PROTECTING THE MYOCARDIUM from ischemic injury during aortic cross-clamping and from reperfusion injury following release of the aortic cross-clamp is one of the most important goals of cardioplegia in cardiac surgery. Inadequate protection may manifest as either arrhythmias or myocardial stunning upon termination of cardiopulmonary bypass. It also may lead to more permanent complications including renal failure and increased short- and long-term mortality. Unfortunately there still are limited ways to provide perioperative myocardial protection.

Ischemic myocardial preconditioning is a powerful protective strategy that attenuates myocardial injury. It is a technique of myocardial protection whereby 1 or more brief nonlethal episodes of myocardial ischemia and reperfusion are applied prior to an index-sustained myocardial ischemic event. It is hypothesized that the brief episodes of nonlethal ischemia slow the rate of adenosine triphosphate (ATP) depletion during subsequent ischemic episodes and that intermittent reperfusion may be beneficial to the myocardium by washing out catabolites that have accumulated during ischemia. Ischemic preconditioning occurs in an early and late stage. The early stage occurs immediately after the stimulus and lasts up to 3 hours, while the weaker late stage starts 12-to-24 hours after the stimulus and lasts 3 days. However, as an ischemic preconditioning protocol involves multiple clamping and unclamping phases of the aorta, it generally is impractical and potentially deleterious.

Remote Ischemic Preconditioning (RIPC)

A variant of ischemic preconditioning that has been explored to limit injury with minimal negative effects and cost is remote ischemic preconditioning (RIPC) whereby a transient preconditioning ischemic stimulus followed by reperfusion in one nonvital organ, vascular bed, or tissue protects distant vital organs or tissues from a sustained, prolonged episode of ischemia. As an example, cycles of ischemia/reperfusion on a limb using a pressure-cuff device such as a sphygmomanometer may protect the heart and other organs from subsequent ischemia. There have been a number of recent, large, randomized controlled studies evaluating the application of RIPC and its effect on cardiovascular outcomes following cardiac surgery.

History of Myocardial RIPC

The first study to evaluate the possible benefits of direct ischemic preconditioning in humans was a small study (n = 14) conducted in 1993 of direct ischemic preconditioning by aortic...
cross-clamping that demonstrated a slowing of the rate of depletion of ATP. The complications associated with multiple aortic manipulations led to a desire to investigate whether RIPC could have similar beneficial effects. A potential for RIPC was seen that same year when it was shown in a canine model that myocardial regional ischemic preconditioning conferred protection. In this study, brief episodes of ischemia in the circumflex branch preconditioned the left anterior descending artery for a 1-hour sustained occlusion and led to reduced infarct size. The concept was further advanced in other animal models where it was shown that brief periods of induced ischemia in the intestine or kidney granted protection for the heart for a subsequent injury. It was further advanced in other animal models where it was shown that brief periods of induced ischemia in the intestine or kidney granted protection for the heart for a subsequent myocardial infarction. An animal model also demonstrated that preconditioning of skeletal muscle could confer protection on other skeletal muscle.

In 2006, Kharbanda et al reported the first demonstration of the benefit of RIPC on myocardial injury associated with aortic cross-clamping and the later dysfunction that is well known to occur during the first hours after cardiopulmonary bypass (CPB) on a porcine animal model. Preconditioned animals required less inotropic support and had reductions in cardiac biomarkers on injury.

