Clinical Policy Bulletin: Remote Ischemic Conditioning

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Policy

Aetna considers remote ischemic conditioning experimental and investigational for the treatment of aneurysmal subarachnoid hemorrhage, myocardial infarction, primary graft dysfunction following lung transplantation, spinal cord injury, traumatic brain injury, and other indications (e.g., for cardiac, cognitive, pulmonary and renal protection during cardiac surgery, endovascular aneurysm repair, spinal surgery, or stroke; not an all-inclusive list) because its effectiveness has not been established.

Background

Coronary heart disease (CHD) is the leading cause of death in the United States. Its major pathophysiological manifestation is acute myocardial ischemia reperfusion injury. Innovative treatment strategies for protecting the myocardium against the detrimental effects of this form of injury are needed to improve clinical outcomes in patients with CHD. In this regard, harnessing the endogenous protection elicited by the heart's ability to “condition” itself, has recently emerged as a powerful new strategy for limiting myocardial injury, preserving left ventricular systolic function and potentially improving morbidity and mortality in patients with CHD. “Conditioning” the heart to tolerate the effects of acute ischemia reperfusion injury can be initiated through the application of several different mechanical and pharmacological strategies. Inducing brief non-lethal episodes of ischemia and reperfusion to the heart either prior to, during, or even after an episode of sustained lethal myocardial ischemia has the capacity to markedly reduce myocardial injury. Interestingly, similar levels of cardio-protection can be achieved by applying the brief episodes of non-lethal ischemia and reperfusion to an organ or tissue remote from the heart, thus obviating the need to “condition” the heart directly. This phenomenon has been termed remote ischemic conditioning (RIC), and it can offer widespread systemic protection to other organs which are susceptible to acute ischemia reperfusion injury such as the brain, liver, intestine or kidney (Hausenloy and Yellon, 2009).
Remote ischemic conditioning is a novel technique of protection against ischemia-reperfusion injury. It entails the use of a blood pressure (BP) cuff to generate intermittent episodes of ischemia in the arm or leg via repeated brief periods of inflation. The objective is to promote innate protective responses, which reduce injury to the heart tissue during an evolving myocardial infarction (MI). Protective effects on heart tissue have been reported when RIC is applied prior to (pre-conditioning), during (per-conditioning), or following (post-conditioning) a sustained myocardial ischemic event, when the conditioning occurs at a site distant from the heart, usually the upper arm (RIC). Protective effects appear in 2 stages: (i) an early effect that appears within minutes of the ischemic conditioning, and (ii) a delayed protective effect occurs within a few days of the induced ischemic conditioning. Although the mechanism underlying this protection is not fully understood, ischemic conditioning suppresses subsequent leukocyte activation and inflammatory response to tissue injury (Saxena et al, 2010).

Initial clinical studies reporting beneficial effects of “conditioning” the heart to tolerate acute ischemia reperfusion injury have been encouraging, however, larger multi-center randomized studies are needed to ascertain if these “conditioning” strategies are able to impact on clinical outcomes.

Hoole and colleagues (2009a) tested the hypothesis that remote ischemic pre-conditioning (RIPC) would protect the left ventricle (LV) from ischemic dysfunction. A total of 42 patients with single-vessel coronary disease and normal LV function were prospectively recruited: 20 patients had repeated conductance catheter assessment of LV function during serial coronary occlusions with/without RIPC; and a further 22 patients underwent serial dobutamine stress echocardiography and tissue Doppler analysis with/without RIPC. Remote ischemic pre-conditioning was induced by 3 cycles of 5-min inflations of a BP cuff around the upper arm. This approach did not reduce the degree of ischemic LV dysfunction during coronary balloon occlusion (Tau, ms: 59.2 (2.8) versus 62.8 (2.8), p = 0.15) and there was evidence of cumulative LV dysfunction despite RIPC [ejection fraction (EF), %: 54.3 (5.8) versus 44.9 (3.7), p = 0.03]. Remote ischemic pre-conditioning did not improve contractile recovery during reperfusion (EF, %: 51.7 (3.6) versus 51.5 (5.7), p = 0.88 and Tau, ms: 55.6 (2.8) versus 56.0 (2.0), p = 0.85). A neutral effect of RIPC on LV function was confirmed by tissue Doppler analysis of ischemic segments at peak dobutamine (V(s), cm s(-1) control: 8.2 (0.4) versus RIPC 8.1 (0.4), p = 0.43) and in recovery. The authors concluded that RIPC does not attenuate ischemic LV dysfunction in humans.

