Remote Ischemic Preconditioning in Human Coronary Artery Bypass Surgery
From Promise to Disappointment?
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Background—we assessed whether remote ischemic preconditioning (RIPC) improves myocardial, renal, and lung protection after on-pump coronary surgery.

Methods and Results—This was a single-center, prospective, randomized (1:1), placebo-controlled trial. Patients, investigators, anesthetists, surgeons, and critical care teams were blinded to group allocation. Subjects received RIPC (or placebo) stimuli (×3 upper limb (or dummy arm), 5-minute cycles of 200 mm Hg cuff inflation/deflation) before aortic clamping. Anesthesia, perfusion, cardioplegia, and surgical techniques were standardized. The primary end point was 48-hour area under the curve (AUC) troponin T (cTnT) release. Secondary end points were 6-hour and peak cTnT, ECG changes, cardiac index, inotrope and vasoconstrictor use, renal dysfunction, and lung injury. Hospital survival was 99.4%. Comparing placebo and RIPC, median (interquartile range) AUC 48-hour cTnT (ng/mL h⁻¹/48 h⁻¹); 28 (19, 39) versus 30 (22, 38), 6-hour cTnT (ng/mL⁻¹); 0.93 (0.59, 1.35) versus 1.01 (0.72, 1.43), peak cTnT (ng/mL⁻¹); 1.02 (0.74, 1.44) versus 1.04 (0.78, 1.51), de novo left bundle-branch block (4% versus 0%) and Q waves (5.3% versus 5.5%), serial cardiac indices, intraaortic balloon pump usage (8.5% versus 7.5%), inotrope (39% versus 50%) and vasoconstrictor usage (66% versus 64%) were not different. Dialysis requirement (1.2% versus 3.8%), peak creatinine (median [interquartile range], 1.2 mg/dL⁻¹ (1.1, 1.4) versus 1.2 (1.0, 1.4)), and AUC urinary albumin-creatinine ratios 69 (40, 112) versus 58 (32, 85) were not different. Intubation times; median (interquartile range), 937 minutes (766, 1402) versus 895 (675, 1180), 6-hour; 278 (210, 338) versus 270 (218, 323) and 12-hour pO₂:FiO₂ ratios 255 (195, 323) versus 263 (210, 308) were similar.

Conclusions—In contrast to prior smaller studies, RIPC did not reduce troponin release, improve hemodynamics, or enhance renal or lung protection.

Clinical Trial Registration—URL: http://www.ukcrn.org.uk. Unique identifier: 4659.

Key Words: coronary disease ■ surgery ■ coronary artery bypass ■ preconditioning

In remote ischemic preconditioning (RIPC), short cycles of repeated limb (or other organ) ischemia provoke a protective effect that can halve the mass of infarction caused by substantive vessel occlusion and reperfusion. In coronary artery bypass grafting (CABG), adverse outcomes predominantly relate to cardiomyocyte injury caused by myocardial protection failure, and there is experimental and clinical evidence that RIPC could attenuate such injury. The adequacy of myocardial protection can be assessed using an array of measurements that are indicative of cardiomyocyte death, injury, or dysfunction. These include cardiac troponin (cTn) release, the incidence of postoperative low cardiac output episodes and ventricular arrhythmias, the need for inotropic support, and functional assessment by hemodynamic monitoring and echocardiography. These measures contribute to an assessment of reversible and irreversible myocardial injury.

In elective percutaneous coronary intervention (PCI), RIPC has been associated with reduced cTnT release, less ECG ST elevation, and a reduced incidence of major adverse cardio-
vascular events. In abdominal aortic aneurysm repair, RIPC induced by intermittent iliac artery occlusion reduces the incidence of myocardial injury and may reduce postoperative renal impairment.

In cardiac surgery, the first clinical report of a protective RIPC effect was in children. RIPC, induced by four 5-minute cycles of lower limb ischemia-reperfusion, resulted in lower cTnI release, reduced inotrope requirements, and lower airway resistance, implying a possible protective effect on myocardial injury, function, and bypass-related lung injury, a finding also demonstrated in experimental models.