The first human study to examine the effects of RIPC was published in 2006. Thirty-seven children undergoing repair of congenital heart defects were randomized to RIPC or control treatment. RIPC was induced using a blood-pressure cuff by four 5-minute cycles of lower limb ischemia and reperfusion. Postoperative levels of troponin I were greater in the control patients compared with the RIPC group (p = 0.04), indicating greater myocardial injury in control patients. Furthermore, post-CPB inotropic support requirement was greater in the control patients compared with RIPC patients at both 3 and 6 hours (p = 0.04 and p = 0.03, respectively). This study was followed by the first adult human trial in 2007 that examined adult patients undergoing elective coronary artery bypass graft surgery (CABG). Fifty-seven patients were randomized to either receive an RIPC protocol consisting of three 5-minute upper limb ischemia/reperfusion cycles prior to aortic cross-clamping or a control stimulus. The protocol was standardized with regard to anesthesia, perfusion, and surgical techniques. No difference was found in the primary outcome total serum troponin-T area under the curve (p = 0.721). Similarly, no differences were seen between the groups in secondary outcome analysis, which looked at hemodynamics including inotropic medication usage, intra-aortic balloon pump usage, measures of cardiac index, and arrhythmias. Additionally, RIPC did not enhance renal or lung protection.

However, the negative study by Rahman et al was criticized because low-risk cardiovascular surgeries generally result in low morbidity and mortality rates, hence postulating that any effect of RIPC would best be studied in high-risk populations. Subsequently, Young et al conducted a small (n = 96), prospective, double-blinded, randomized study evaluating the efficacy of RIPC in a heterogenous group undergoing high-risk cardiac surgery while under a standardized combined volatile/intravenous anesthesia and hypothesized that RIPC induced by three 5-minute upper limb ischemia/reperfusion cycles would reduce postoperative high-sensitivity troponin-T (hsTNT) levels, vasopressor requirements, and incidence of acute

**Effect of RIPC on Clinical Outcomes**

Most of the early studies in RIPC focused on surrogate markers of RIPC outcomes, generally using biomarkers of ischemic and reperfusion injury. In 2010, studies began to move beyond surrogate markers of outcome and focus on intermediate- and long-term clinical outcomes (Table 1). Rahman et al led this effort by assessing reversible and irreversible myocardial injury by measuring the incidence of inotropic support, postoperative low-cardiac-output episodes, ventricular arrhythmias, and functional assessment by hemodynamic monitoring and echocardiography in CABG patients. In a single-center, prospective, randomized (1:1), double-blinded placebo-controlled trial, 162 patients were randomized to either receive an RIPC protocol consisting of three 5-minute upper limb ischemia/reperfusion cycles of 200 mmHg cuff inflation/deflation prior to aortic cross-clamping or a control stimulus. The protocol was standardized with regard to anesthesia, perfusion, and surgical techniques. No difference was found in the primary outcome total serum troponin-T area under the curve in 48 hours (p = 0.721). Similarly, no differences were seen between the groups in secondary outcome analysis, which looked at hemodynamics including inotropic medication usage, intra-aortic balloon pump usage, measures of cardiac index, and arrhythmias. Additionally, RIPC did not enhance renal or lung protection.

Physiology of RIPC

The precise protective mechanism through which RIPC exerts its protection is still uncertain but likely consists of interplay among a number of components. A provocative discovery that provided some insight into the mechanism was that coronary effluent released from donor rabbit hearts throughout a preconditioning stimulus (3 cycles of 5-minute global ischemia with 10-minute reperfusion) provided protection when infused into a donor heart that underwent 40 minutes of sustained global ischemia. The magnitude of protection was equal to the protection seen in the donor heart itself. This led to the proposal that several different mechanisms may be involved in RIPC, including release of an as-yet unidentified blood-borne humoral factor as well as neuronal signal transfer from the remote organ to the heart. These protective signals lead to activation of intracellular survival signaling pathways in the target organ. The final common pathway involves induction of a cascade of intracellular kinases and subsequent alteration of mitochondrial function within the cell. A graphic illustrating the principles of RIPC is shown in Figure 1.
kidney injury. A high-risk cardiac surgery was defined as double-valve surgery, triple-valve surgery, mitral valve surgery, CABG plus valve(s), CABG with ejection fraction < 50%, or any repeat cardiac surgery. The hypothesis was rejected when outcomes demonstrated that RIPC did not reduce postoperative hsTNT levels, inotropic support requirements, or renal injury. In fact, the trial even suggested an increase in hsTNT levels and inotropic support requirements in subjects receiving RIPC. This study further contrasted with previous studies that had demonstrated either reduced troponin levels or no significant difference. However, both this negative study of Young et al as well Rahaman et al’s negative study was criticized for inducing the RIPC stimulus following sternotomy, rather than prior to surgical start.

