PCI. Of the 333 patients who were initially randomized, 82 were excluded because they did not meet study criteria on arrival to the hospital, 32 were lost to follow-up, and 77 did not complete follow-up with imaging data to calculate the myocardial salvage index.

The myocardial salvage index was higher in the RIC group at 30 days (mean difference 0.12, 95% confidence interval [CI] 0.01 to 0.21;  $P = 0.0333$ ), suggesting less heart muscle damage. This was a per-protocol analysis of patients who completed follow-up, with 57.4% of the original cohort being excluded from the final analysis. Hence, the true impact of these results requires careful interpretation. Furthermore, no statistically significant differences in the secondary end points (including final infarct size at 30 days, troponin T concentrations, ST-segment resolution, death, reinfarction, left ventricular ejection fraction, and hospital admission for heart failure within 30 days) were observed. It should be noted that the infarct-related artery was not occluded prior to PCI in 50% of the included patients, which indicates that spontaneous reperfusion may have potentially diluted the beneficial effects of RIC. The presence of collateral blood flow to the area at risk in the left ventricle, which would be expected to reduce myocardial infarct size, was also not controlled for in this study. No differences in major adverse coronary events including death (n = 3 per group), reinfarction (n = 1 per group), and heart failure (n = 3 per group) were observed.

**Table 1: Remote Ischemic Conditioning in Acute Myocardial Infarction Trials**

Study Design and Location	Methods	Main Findings
<p>Bøtker et al., 2010<sup>31</sup></p> <p><b>RCT, single-centre, single-blinded (outcomes assessor)</b></p> <p>Denmark</p>	<p><b>Inclusion criteria</b>                      ≥ 18 years, presenting with chest pain before admission to hospital within 12 hours onset, ST-segment elevation MI, assigned to receive PCI on hospital arrival.</p> <p><b>Exclusion criteria</b>                      Left bundle branch block, previous MI, thrombolytic treatment in the past 30 days, previous CABG, left main stem stenosis requiring CABG, severe heart failure requiring mechanical ventilation or use of an intra-aortic pump.</p>	<p><b>Mean (SD) myocardial salvage index at 30 days</b>                      RIC plus PCI (n = 73): 0.69 (0.27)                      PCI (n = 69): 0.57 (0.26)                      (P = 0.0333)</p> <p><b>Mean (SD) final infarct size at 30 days (% of left ventricle)</b>                      RIC plus PCI (n = 109): 8 (10)                      PCI (n = 110): 12 (13)                      (P = 0.10)</p>
<p>Munk et al., 2010<sup>32</sup></p> <p><b>RCT, sub-trial of Bøtker et al., 2010<sup>31</sup></b></p>	<p><b>Study groups</b>                      RIC                      (4 × 5 min. cycles of inflation/deflation of upper arm blood pressure cuff delivered in ambulance prior to PCI)                      (n = 166)</p> <p>versus</p> <p>PCI (n = 167)</p>	<p><b>Mean (SD) LVEF at 30 days</b>                      RIC plus PCI (n = 103): 0.54 (0.08)                      PCI (n = 103): 0.53 (0.10)                      (P = 0.42)</p> <p><b>Mean (SD) LVEF at 30 days with AAR ≥ 35%</b>                      RIC plus PCI (n = 23): 0.51 (0.07)                      PCI (n = 20): 0.46 (0.09)                      (P = 0.046)</p> <p><b>Mean (SD) LVEF at 30 days with LAD coronary artery occlusion</b>                      RIC plus PCI (n = 47): 0.55 (0.08)                      PCI (n = 50): 0.50 (0.11)                      (P = 0.04)</p>
<p>Sloth et al., 2014<sup>37</sup></p> <p><b>RCT, extension study of Bøtker et al., 2010<sup>31</sup></b></p>		<p><b>Primary composite end point MACCE N (%)</b>                      RIC plus PCI (n = 126): 17 (13.5)                      PCI (n = 125): 32 (25.6)                      HR 0.49 (95% CI 0.27 to 0.89; P = 0.018)</p> <p><b>All-cause mortality N (%)</b>                      RIC plus PCI (n = 126): 5 (4.0)                      PCI (n = 125): 15 (12.0)                      HR 0.32 (95% CI 0.12 to 0.88; P = 0.027)</p> <p><i>Cardiac mortality</i>                      RIC plus PCI (n = 126): 2 (1.6)                      PCI (n = 125): 5 (4.0)                      HR 0.39 (95% CI 0.08 to 2.00; P = 0.258)</p> <p><i>Non-cardiac mortality</i>                      RIC plus PCI (n = 126): 3 (2.4)                      PCI (n = 125): 10 (8.0)                      HR 0.28 (95% CI 0.08 to 0.1.03; P = 0.056)</p> <p><b>MI N (%)</b>                      RIC plus PCI (n = 126): 8 (6.4)                      PCI (n = 125): 11 (8.8)                      HR 0.69 (95% CI 0.28 to 1.71; P = 0.423)</p> <p><b>Readmission for heart failure N (%)</b>                      RIC plus PCI (n = 126): 4 (3.2)                      PCI (n = 125): 7 (5.6)                      HR 0.54 (95% CI 0.16 to 1.85; P = 0.327)</p> <p><b>Ischemic stroke/Transient ischemic attack N (%)</b>                      RIC plus PCI (n = 126): 3 (2.4)                      PCI (n = 125): 4 (3.2)                      HR 0.72 (95% CI 0.16 to 3.23; P = 0.670)</p>