Two studies in CABG patients, one investigating RIPC in CABG undertaken using predominantly intermittent ischemic arrest and a second using cardioplegia, have been reported. Both were single blinded, used a 3-cycle upper arm RIPC stimulus, and both demonstrated a significant reduction of cTnI area-under-the-curve (AUC) release of >40%. Clinical and hemodynamic outcomes, however, were not reported. Much of the cardiac injury associated with CABG appears to be a reversible phenomenon manifest as transiently subnormal cardiac output and a temporary need for inotropic support. The role of RIPC in affording protection against such postischemic dysfunction is far less clear.

The aims of this study were to confirm the role of RIPC in reducing troponin release and to ascertain if this is accompanied by an enhanced protection against postoperative cardiac, renal, and pulmonary dysfunction.

Patients and Methods
This was a single-center, double-blind, prospective, randomized, placebo-controlled trial in patients undergoing isolated first time multivessel CABG on cardiopulmonary bypass (CPB) with recruitment between January 2007 and March 2009. Subjects were randomly assigned on a 1:1 basis. The RIPC stimulus comprised 3×5-minute cycles of upper-limb 9-cm cuff inflation to 200 mm Hg separated by 5-minute periods of cuff deflation. The placebo stimulus was an identical cuff inflation cycle applied to a wooden cylinder acting as a dummy arm. Approval was obtained from the local research ethics committee (RRK 3773), the trial was registered with the UK Clinical Research Network (No. 4659; www.ukcrn.org.uk), and written informed consent was obtained from each study subject. We included both elective and urgent (postacute coronary syndrome) adult patients undergoing multivessel CABG on CPB. Patients with ST elevation myocardial infarction within 30 days, any angina pain within 48 hours of procedure, diabetes mellitus, pregnancy, preoperative dialysis, intended additional non-CABG surgery, or radial artery usage were excluded. All referred patients were considered for entry and all eligible patients were approached for consent. Before the trial, computer-generated randomization schedules, stratified by surgeon, were generated and placed in sequentially numbered sealed envelopes. Patients, investigators, anesthetists, surgeons, echocardiographers, and critical care teams were all blinded to group allocation.

Study Protocol
Premedication, anesthesia, perfusion, cardioplegia, and surgical techniques were standardized. Anesthesia was induced with etomidate, fentanyl, and pancuronium and maintained with propofol and alfentanil, supplemented on CPB by enflurane or sevoflurane.

After induction, 2 separate 9-cm blood pressure cuffs were placed around the left upper arm and the adjacent dummy arm, which were connected to an inflating device with a switch mechanism determining which cuff was inflated. The patient was then prepped and draped, obscuring the visibility of both cuffs. At this point, an operating room technician uninvolved in the study accessed the randomization code and covertly switched inflation to the appropriate cuff. According to allocation, the native or dummy arm then underwent the cycles of cuff inflation and deflation. In each case, the correct cuff inflation was verified by the operating room technician by the persistence or disappearance of a pulsatile signal on a (silenced) pulse oximeter obscured from the view of investigators and all clinical staff. The signal category was recorded and remained confidential until unblinding and analysis.

CPB was conducted at 34°C using a membrane oxygenator. Intermittent antegrade cold blood St Thomas cardioplegia (Martindale Pharmaceuticals, Essex, United Kingdom) was used for myocardial protection with an induction dose of 12 mL/kg−1 followed by maintenance administration each 15 to 20 minutes. All anastomoses were constructed during a single cross-clamp period. CPB separation occurred at 36°C to 37°C nasopharyngeal temperature using atrial or dual-chamber epicardial pacing to achieve a target heart rate of 90 min−1.