A recent European study that specifically investigated the possible effects of RIPC preventing acute kidney injury in high-risk patients undergoing cardiac surgery did find renal protection. This outcome was significant as up to 30% of patients develop acute kidney injury after cardiac surgery, and this injury influences short- and long-term postoperative morbidity and mortality. Despite the significance of this complication, a preventive measure is yet to be identified. Three previous smaller single-center trials had demonstrated opposing results. This multicenter, randomized, double-blind, controlled clinical trial studied acute kidney injury as defined by the Kidney Disease: Improving Global Outcomes Criteria in 240 patients. The RIPC protocol consisted of three 5-minute upper limb ischemia/reperfusion cycles after induction yet prior to incision. The study found that significantly fewer patients in the RIPC group developed acute kidney injury within 72 hours (15% absolute risk reduction, p = 0.02). In addition, the use of renal replacement therapy and length of stay in the intensive care unit (ICU) also were reduced (10% absolute risk reduction, p = 0.01; 3 days median difference, p = 0.04, respectively). No difference was found in groups among rate of stroke, myocardial infarction, time on mechanical ventilation, length of hospital stay, and in-hospital, and 30-day mortality.

Two other studies have shown significant beneficial effects of RIPC on clinical outcomes. In a randomized study of 180 patients undergoing cardiac surgery with CPB, Candilio et al. reported decreases in the incidences of postoperative atrial fibrillation, acute kidney injury, and ICU length of stay in patients receiving RIPC. Thielmann et al. showed reductions in long-term (1-year) mortality and major cardiac and cerebral adverse events, in addition to less myocardial damage, with RIPC in a randomized study of 329 patients undergoing CABG.