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<p>Rentoukas et al., 2010<sup>33</sup></p> <p><b>RCT, single-centre, single-blinded (outcomes assessor)</b></p> <p>Greece</p>	<p><b>Inclusion criteria</b> Age 35 to 75 years, acute ST-segment elevation MI with accompanying chest pain, symptom onset not more than 6 hours before presentation.</p> <p><b>Exclusion criteria</b> Cardiogenic shock and moderate-to-severe renal failure.</p> <p><b>Study groups</b> RIC (3 × 4 min. cycles of inflation/deflation of upper arm cuff initiated on arrival to hospital 10 min. prior to PCI) plus PCI (n = 33)</p> <p>versus</p> <p>RIC with morphine infusion 5 min. prior PCI (n = 33)</p> <p>versus</p> <p>PCI (cuff placed on upper arm and inflated to a pressure below diastolic blood pressure and normal saline solution infusion) (n = 30)</p>	<p><b>Proportion with ST-segment resolution ≥ 80% at 30 min.</b> RIC plus PCI (n = 33): 73% RIC with morphine plus PCI (n = 33): 82% PCI (n = 30): 53% (P = 0.045 RIC groups versus PCI)</p> <p><b>Mean (SD) reduction of ST-segment deviation score (%)</b> RIC plus PCI (n = 33): 69.9 (29.1) RIC with morphine plus PCI (n = 33): 87.3 (15.4) PCI (n = 30): 53.2 (35.2) (P = 0.054 RIC versus PCI) (P = 0.00001 RIC with morphine versus PCI) (P = 0.036 RIC with morphine versus RIC)</p> <p><b>Mean (SD) peak troponin I levels (ng/mL)</b> RIC plus PCI (n = 33): 166.0 (160.8) RIC with morphine plus PCI (n = 33): 103.3 (76.5) PCI (n = 30): 255.5 (194.5) (P = 0.062 RIC versus PCI) (P = 0.0004 RIC with morphine versus PCI) (P = 0.063 RIC with morphine versus RIC)</p>
<p>Prunier et al., 2014<sup>34</sup></p> <p><b>RCT, multi-centre, single-blinded (outcomes assessor)</b></p> <p>France</p>	<p><b>Inclusion criteria</b> ≥ 18 years, ST-segment elevation MI admitted to the catheterization laboratory within 6 hours of symptom onset.</p> <p><b>Exclusion criteria</b> History of MI, cardiogenic shock, cardiac arrest before admission, arrhythmias requiring electric shock before admission, occlusion site elsewhere than LAD coronary and right coronary artery, reperfusion or collateral flow before PCI, external electric shock for cardioversion within first 3 days, cardiac surgery within first 3 days, missing CK-MB data.</p> <p><b>Study groups</b> RIC (3 × 5 min. cycles of inflation/deflation of upper arm cuff initiated on arrival to hospital prior to PCI) (n = 36)</p> <p>versus</p> <p>RIC with IPost (4 × 1 min. cycles of inflation/deflation of angioplasty balloon after PCI) (n = 71)</p> <p>versus</p> <p>PCI (n = 44)</p>	<p><b>Mean (SD) CK-MB AUC at 72 hours (a.u.)</b> RIC plus PCI (n = 18): 5,038 (3,187) RIC with IPost plus PCI (n = 20): 5,156 (2,799) PCI (n = 17): 7,222 (3,021) (ANOVA, P = 0.061)</p> <p><b>Mean (SD) CK-MB AUC to AAR ratio (a.u.)</b> RIC plus PCI (n = 18): 138 (71) RIC with IPost plus PCI (n=20): 132 (70) PCI (n=17): 206 (66) (P = 0.006 RIC versus PCI) (P = 0.002 RIC with IPost versus PCI) (P = 0.797 RIC with IPost versus RIC)</p> <p><b>Mean (SD) peak CK-MB level to AAR ratio (a.u.)</b> RIC plus PCI (n = 18): 7.34 (4.04) RIC with IPost plus PCI (n = 20): 7.61 (4.76) PCI (n = 17): 11.55 (3.78) (P = 0.006 RIC versus PCI) (P = 0.007 RIC with IPost versus PCI) (P = 0.844 RIC with IPost versus RIC)</p>