Inotropic support, initially with dopamine (200 mg/50 mL−1 D5%W) at 5 to 10 μg/kg−1/min−1, was commenced if the cardiac index (CI) was ≤2.2 L/min−1/m2 in the presence of a central venous pressure (CVP) of ≥12 mm Hg, pulmonary capillary wedge pressure (PCWP) of ≥14 mm Hg, and heart rate of ≥90 min−1 in a coordinated rhythm (sinus, AAI pacing, or DDD pacing in order of preference). Escalation of inotropic therapy with epinephrine or norepinephrine or intraaortic balloon pump (IABP) insertion would then be at clinician discretion. Introduction of support was also permitted if the operating surgeon identified poor contractility at separation of CPB or if marginal hemodynamics were noted by attending physicians on the intensive care unit (ICU). Intraoperative boluses of phenylephrine were used to maintain a mean arterial pressure of ≥55 mm Hg during CPB and ≥65 mm Hg after separation in the context of a low systemic vascular resistance. Phenylephrine was also used as a postoperative vasoconstrictor at 0 to 0.4 μg/kg−1/min−1 and substituted as necessary norepinephrine.

Exubation, ICU and hospital discharge criteria, and postoperative atrial fibrillation management were standardized.

Study Investigations
Baseline demographic and clinical data were recorded. Hemodynamic studies were performed before sternotomy, after sternal closure, and 2, 4, 6, 9, and 12 hours after reperfusion. During this 12-hour period, need for IABP and the usage and dosage of any inotropic support was noted. Low cardiac output episodes (defined as a CI ≤2.2 L/min−1/m2 with CVP ≥12 mm Hg and/or PCWP ≥14 mm Hg in the presence of a native or paced synchronized rhythm and heart rate of 90 to 110 min−1) were recorded. Cardiac troponin T (cTnT) samples were drawn at baseline and 6, 12, 24, and 48 hours after reperfusion and analyzed using a commercially available assay (Elecsys 170; Roche Diagnostics, Burgess Hill, West Sussex, United Kingdom). The coefficients of variation for serum cTnT at mean values of 0.07 and 2.24 ng/mL−1 were 10.2% and 9.3%, respectively.

An ECG was performed before surgery and on postoperative days 1 and 4. Perioperative myocardial infarction, assessed by an independent cardiologist, was defined by the presence of new left bundle-branch block or new Q waves of 2 mm in depth in 2 contiguous leads by postoperative day 4. Continuous ECG recording was commenced 12 hours before surgery and continued for 48 hours after surgery. Ventricular tachycardia/ fibrillation incidence was noted in the preoperative 12 hours, the 10-minute period after reperfusion, and up to 48 hours after surgery. Treated episodes of atrial fibrillation to day 4 were noted along with time to extubation, ICU, and hospital length of stay (LOS). When logistically possible, transthoracic contrast echocardiography was performed to assess left ventricular ejection fraction and end-systolic volume index before surgery and 5 to 7 days after surgery. Postoperative creatinine was measured on days 0 and 4. Urinary albumin-creatinine ratios were assessed at 0, 12, and 24 hours, and α-1 microglobulin at 0 and 24 hours. Urine albumin and α-1 microglobulin were both measured by automated immunoturbidimetry. Arterial pO2 (mm Hg):FiO2 ratios were assessed at 6 and 12 hours after surgery.
End Points and Sample Size
The primary end point was cTnT 48-hour AUC release. Previous studies suggested a large treatment effect: a standardized difference of 0.8. We hypothesized that RIPC would reduce cTnT AUC by a standardized difference of 0.6. At 90% power and 5% α, this required a sample size of 120 subjects, which we increased by 33% to accommodate withdrawal or missing data points.

Secondary cardiac end points were 6-hour and peak cTnT, incidence of myocardial injury on 12-lead ECG, serial cardiac and left ventricular stroke work indices (CI, LVSWI), low cardiac output episode (LCOE) incidence, inotrope usage and dosage, reperfusion ventricular fibrillation, and perioperative ventricular tachyarrhythmia incidence and functional echocardiographic change, ICU and hospital LOS, and the renal and lung data listed above.