In order to obtain more clarity from these conflicting studies (that generally have studied relatively small populations in single institutions), several large multicenter trials have been performed for the past several years evaluating several clinical outcomes including death, myocardial infarction, atrial fibrillation, stroke, delirium, acute renal failure, and length of stay in the ICU. Two of these large trials published results in 2015. Mehbohm et al conducted the Remote Ischemic Preconditioning for Heart Surgery (RIPHeart) study, which was a large (n = 1,385), prospective, double-blind, multicenter, randomized, controlled study in adults undergoing elective cardiac surgery with CPB while under anesthesia with intravenous propofol. The trial compared RIPC, induced by four 5-minute upper-limb ischemia/reperfusion cycles, with a sham procedure.
including anesthetic management, was following anesthesia induction. Of note, preoperative care, four 5-minute upper-limb ischemia/reperfusion cycles of RIPC randomized with the RIPC group undergoing a protocol of surgery (with or without concomitant valve surgery) were risk patients (EuroSCORE 5) undergoing on-pump CABG surgery (with or without concomitant valve surgery) were randomized with the RIPC group undergoing a protocol of four 5-minute upper-limb ischemia/reperfusion cycles of RIPC following anesthesia induction. Of note, preoperative care, including anesthetic management, was not standardized; although almost 90% of patients received propofol. There were no differences in the primary outcomes of a composite of death from cardiovascular causes, nonfatal myocardial infarction, coronary revascularization, or stroke within 12 months of surgery (26.5% in the RIPC group and 27.7% in the sham-RIPC group, p = 0.58). There were also no differences between the groups in the secondary endpoints of preoperative myocardial injury (area under the curve at 72 hours of high-sensitivity assay of serum troponin T), acute renal injury, length of stay in the ICU and hospital, need for inotropic support, and distance on the 6-minute walk test. Post hoc subgroup analyses of anesthetic regimen and timing of RIPC regimen prior to aortic cross-clamping demonstrated no effect on the effectiveness of RIPC. A second, recent, large (n = 1,612) multicenter, randomized, sham-controlled trial evaluating the effects of RIPC on outcome was the Effect of Remote Ischemic Preconditioning on Clinical Outcomes in Patients Undergoing Coronary Artery Bypass Graft Surgery (ERICCA) study. Moderate- and high-risk patients (EuroSCORE > 5) undergoing on-pump CABG surgery (with or without concomitant valve surgery) were randomized with the RIPC group undergoing a protocol of four 5-minute upper-limb ischemia/reperfusion cycles of RIPC following anesthesia induction. Of note, preoperative care, including anesthetic management, was not standardized; although almost 90% of patients received propofol. There were no differences in the primary outcomes of a composite of death from cardiovascular causes, nonfatal myocardial infarction, coronary revascularization, or stroke within 12 months of surgery (26.5% in the RIPC group and 27.7% in the sham-RIPC group, p = 0.58). There were also no differences between the groups in the secondary endpoints of preoperative myocardial injury (area under the curve at 72 hours of high-sensitivity assay of serum troponin T), acute renal injury, length of stay in the ICU and hospital, need for inotropic support, and distance on the 6-minute walk test. Post hoc subgroup analyses of anesthetic regimen and timing of RIPC regimen prior to aortic cross-clamping demonstrated no effect on the effectiveness of RIPC. A trial currently still in the recruitment stage is the Impact of Remote Ischemic Preconditioning Preceding Coronary Artery Bypass Grafting on Inducing Neuroprotection (RIPCAGE) trial. This study will consist of an RIPC protocol of three 5-minute upper limb ischemia/reperfusion cycles in CABG patients in order to evaluate the incidence of brain injury, including new ischemic lesions, on brain magnetic resonance imaging, new impairment in brain connectivity on resting-state functional magnetic resonance imaging, and significant new declines of neurocognitive performance evidenced by neurocognitive testing. The hypothesis is that RIPC will reduce the incidence of neurologic complications resulting from cardiac surgery with CPB. Secondary endpoints will include markers of myocardial injury and incidence of major cardiac adverse events.

**Table 1**

Published Data for Remote Ischemic Preconditioning in Cardiac Surgery

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Number of patients (control/intervention)</th>
<th>Type of surgery</th>
<th>Anesthesia</th>
<th>Outcomes studied</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rahman 201020</td>
<td>82/80</td>
<td>CABG</td>
<td>Standardized-propofol infusion plus opioids with volatile anesthetics used while on CPB</td>
<td>Troponin release, inotrope requirement, cardiac index, arrhythmias, AKI, ICU LOS, Arterial pO2:FIO2 ratios</td>
<td>No effect</td>
</tr>
<tr>
<td>Young 201221</td>
<td>48/48</td>
<td>High-risk cardiac surgery (multiple valve or CABG/valve)</td>
<td>Standardized volatile anesthetic based</td>
<td>Troponin release, AKI, inotrope requirement</td>
<td>No effect</td>
</tr>
<tr>
<td>Thielmann 201322</td>
<td>167/162</td>
<td>CABG</td>
<td>Not standardized</td>
<td>Troponin release, mortality</td>
<td>Decreased troponin release, decreased mortality</td>
</tr>
<tr>
<td>Candilio 201423</td>
<td>90/90</td>
<td>CABG and/or valve</td>
<td>Not standardized</td>
<td>Troponin release, AKI, inotrope requirement, ICU LOS, AF, mortality, stroke</td>
<td>Decreased troponin release, decreased AF, decreased AKI, decreased ICU LOS</td>
</tr>
<tr>
<td>Meybohm 201524</td>
<td>693/692</td>
<td>CABG and/or valve</td>
<td>Standardized propofol</td>
<td>Mortality, MI, stroke, ARF, troponin release, ICU LOS, new onset AF</td>
<td>No effect</td>
</tr>
<tr>
<td>Hausenloy 201525</td>
<td>811/801</td>
<td>CABG with or without valve</td>
<td>Not standardized</td>
<td>Mortality, MI, stroke, coronary revascularization, troponin release, AKI, ICU LOS, inotrope score</td>
<td>No effect</td>
</tr>
</tbody>
</table>