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<p>White et al., 2014<sup>35</sup></p> <p><b>RCT, single-centre, single-blinded (outcomes assessor)</b></p> <p>United Kingdom</p>	<p><b>Inclusion criteria</b> Age 18 to 80 years, presenting within 12 hours of onset of chest pain, ST-segment elevation MI, and complete occlusion in the infarct-related artery prior to PCI.</p> <p><b>Exclusion criteria</b> Cardiac arrest (pre- or post-PCI), cardiogenic shock, previous MI or CABG, significant coronary collateralization to the AAR, and any contraindication to CMR imaging.</p> <p><b>Study groups</b> RIC (4 × 5 min. cycles of inflation/deflation of upper arm cuff on arrival to hospital prior to PCI) (n = 159)</p> <p>versus</p> <p>PCI alone (uninflated cuff placed on upper arm for 40 min.) (n = 164)</p>	<p><b>Mean (SD) infarct size at days 3 to 6 (% of left ventricle)</b> RIC plus PCI (n = 43): 18.0 (10) PCI (n = 40): 24.5 (12.0) (P = 0.009)</p> <p><b>Mean (SD) troponin T levels at 24 hours (ng/mL)</b> RIC plus PCI (n = 89): 2,296 (263) PCI (n = 84): 2,736 (325) (P = 0.037)</p> <p><b>Mean (SD) extent of edema at days 3 to 6 (% of left ventricle)</b> RIC plus PCI (n = 43): 28.5 (9) PCI (n = 40): 35.1 (10) (P = 0.003)</p> <p><b>Mean (SD) myocardial salvage index at days 3 to 6</b> RIC plus PCI (n = 43): 0.42 (0.29) PCI (n = 40): 0.28 (0.29) (P = 0.031)</p>
<p>Yamanaka et al., 2015<sup>36</sup></p> <p><b>RCT, multi-centre, single-blinded (outcomes assessor)</b></p> <p>Japan</p>	<p><b>Inclusion criteria</b> Age 20 years or older, presenting with chest pain within 24 hours of onset, ST-segment elevation MI, clinically assigned to receive PCI.</p> <p><b>Exclusion criteria</b> Left bundle branch block, previous CABG, severe heart failure requiring percutaneous cardiopulmonary support, severe chronic kidney disease requiring dialysis or continuous hemodiafiltration.</p> <p><b>Study groups</b> RIC (3 × 5 min. cycles of inflation/deflation of upper arm cuff on arrival to hospital prior to PCI) (n = 63)</p> <p>versus</p> <p>PCI alone (uninflated cuff placed on upper arm for 30 min.) (n = 62)</p>	<p><b>CI-AKI at 48 to 72 hours N (%)</b> RIC plus PCI (n = 47): 5 (10.6) PCI (n = 47): 17 (36.2) (P = 0.003)</p> <p><b>Mean (SD) serum creatinine levels at 48 to 72 hours (mg/dL)</b> RIC plus PCI (n = 47): 0.81 (0.21) PCI (n = 47): 1.03 (0.61) (P = 0.02)</p> <p><b>Ventricular tachycardia/ Ventricular fibrillation within 24 hours N (%)</b> RIC plus PCI (n = 47): 1 (2) PCI (n = 47): 7 (14) (P = 0.02)</p> <p><b>Mean (SD) peak creatinine kinase (IU/L)</b> RIC plus PCI (n = 47): 2,648 (1,929) PCI (n = 47): 3,653 (2,894) (P = 0.04)</p>

Note: A P-value of < 0.05 is considered statistically significant for between-group comparisons.