Statistical Analysis
Data were analyzed with statistical package SPSS 15.0 (Chicago, Ill). Categoric or ordinal data were compared by using χ² tests or Kendall tau b, respectively. Continuous data are presented as mean±standard deviation or median(lower, upper quartiles). Normally distributed data were compared using independent 2-sided t tests. Repeated-measures analysis of variance (RMANOVA) was used for serial measurements. Skewed data were either logarithmically transformed or analyzed nonparametrically (Mann-Whitney U test). The cTnT data were not normally distributed. We therefore undertook logarithmic transformation of these data before estimating missing troponin values (6% measurements) for each group and at each sampling time using a General Linear Model. This allowed cTnT AUC generation for each patient. The cTnT AUC data then required logarithmic transformation to allow parametric analysis.

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results
Of 313 possible subjects, 206 met the inclusion criteria and were initially enrolled, 8 of whom were withdrawn before randomization for logistical reasons (Figure 1). Continuous ECG monitoring was performed in 146 patients (control, 76; RIPC, 70; P=0.721) (Figure 2). When completely sampled patients (n=123; 76%) were considered, the results were similar (RIPC, 39.3 [20.8 to 39.2] versus 27 [17.4 to 39.6] ng/48 h/mL⁻¹; P=0.451). Other cardiac injury indices were not different (Table 2). There was no difference between the groups when AUC cTnT release was considered for elective (RIPC, 31.7 [23.4 to 40.9] versus 27.6 [17.4 to 39.5] ng/48 h/mL⁻¹; P=0.260) or urgent patients (RIPC, 28.0 [18.1 to 35.3] versus 28.4 [19.4 to 36.3] ng/48 h/mL⁻¹; P=0.765).

Myocardial Injury
Of 810 possible cTnT measurements, 758 (94%) were assayed. Using a general linear model, there was no difference in 48-hour AUC cTnT (RIPC, 30.1 [22.2 to 38.1] versus 27.7 [18.9 to 39] ng/48 h/mL⁻¹; P=0.721) (Figure 2). When completely sampled patients (n=123; 76%) were considered, the results were similar (RIPC, 29.3 [20.8 to 39.2] versus 27 [17.4 to 39.6] ng/48 h/mL⁻¹; P=0.451). Other cardiac injury indices were not different (Table 2). There was no difference between the groups when AUC cTnT release was considered for elective (RIPC, 31.7 [23.4 to 40.9] versus 27.6 [17.4 to 39.5] ng/48 h/mL⁻¹; P=0.260) or urgent patients (RIPC, 28.0 [18.1 to 35.3] versus 28.4 [19.4 to 36.3] ng/48 h/mL⁻¹; P=0.765).

Hemodynamic Effects
Similar numbers in each group experienced LCOEs or required IABP (Table 2). Over the measurement period, the CI increased in both groups, but there was no significant difference between groups (Figure 3). Serial LVSWI was not different (P=0.844; RMANOVA; data not shown).

Inotrope and Vasoconstrictor Requirements
During surgery, all patients required phenylephrine administration at similar dosage (RIPC, 0.36 [0.22, 0.63] versus 0.43 [0.25, 0.67] mg/kg⁻¹; P=0.622). A similar number of patients in each group required inotropes (Table 2 and Figure 4) at equivalent dosages (Figure 5).

Arrhythmias
Continuous ECG monitoring was performed in 146 patients (control, n=70; RIPC, n=76). There was no difference in the incidence of reperfusion ventricular fibrillation during the 10 minutes after AXCl release (control, 11.4%; RIPC, 15.8%; P=0.48) or in the subsequent 2-hour period (control, 4.3%; RIPC, 2.6%; P=0.67). After the reperfusion period there were no episodes of sustained ventricular tachyarrhythmia requiring treatment. Brief nonsustained ventricular tachyarrhythmias occurred in 43 of 70 (62%) control and 48 of 76 (63%) RIPC patients in the first postoperative hours (P=1.0).

