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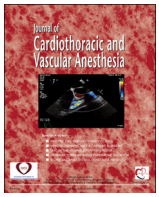

Expert Review

Remote Ischemic Preconditioning in Cardiac Surgery: Is There a Proven Clinical Benefit?

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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.[1] 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.[2] 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.[3] 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

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cross-clamping that demonstrated a slowing of the rate of depletion of ATP.[4]

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.[5] 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[6] or kidney[7] 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.[8]

In 2006, Kharbanda et al[9] 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.[10] 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).[11] Fifty-seven patients were administered an RIPC protocol consisting of three 5-minute upper limb ischemia/reperfusion cycles of inflation of an upper arm cuff to 200 mmHg administered after induction of anesthesia under combined volatile/intravenous anesthesia. Total serum troponin-T area under the curve (up to 72 hours) was found to be reduced by 43% in the RIPC group ($p = 0.005$). However, the results of this study were limited in that the surgical technique consisted of the use of intermittent cross-clamp fibrillation, rather than cold-blood cardioplegia, the technique most commonly used for myocardial protection during on-pump cardiac surgery. In order to confirm these results in a CABG population who received cold-blood cardioplegia for myocardial protection, Venugopal et al[12] performed a single-center, single-blinded, randomized controlled trial of 45 patients. RIPC reduced absolute serum troponin-T release by 42.4% ($p = 0.019$).

Physiology of RIPC

The precise protective mechanism through which RIPC exerts its protection is still uncertain[13] but likely consists of interplay among a number of components.[14,15] 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.[16] 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.[17] These protective signals lead to activation of intracellular survival signaling pathways in the target organ.[18] The final common pathway involves induction of a cascade of intracellular kinases and subsequent alteration of mitochondrial function within the cell.[19] A graphic illustrating the principles of RIPC is shown in Figure 1.[19]

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.[20] 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.

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

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