AAR = area at risk; ANOVA = analysis of variance; AUC = area under the curve; CABG = coronary artery bypass grafting; CI = confidence interval; CI-AKI = contrast medium-induced acute kidney injury; CK-MB = creatine kinase-MB isoenzyme; CMR = cardiac magnetic resonance; HR = hazard ratio; IPost = local ischemic post-conditioning; LAD = left anterior descending; LVEF = left ventricular ejection fraction; MACCE = major adverse cardiovascular and cerebrovascular event; MI = myocardial infarction; min. = minutes; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; RIC = remote ischemic conditioning; SD = standard deviation.

Unpublished results presented at the American Heart Association 2014 Scientific Sessions from a retrospective analysis of the original cohort assessed by Bøtker et al. suggest that RIC may have a cardioprotective effect on STEMI patients who do not have timely access to PCI.<sup>38</sup> A delay in the initiation of PCI was associated with a reduction in the myocardial salvage index ( $P = 0.008$ ) and an increase in the final infarct size ( $P = 0.043$ ) in patients treated with PCI alone. These effects were attenuated in patients treated with RIC ( $P = 0.737$  and  $P = 0.628$ , respectively). Unpublished results from a post-hoc analysis evaluating the effects of cardiovascular risk factors (including age, gender, smoking status, obesity, diabetes mellitus, hypertension, and left ventricular hypertrophy) and medication (including beta blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, and statins) on the efficacy of RIC were presented at the 2014 European Society of Cardiology Congress.<sup>39</sup> Stratified analyses for the difference in myocardial salvage index between the two groups showed that the effect of RIC tended to be reduced among smokers, but was consistent for all other subgroups, regardless of the presence of cardiovascular risk factors and medication use.

Munk et al. assessed the effect of RIC on left ventricular function using echocardiography and SPECT in a sub-trial ( $n = 242$ ) of the original patient cohort.<sup>32</sup> No statistically significant differences in left ventricular function at day 1 and after 30 days between RIC and PCI only groups were observed. This may be explained by the predominance of patients with a small-to-moderate area at risk and the limitations of accurately measuring small differences in left ventricular function with echocardiography. In a subgroup of patients at a high risk of developing a large infarction (i.e., those with a myocardial area at risk  $\geq 35\%$  and those with the occlusion occurring in the left anterior descending coronary artery), RIC improved left ventricular function at 30 days ( $P = 0.046$  and  $P = 0.04$  for these subgroups, respectively). These results should be interpreted with caution, as the subgroup analyses were not pre-specified in the original trial design and a type I error cannot be ruled out.

Sloth et al. investigated whether the changes reported by Bøtker et al. in surrogate biomarkers for reperfusion injury with RIC translated into improvements in long-term clinical outcomes in STEMI patients.<sup>37</sup> The primary outcome was major adverse cardiovascular

and cerebrovascular events (MACCEs), defined as a composite end point encompassing all-cause mortality, non-fatal myocardial infarction, readmission for heart failure, and ischemic stroke/transient ischemic attack. The individual components of the primary end point comprised the secondary end points. Outcome data were obtained from Danish nationwide medical registries, with a median follow-up of 3.8 years. Trial staff members responsible for collection and analyses of follow-up data were blinded to treatment assignment. In the per-protocol analysis of 251 patients fulfilling trial criteria, significantly fewer MACCEs in the RIC group were observed compared with the PCI-only group (hazard ratio [HR] 0.49, 95% CI 0.27 to 0.89;  $P = 0.018$ ). This reduction was driven by a difference in all-cause mortality (HR 0.32, 95% CI 0.12 to 0.88;  $P = 0.027$ ). The predominant difference in all-cause mortality was the lower rate of cancer deaths in the RIC group. The authors are cautious of these findings, as the original study was not adequately powered to detect differences in clinical outcomes.