The overall incidence of treated atrial fibrillation was 58 (36%): control, 30 (37%) versus RIPC, 28 (35%) (P=0.871).
Table 1. Preoperative and Intraoperative Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control (n=82)</th>
<th>RIPC (n=80)</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>Preoperative factors</strong></td>
<td></td>
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<tr>
<td>Age</td>
<td>65 (60, 73)</td>
<td>63 (57, 71)</td>
<td>0.19</td>
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<tr>
<td>Male sex, n (%)</td>
<td>72 (88)</td>
<td>71 (89)</td>
<td>0.59</td>
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<tr>
<td>CCS Angina Class</td>
<td>2 (1, 2)</td>
<td>1 (1, 2)</td>
<td>0.54</td>
</tr>
<tr>
<td>NYHA Class</td>
<td>2 (1, 2)</td>
<td>2 (1, 3)</td>
<td>0.25</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28 (25,31)</td>
<td>27.5 (26,30)</td>
<td>0.80</td>
</tr>
<tr>
<td>Elective, n (%)</td>
<td>38 (46)</td>
<td>42 (52)</td>
<td>0.53</td>
</tr>
<tr>
<td>Urgent, n (%)</td>
<td>44 (54)</td>
<td>38 (48)</td>
<td>0.53</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>59 (72)</td>
<td>61 (76)</td>
<td>0.59</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>52 (63)</td>
<td>44 (55)</td>
<td>0.34</td>
</tr>
<tr>
<td>History of TIA, n (%)</td>
<td>4 (5)</td>
<td>3 (4)</td>
<td>1.00</td>
</tr>
<tr>
<td>History of CVA, n (%)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>71 (87)</td>
<td>76 (85)</td>
<td>0.01</td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>70 (85)</td>
<td>73 (91)</td>
<td>0.33</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>16 (20)</td>
<td>10 (13)</td>
<td>0.29</td>
</tr>
<tr>
<td>Potassium channel blocker, n (%)</td>
<td>18 (22)</td>
<td>12 (15)</td>
<td>0.31</td>
</tr>
<tr>
<td>Angiotensin II antagonist, n (%)</td>
<td>7 (9)</td>
<td>6 (8)</td>
<td>1.00</td>
</tr>
<tr>
<td>ACE I, n (%)</td>
<td>57 (70)</td>
<td>48 (60)</td>
<td>0.25</td>
</tr>
<tr>
<td>β-blocker, n (%)</td>
<td>68 (83)</td>
<td>63 (79)</td>
<td>0.55</td>
</tr>
<tr>
<td>Oral nitrates, n (%)</td>
<td>30 (37)</td>
<td>18 (23)</td>
<td>0.06</td>
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<tr>
<td>Ca²⁺ channel blockers, n (%)</td>
<td>31 (38)</td>
<td>26 (33)</td>
<td>0.51</td>
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<tr>
<td>Pre-CBP IABP, n (%)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Fasting glucose &gt;7 mmol/L⁻¹, n (%)</td>
<td>0 (0)</td>
<td>3 (4)</td>
<td>0.33</td>
</tr>
<tr>
<td>Fasting triglycerides, mmol/L⁻¹</td>
<td>1.4 (1.1, 1.7)</td>
<td>1.3 (1.0, 1.7)</td>
<td>0.81</td>
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<tr>
<td>Fasting cholesterol, mmol/L⁻¹</td>
<td>3.6 (2.9, 4.3)</td>
<td>3.6 (3.2, 4.4)</td>
<td>0.20</td>
</tr>
<tr>
<td>Creatinine, mg/dL⁻¹</td>
<td>1.09±0.18</td>
<td>1.11±0.18</td>
<td>0.44</td>
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<tr>
<td>Preoperative pO₂/FiO₂ ratio</td>
<td>397 (353,476)</td>
<td>413 (360,480)</td>
<td>0.31</td>
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<tr>
<td>Euroscore</td>
<td>3 (2, 5)</td>
<td>3 (2, 4.5)</td>
<td>0.10</td>
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<tr>
<td>Logistic Euroscore</td>
<td>2.5 (1.5, 4.3)</td>
<td>1.9 (1.3, 3.4)</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Intraoperative factors</strong></td>
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</tr>
<tr>
<td>Anesthetic agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enflurane, n (%)</td>
<td>65 (79)</td>
<td>64 (80)</td>
<td>0.46</td>
</tr>
<tr>
<td>Sevoflurane, n (%)</td>
<td>15 (18)</td>
<td>15 (19)</td>
<td>0.10</td>
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<tr>
<td>Propofol, n (%)</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>0.22</td>
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<tr>
<td>Bypass time, min</td>
<td>96±22</td>
<td>100±23</td>
<td>0.25</td>
</tr>
<tr>
<td>Cross-clamp time, min</td>
<td>71±18</td>
<td>76±21</td>
<td>0.08</td>
</tr>
<tr>
<td>No. of grafts</td>
<td>3.5 (3, 4)</td>
<td>3 (3, 4)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