Abbreviations: AF, postoperative atrial fibrillation; AKI, acute kidney injury; ARF, acute renal failure; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; ICU, intensive care unit; LOS, length of stay; MI, myocardial infarction.
stay in the ICU or hospital, or mortality. Interestingly, beta-blockers and volatile anesthetics appeared to attenuate the cardioprotective effects of RIPC. These findings contrasted with the proven protective effects that perioperative beta-blockers provide and also the possible anesthetic preconditioning that volatile anesthetics can produce. Further studies need to be undertaken in order to elucidate why the combination of RIPC with beta-blockers and/or volatile anesthetics leads to an attenuated response.

A 2014 systematic review and meta-analysis evaluated 23 trials totaling 2,200 patients who underwent an RIPC protocol during major adult cardiovascular surgery.36 Pooled data demonstrated that RIPC was not associated with any significant difference in outcomes including perioperative myocardial infarction, renal failure, stroke, mesenteric ischemia, ICU or hospital length of stay, and/or mortality.

The most recent and largest meta-analysis included 27 trials totaling 5,652 patients including the 2 recent large randomized clinical trials.57 In contrast to previous meta-analyses, significant clinical differences were found; although no differences were found in mortality (odds ratio [OR] 1.10, 95% confidence interval [CI], 0.81 to 1.51). RIPC reduced the risk of myocardial infarction from 12.6% to 10.2% (OR 0.72, 95% CI, 0.52 to 1.00; p = 0.05; number needed to treat [NNT] = 42), acute renal failure from 22.9% to 20.6% (OR 0.73, 95% CI, 0.53 to 1.00; p = 0.05; NNT = 44), as well as the composite of all-cause mortality, myocardial infarction, stroke, or acute renal failure from 43.2% to 39.2% (OR 0.60, 95% CI, 0.39 to 0.90; p = 0.01; NNT = 25). Randomization to the RIPC group also was associated with significantly shorter ICU stay (weighted mean difference of −0.49 days; 95% CI −0.55 to −0.43 days) as well as hospital stay (weighted mean difference of −0.15 days; 95% CI −0.27 to −0.03 days). Subgroup analysis of trials that did not use propofol found even more profound benefit.

Conclusion

The search for a magical myocardial protective strategy that could be administered successfully remains frustrating.38 RIPC has advantages over conventional ischemic preconditioning due to its safety and feasibility. However, more than 20 years after the introduction of RIPC in animal models, the evidence regarding the effects that it may have on outcomes in cardiovascular surgery is still relatively scant and conflicting. Recent studies, however, seem to be diminishing the previous belief that this simple undertaking could lead to significant changes in clinical outcome. Unfortunately, the studies have been flawed due to heterogeneity in study inclusion and exclusion criteria, differences in design of RIPC protocol, as well as failure to establish ideal RIPC protocols including timing, length, location, and intensity of stimulus. In addition, not all studies standardized anesthetic plans, and no well-designed study has been undertaken to study the effects of anesthetics on RIPC and determine best RIPC anesthetic protocol. The interaction between RIPC and another preconditioning pathway likely associated with volatile anesthetics has to be scrutinized carefully.39,40 This limits the ability for extrapolation at present. Larger multicenter studies need to continue to be performed in the high-risk cardiovascular surgery population. No longer is the study of surrogate endpoints appropriate, but significance will come only from demonstrating effects on outcome. The current literature does not support a significant effect of RIPC on clinical outcomes but future studies may prove otherwise.

References

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