Rentoukas et al. tested the effects of RIC initiated prior to PCI combined with morphine administration in STEMI patients.<sup>33</sup> They enrolled 96 patients who were randomly assigned to one of three reperfusion strategies: PCI alone, RIC plus PCI, and RIC plus PCI with morphine. Spontaneous reperfusion or collateral blood flow to the area at risk prior to PCI were not controlled for in this study. The ST-segment deviation score was calculated as the sum of all ST-segment deviations from baseline in a standard 12-lead electrocardiogram. The primary end point was the number of patients achieving full ST-segment resolution (defined as  $\geq 80\%$  reduction of the ST-segment deviation score) 30 minutes after PCI. The difference in the number of patients achieving full ST-segment resolution was statistically significant in the two RIC groups (RIC 73%, RIC with morphine 82%) compared with the PCI alone group (53%;  $P = 0.045$ ). The addition of morphine to RIC did not improve the number of patients achieving full ST-segment resolution compared with patients receiving RIC alone. However, morphine administration with RIC was associated with greater reductions in secondary outcomes including peak troponin I levels and degree of ST-segment return to baseline (expressed as the percent reduction in ST-segment deviation score) compared with the PCI alone group (103.3 ng/mL versus 194.5 ng/mL;  $P = 0.0004$  and 15.4% versus 35.2%;  $P = 0.00001$ , respectively). The differences between the RIC group

and the PCI alone group did not achieve statistical significance for these secondary outcomes.

Prunier et al. investigated whether RIC in combination with local ischemic conditioning would reduce myocardial infarct size in STEMI patients.<sup>34</sup> A total of 151 patients were randomized to one of the following groups: PCI alone (n = 44), RIC plus PCI (n = 36), or RIC with local ischemic conditioning plus PCI (n = 71). Given that randomization had to be performed prior to PCI, several of the exclusion criteria were unknown at the time of randomization. Of the 151 patients who were initially randomized, 91 were excluded because they did not meet study criteria on arrival to the hospital, and five were excluded at the time of blinded analysis. The primary end point was the area under the curve (AUC) of serum creatinine kinase-MB isoenzyme (CK-MB) release as a surrogate marker of infarct size 72 hours after PCI. The per-protocol analysis showed that the differences in the CK-MB AUC among the three groups were not statistically significant (RIC 5038 a.u., RIC with local ischemic conditioning 5156 a.u., PCI 7222; ANOVA,  $P = 0.061$ ). The benefits of RIC appeared to be greater when infarct size was corrected based on the area at risk. Peak CK-MB, CK-MB AUC to area at risk ratio, and peak CK-MB level to area at risk ratio were all statistically significantly reduced in the RIC groups compared with the PCI group. There was no benefit of adding local ischemic conditioning to RIC.

White et al. randomly assigned 323 STEMI patients to PCI with (n = 159) or without RIC (n = 164).<sup>35</sup> The primary end point was myocardial infarct size measured by cardiac magnetic resonance (CMR) on days 3 to 6 after admission. CMR is expected to be more sensitive to either serum cardiac enzymes or SPECT for measuring the reduction in myocardial infarct size.<sup>40</sup> Of the 323 patients who were initially randomized, 55 were excluded due to premature discontinuation, 71 were excluded because they did not meet study criteria on arrival to the hospital, and 114 did not complete CMR for estimation of myocardial infarct size. Results showed that RIC significantly reduced myocardial infarct size compared with the PCI alone group (18.0% versus 24.5%;  $P = 0.009$ ). In a multivariable analysis adjusting for the effects of baseline demographic measures (including age, gender, body mass index, smoking status, hypertension, dyslipidemia, diabetes, family history of coronary artery disease, pre-infarct angina, ischemia time), the reduction in myocardial infarct size remained statistically significant

( $P = 0.025$ ). RIC was also found to reduce the extent of myocardial edema ( $P = 0.003$ ), reduce troponin T levels at 24 hours ( $P = 0.037$ ), and improve the myocardial salvage index ( $P = 0.031$ ).

Yamanaka et al. investigated whether RIC could reduce contrast medium-induced acute kidney injury (CI-AKI), a complication that occurs after the administration of the dye used to locate the area of coronary artery occlusion during PCI.<sup>36</sup> A total of 125 STEMI patients were randomly assigned on arrival to hospital to PCI with (n = 63) or without RIC (n = 62). Twenty-nine patients were excluded because they did not meet the inclusion criteria or withdrew informed consent. The primary end point was the incidence of CI-AKI, which was defined as an increase in serum creatinine greater than 0.5 mg/dL or more than 25% over the baseline value 48 to 72 hours after administration of contrast medium. RIC significantly reduced CI-AKI compared with the PCI alone group (10.6% versus 36.2%;  $P = 0.003$ ). Multivariate logistic analysis showed that this protective effect was independent of other risk factors such as age, gender, and smoking status. Serum creatinine was significantly higher in the PCI alone group than in the RIC group 48 to 72 hours after contrast medium injection ( $1.03 \pm 0.61$  mg/dL versus  $0.81 \pm 0.21$  mg/dL;  $P = 0.02$ ). Infarct size (estimated by peak creatinine kinase) was significantly higher in the PCI alone group than in the RIC group ( $3,653 \pm 2,894$  IU/L versus  $2,648 \pm 1,929$  IU/L;  $P = 0.04$ ). The incidence of sustained ventricular tachycardia or ventricular fibrillation within 24 hours after PCI was significantly lower in the RIC group (2% versus 14%;  $P = 0.01$ ). There was no difference between the groups in left ventricular function two weeks after PCI. The incidence of MACCEs (including severe heart failure, ischemic stroke, left ventricular perforation, and cardiac death) 30 days following PCI tended to be lower in the RIC group (two patients, 4%) compared with the PCI only group (seven patients, 14%), but the difference was not statistically significant ( $P = 0.07$ ). However, the study was not powered to detect differences in clinical end points.