CCS indicates Canadian Cardiovascular Society; NYHA, New York Heart Association; TIA, transient ischemic attack; CVA, cerebrovascular accident; ACE-I, angiotensin-converting enzyme inhibitor; and IABP, intraaortic balloon pump.

Continuous data are reported as mean±SD or median (lower, upper quartile).

Echocardiography
Preoperative and postoperative echocardiography was undertaken in 72 patients (control, n=38; RIPC, n=34; Table 3). No difference between preoperative and postoperative measurements was identified within (RIPC LVEF preop versus postop, P=1.0; control LVEF preop versus postop, P=0.915).

Renal and Lung Outcomes
Day 4 creatinine levels and Δcreatinine between days 0 to 4 were not different. Similar numbers of patients had increases >0.5 mg/dL⁻¹. Three RIPC patients (3.8%) and 1 (1.2%) patients (control, n=38; RIPC, n=34; Table 3). No difference between preoperative and postoperative measurements was identified within (RIPC LVEF preop versus postop, P=1.0; control LVEF preop versus postop, P=0.915).

Figure 2. Cardiac troponin T release over 48 hours. Medians and interquartile ranges are presented. No difference in release profiles was identified on AUC analysis (P=0.721).
control patient required temporary dialysis. There was no difference in 24-hour AUC urine albumin-creatinine ratios or 24-hour urine \( \alpha \)-microglobulin levels (Table 2). Time to extubation and preoperative and postoperative pO\(_2\):FiO\(_2\) ratios were similar (Tables 1 and 2).

**Discussion**

This double-blind study, using an identical RIPC stimulus and cTnT assay, has not corroborated previous smaller single-blind studies that found RIPC to reduce troponin release after on-pump CABG. This absence of effect on measurable myocardial injury is matched by a failure to demonstrate any advantage of RIPC in terms of cardiac performance, inotrope requirement, echocardiographic function, arrhythmia protection, or renal and lung outcomes. Our study suggests that RIPC, like its predecessor classic cardiac ischemic preconditioning (IP), has not fulfilled the promise of a practically useful form of improved myocardial protection.

Although early studies using classical IP reported reduced troponin release,\(^{11,12}\) improvement in high-energy phosphate conservation and reduced inotrope requirements, these effects were replicated in some but not all studies.\(^{13-16}\) The clinical effect was less obvious and in some reports detrimental,\(^{17}\) and this frustrated the use of classic IP as a surgical myocardial protective adjunct.

There is debate regarding the site of origin and significance of troponin release during on-pump CABG. Troponin release may be indicative of myofibrillar damage and myocyte necrosis or changes in sarcolemmal permeability with leakage from cytosolic pools.\(^{18,19}\) RIPC may protect against necrosis-related but not cytosolic release. CPB may itself affect sarcolemmal permeability or may have a preconditioning effect that precludes further protection by RIPC.\(^{16}\)

Post-CABG myocardial injury often manifests as a transient period of reversible dysfunction, treatable by hemodynamic optimization and temporary inotropic support. This implies a cardiac stunning phenomenon, and the role of RIPC as a protective measure against stunning is unclear. During clinical PCI, RIPC has been shown to not attenuate postischemic stunning.\(^{10}\) Our hemodynamic data suggest that there is similar absence of effect on reversible dysfunction in CABG.