A large-scale trial is currently evaluating whether the autoRIC Device when used prior to PCI in STEMI patients can improve cardiovascular mortality and hospitalization for heart failure at one year.<sup>41</sup> The multi-centre, single-blinded RCT is being conducted at various sites in Europe and is expected to enroll 2,300 patients. RIC will be delivered in the ambulance during transport to the PCI unit. In recruiting centres



where randomization occurs at the hospital or in cases with short transportation time, RIC will continue during PCI until successful or until immediately before reperfusion. Secondary outcomes are myocardial infarct size on day 3; left ventricular function on day 3 and at three months post-PCI; and reinfarction, stroke, and revascularization at one year. A second large, multi-centre RCT in the United Kingdom (UK) is also evaluating whether the autoRIC Device can improve cardiovascular mortality and hospitalization for heart failure at one year. This trial will enroll 1,700 STEMI patients presenting to the hospital emergency department, who will receive RIC treatment prior to PCI. The estimated completion date for both trials is December 2016.

Another single-blinded, single-centre RCT is currently recruiting 100 STEMI patients in Korea to evaluate whether RIC can reduce infarct size.<sup>42</sup> The primary end point is myocardial salvage index measured by CMR three to five days after PCI. Study completion is expected in July 2017.

## Adverse Effects

No safety issues or complications associated with RIC were observed in any of the trials.<sup>31,33-36</sup>

## Cost

The price of the autoRIC Device in Canada ranges between \$1,400 and \$2,100 and is expected to have an average lifespan of five to six years. The price for the single-use cuff is \$105.

## Concurrent Developments

There are several other approaches currently under investigation for the prevention of ischemia-reperfusion injury in STEMI patients.

### Remote Ischemic Conditioning in Thrombolitically Treated STEMI Patients

The first study evaluating RIC in STEMI patients treated with thrombolysis is being conducted in Mauritius, a developing country with a high prevalence of cardiovascular disease but with limited access to PCI.<sup>43</sup> The single-blinded, multi-centre RCT is evaluating 520 patients (40% diabetic, 40% hypertensive) for the primary outcome of myocardial infarct size (measured by 24-hour AUC of serum CK-MB and troponin T sampled up to 24 hours post-thrombolysis). Preliminary results presented at the 2014

European Society of Cardiology Congress show that RIC reduced myocardial infarct size by 17% compared with PCI alone (statistical significance not reported).<sup>44</sup>

### Remote Ischemic Post-Conditioning of Lower Limb

One open-label, multi-centre RCT (n = 96) has shown that RIC using a blood pressure cuff on the upper thigh initiated at the same time as PCI in STEMI patients can decrease enzymatic infarct size (measured by the median area under the CK-MB curve 72 hours after randomization) when compared with PCI alone (relative reduction [RR] 20%, 95% CI 0.2% to 28.7%;  $P = 0.043$ ).<sup>45</sup> Improvements were also noted in edema volume three to five days after randomization (RR 20.6%, 95% CI 2.6% to 42.2%;  $P = 0.049$ ) and ST-segment resolution greater than 50% 60 minutes after reperfusion (66% versus 37%;  $P = 0.015$ ). Another open-label, multi-centre RCT is currently recruiting participants to test if RIC during and after PCI on a lower limb can reduce ischemia-reperfusion injury in an estimated 120 STEMI patients.<sup>46</sup> The primary outcome is myocardial infarct size measured using CMR at four to seven days. Other outcome measures include myocardial infarct size and left ventricular function at six months. Study completion is estimated to occur in April 2015.

### Local Ischemic Post-Conditioning

A large (n = 2000), multi-centre, single-blinded RCT in Denmark is studying the efficacy of local ischemic post-conditioning for STEMI patients.<sup>47</sup> Following reopening of the infarct-related coronary artery with PCI, local ischemic post-conditioning will be applied with brief episodes of ischemia followed by reperfusion using an angioplasty balloon. Participants will be randomly assigned to one of three groups: conventional PCI (immediate stent placement), PCI with deferred stenting (after 48 hours), or conventional PCI with local ischemic conditioning. The primary outcome is a combined end point of all-cause mortality and heart failure at two years. Study completion is anticipated to occur in February 2019.

### Pharmacological Conditioning

Increasing knowledge of the mechanistic pathways involved in ischemic conditioning has encouraged the identification of potential targets for pharmacological intervention against ischemia-reperfusion injury.<sup>7</sup> Phase 2 trials have shown that infusion before PCI of various pharmacological agents including cyclosporine, exenatide, and metoprolol can reduce infarct size in STEMI patients undergoing PCI.<sup>12</sup> One phase 2 trial (n = 270) has reported positive long-term effects of

intravenous infusion of metoprolol before reperfusion with PCI in STEMI patients.<sup>48</sup> Left ventricular ejection fraction was significantly higher at six months in the metoprolol group (adjusted treatment effect 3.49%, 95% CI 0.44% to 6.55%;  $P = 0.025$ ). At a median follow-up of two years, hospital admission for heart failure was also lower in the metoprolol group (HR 0.32, 95% CI 0.015 to 0.95;  $P = 0.046$ ). A large-scale phase 3 trial is currently underway to determine whether cyclosporine infusion prior to PCI in STEMI patients can improve long-term clinical outcomes.<sup>49</sup> An estimated 972 patients will be assessed for the primary outcome measure of the combined incidence of total mortality, hospitalization for heart failure, and left ventricular remodelling at one year after treatment. The estimated study completion date is February 2017.

## Rate of Technology Diffusion

The discovery that RIC can be delivered safely and non-invasively has extended its potential application to several clinical settings involving protection from acute ischemia-reperfusion injury in other vital organs such as the brain, kidney, intestine, and liver.<sup>50</sup> Over the past few years, RIC has been extensively studied for various indications in over 20,000 patients currently enrolled or having completed trials.<sup>51</sup>

### **Trials Investigating the autoRIC Device for Other Indications**

Two phase 2 trials are currently investigating the efficacy of the autoRIC Device when used at home over a four-week period for reducing the progression to heart failure following STEMI.<sup>52,53</sup> The first trial is a single-centre RCT in the UK comparing chronic RIC to sham conditioning in 90 patients.<sup>52</sup> The primary outcome is mean change in left ventricular ejection fraction at four months. The second trial is a Canadian multi-centre RCT comparing chronic RIC with sham conditioning in 82 patients.<sup>53</sup> The primary outcome of the study is change from baseline in left ventricular end diastolic volume at 28 days post-PCI. Study completion is anticipated in 2015 for both trials.

A single-centre RCT in Canada is evaluating the ability of the autoRIC Device to reduce acute kidney injury induced by intraoperative renal ischemia during partial nephrectomy.<sup>54</sup> Twenty-four adult patients with renal carcinoma scheduled to undergo partial nephrectomy are enrolled. The primary outcome is change in kidney function 24 hours following the surgical procedure. Study completion was anticipated in May 2014, but results have not yet been released. Another Canadian

study is slated to begin recruiting participants to evaluate whether the autoRIC Device improves the ability of trauma patients with hemorrhagic shock to clot blood.<sup>55</sup> The single-centre RCT will measure changes in markers for inflammation and coagulation over 24 hours in an estimated 40 patients. Study completion is estimated in September 2016.