In previous reports, classical IP reduced postoperative ventricular tachyarrhythmias significantly, and we investigated whether RIPC could replicate this finding.\(^{20}\) We found a much lower overall incidence of reperfusion fibrillation and a lower overall rate in the postoperative 48-hour period. This suggests important differences in protection efficacy between studies, but the lower arrhythmia incidence in the current study makes it underpowered to exclude a lack of protection by RIPC for this end point.

The preconditioning stimulus in this study would affect a smaller mass of tissue than that used by Ali et al\(^5\) in their study of abdominal aortic aneurysm surgery. However, the stimulus that we used in terms of stimulus site, cuff pressure, number of inflations and interval between inflations is identical to that affording endothelial protection or reducing troponin release in other studies and the same troponin assay was used.\(^{8,9,21-24}\) To remove inadvertent bias, we developed a scrupulous technique to blind the surgeon, anesthetist, and investigators from the group allocation. The stimulus was administered within an appropriate time frame for the first window of conditioning and delivery verified by observing disappearance of the oximetry pulse signal. In contrast to the earlier CABG studies, the stimulus was applied later, after skin incision, to ensure investigator blinding; this is unlikely to have produced a major difference in cardioprotection because other studies have also used intraoperative condition-

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**Figure 3.** Serial CI measurements in each group (mean±SD). CI increased from preoperative values in both groups (\( P<0.001 \)) but was not different between groups (\( P=0.620 \); RMANOVA).

**Figure 4.** Incidence of individual inotrope usage in the first two 6-hour periods. Dopa indicates dopamine; Epi, epinephrine; and NorE, norepinephrine.
ing stimuli. In the single-blind studies, statistical significance was attained by the much smaller variances observed in cTnT levels in the RIPC group. In the current study, the cTnT release in both groups was similar to that of the control groups in the previous reports. The study design also had important similarities; most patients received a volatile halogenated anesthetic agent peribypass and high percentages of patients received preoperative statins. Isoflurane, a known preconditioning agent, was specifically avoided in the current study.

Other differences exist between the present study and those previously reported. We noted that a higher preoperative usage of β-blockers continued until the morning of surgery. Our bypass and cross-clamp times were slightly longer because we used a single-clamp technique and we included nonelective patients who had angina or an acute coronary syndrome within 30 days of surgery. However, no patients had had angina within 48 hours of surgery, and we observed no differences between those admitted electively and more urgent cases.

In pediatric cardiac and elective abdominal aneurysm surgery, studies have documented troponin release attenuation, improved airway resistance, and improved renal function. On this basis, we hypothesized that lung and renal outcomes may be improved by RIPC during CABG. No difference in postoperative outcomes was identified in the limited parameters assessed.

Thus, we conclude that RIPC, using the stimulus size, site, and timing used in this study, fails to augment myocardial or other end-organ protection in patients undergoing CABG. Whether it may have a specific role in higher-risk patients undergoing surgery with prolonged cross-clamp times or even cardiac transplantation warrants further study. RIPC can also produce a second window of protection 24 hours after the conditioning stimulus, a phenomenon that could not be investigated in the current study; this also requires separate investigation.

**Limitations**

Despite its true double-blind status, the confirmation of stimulus delivery and its objective clinical and biochemical end points our study remains undersized to detect smaller differences in a protective effect of RIPC and does not explore effect in a higher risk population. Subtle differences in conditioning status may occur in patients presenting with urgent coronary syndrome status that prevents further conditioning in this group.

**Acknowledgments**

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**Disclosures**

None.

**References**


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