### **Trials Investigating Remote Ischemic Conditioning for Other Indications**

Results from a recent systematic review indicate that RIC significantly reduces the incidence of periprocedural myocardial infarction in patients undergoing elective PCI (pooled odds ratio [OR] 0.577, 95% CI 0.400 to 0.833;  $P = 0.003$ ) (four studies, 636 patients).<sup>56</sup> In addition, long-term outcomes of RIC in patients undergoing elective PCI ( $n = 972$ ) have recently been reported.<sup>57</sup> Over a follow-up of up to six years, patients receiving RIC in addition to PCI had a lower MACCE rate (HR 0.58, 95% CI 0.35 to 0.97;  $P = 0.039$ ). The number needed to treat to prevent one MACCE at six years was eight and the absolute risk reduction was 0.13. In a systematic review of patients undergoing major adult cardiovascular surgery (2,200 patients, 23 trials), RIC was not associated with a statistically significant effect on clinical end points including death, perioperative myocardial infarction, renal failure, stroke, mesenteric ischemia, and hospital length of stay.<sup>58</sup> However, one study has indicated that RIC may have long-term benefits in patients undergoing CABG.<sup>59</sup> The trial randomized 329 patients to receive surgery preceded by RIC or surgery alone.<sup>59</sup> Over a mean follow-up of 1.54 years, patients receiving RIC had lower all-cause mortality (HR 0.27, 95% CI 0.08 to 0.98;  $P = 0.046$ ).

A large-scale, multi-centre RCT in the UK is currently investigating the effect of RIC on clinical outcomes in high-risk patients undergoing CABG.<sup>60</sup> The primary combined end point of cardiovascular death, non-fatal myocardial infarction, coronary revascularization, and stroke will be assessed in 1,610 participants at one year post-surgery. Study completion is anticipated in March 2015. Another large-scale, multi-centre RCT evaluating the effects of RIC on a composite outcome (all-cause mortality, non-fatal myocardial infarction, stroke, and acute renal failure) until hospital discharge in cardiac surgical patients in Germany was terminated in September 2014 after failing to recruit the anticipated 2,070 participants.<sup>61</sup>

Several ongoing trials are also evaluating RIC for other indications including stroke, heart failure, kidney injury following cardiac surgery or elective coronary angiography, organ transplantation, cardiovascular surgery in children, orthopedic surgery, thoracic surgery, and abdominal surgery.<sup>51</sup>

## Implementation Issues

RIC is emerging as a promising adjunctive treatment to PCI for the prevention of ischemia-reperfusion injury in STEMI patients. The autoRIC Device provides a time-efficient option for the consistent delivery of RIC that can be performed before or at the time of hospital admission. Although use of the autoRIC Device will necessitate using health care resources in terms of the cost of the device, there are no related infrastructure costs and minimal training will be required.

Evidence to support the efficacy of RIC for the reduction of ischemia-reperfusion injury in STEMI patients is largely based on short-term improvements in surrogate end points using a standard blood pressure cuff and stopwatch.<sup>31-35</sup> RIC has also been shown to decrease the incidence of CI-AKI and dysrhythmic events following PCI in STEMI patients.<sup>36</sup> The only trial that has assessed long-term clinical outcomes noted that the reduction in MACCE was driven by non-cardiac mortality but was not adequately powered to detect differences in clinical end points.<sup>37</sup> Ongoing, multi-centre clinical trials will help determine the effect of the autoRIC Device on clinical outcomes.<sup>41</sup> If the results demonstrate a reduction in cardiovascular mortality or hospitalization for heart failure following STEMI, this could have a significant impact on the Canadian health care system.

Further research is required to clarify several other knowledge gaps.<sup>11,62-64</sup> It is not known whether the benefit achieved from RIC is dependent on the method for reperfusion (i.e., PCI versus thrombolysis). More studies are required to support treatment decisions in subpopulations and the optimal timing for RIC delivery with regard to symptom onset and initiation of reperfusion. Although current evidence suggests that comorbidities and concomitant medications do not influence the beneficial effects of RIC in STEMI patients, this needs to be confirmed in large-scale studies. Furthermore, while there have been no safety issues or complications associated with RIC, the potential for adverse effects in certain patients, such as those treated with thrombolysis, requires further assessment. The effect of RIC on other clinical

manifestations of ischemia-reperfusion injury such as myocardial stunning (a reversible post-ischemic contractility dysfunction) and microvascular dysfunction (failure of blood to reperfuse the post-ischemic vasculature) has not been explored. The optimal RIC protocol in terms of the number and duration of cycles and stimulus site (use of upper versus lower limbs, bilateral versus unilateral position, or combinations) has yet to be determined. Assessing whether there is a real-time marker that can be used to signal that a conditioned state has been achieved will also be of interest.

In summary, the effects of RIC on clinical outcomes such as quality of life, hospitalization, heart failure, and mortality will be required before translation into current clinical practice for STEMI. Pending confirmatory evidence to support routine use, health care practitioners interested in piloting RIC as an adjunctive treatment for STEMI patients will need to ensure that the RIC protocol does not delay the initiation of PCI, and consider possible adverse effects such as bruising and hematomas in thrombolytically treated patients.

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