In a prospective, randomized control trial (RCT), Hoole et al (2009b) evaluated the ability of RIPC to attenuate cardiac troponin I (cTnI) release after elective percutaneous coronary intervention (ePCI). A total of 242 consecutive patients undergoing ePCI with undetectable pre-procedural cTnI were recruited. Subjects were randomized to receive RIPC (induced by 3 cycles of 5-min inflations of a BP cuff to 200 mmHg around the upper arm, followed by 5-min intervals of reperfusion) or control (an uninflated cuff around the arm) before arrival in the catheter laboratory. The primary outcome was cTnI at 24 hrs after PCI. Secondary outcomes included renal dysfunction and major adverse cardiac and cerebral event rate at 6 months. The median cTnI at 24 hrs after PCI was lower in the RIPC compared with the control group (0.06 versus 0.16 ng/ml; p = 0.040). After RIPC, cTnI was less than 0.04 ng/ml in 44 patients (42 %) compared with 24 in the control group (24 %; p = 0.01). Subjects who received RIPC experienced less chest discomfort (p = 0.0006) and ECG
ST-segment deviation (p = 0.005) than control subjects. At 6 months, the major adverse cardiac and cerebral event rate was lower in the RIPC group (4 versus 13 events; p = 0.018). The authors concluded that RIPC reduces ischemic chest discomfort during ePCI, attenuates procedure-related cTnI release, and appears to reduce subsequent cardiovascular events.

Hoole and associates (2009c) hypothesized that a RIPC stimulus would reduce coronary microvascular resistance (R(p)) and improve coronary blood flow during ePCI. These researchers prospectively recruited 54 patients with multi-vessel disease (MVD; n = 32) or single-vessel disease (SVD) awaiting ePCI. Patients with MVD had non-target vessel (NTV) index of micro-circulatory resistance (IMR) determined, before and after target vessel PCI (cardiac RIPC). The effect of arm RIPC on serial R(p) was assessed in patients with SVD. Target vessel balloon occlusion did not alter the NTV IMR: 16.5 (12.4) baseline versus 17.6 (11.6) post-cardiac RIPC, p = 0.65 or hyperaemic transit time. Arm RIPC did not alter R(p) in patients with SVD: R(p), mm Hg.cm(-1).s(-1): 3.5 (1.9) baseline versus 4.1 (3.0) post-arm RIPC, p = 0.19 and coronary flow velocity remained constant. The authors concluded that RIPC stimuli during ePCI do not affect coronary microvascular resistance or coronary flow in humans.

In a RCT, Walsh and associates (2009) examined if RIPC has the ability to reduce renal and cardiac damage following endovascular aneurysm repair (EVAR). A total of 40 patients (all men; mean age of 76 +/- 7 years) with abdominal aortic aneurysms averaging 6.3 +/- 0.8 cm in diameter were enrolled in the trial. Eighteen patients (mean age of 74 years, range of 72 to 81) were randomized to RIPC and completed the full RIPC protocol; there were no withdrawals. Twenty-two patients (mean age of 76 years, range of 66 to 80) were assigned to the control group. Remote ischemic pre-conditioning was induced using sequential lower limb ischemia. Serum and urinary markers of renal and cardiac injury were compared between the groups. Urinary retinol binding protein (RBP) levels increased 10-fold from a median of 235 micromol/L to 2,356 micromol/L at 24 hrs (p = 0.0001). There was a lower increase in the RIPC group, from 167 micromol/L to 413 micromol/L at 24 hrs (p = 0.04). The median urinary albumin:creatinine ratio was significantly lower in the RIPC group at 24 hrs (5 versus 8.8, p = 0.06). There were no differences in the rates of renal impairment or major adverse cardiac events. The authors concluded that RIPC reduces urinary biomarkers of renal injury in patients undergoing elective EVAR. They noted that this small pilot trial was unable to detect an effect on clinical endpoints; further trials are needed.

In a single-center, single-blinded RCT, Venugopal et al (2009) examined if RIPC is cardio-protective in coronary artery bypass grafting (CABG) patients receiving cold-blood cardioplegia. Adults patients (18 to 80 years) undergoing elective CABG surgery with or without concomitant aortic valve surgery with cold-blood cardioplegia were enrolled. Patients with diabetes, renal failure (serum creatinine greater than 130 mmol/L), hepatic or pulmonary disease, unstable angina or MI within the past 4 weeks were excluded. Participants were randomized to receive either RIPC (n = 23) or control (n = 22) after anesthesia. Remote ischemic pre-conditioning comprised 3 cycles of 5-min right forearm ischemia, induced by inflating a BP cuff on the upper arm to 200 mmHg, with an intervening 5-min reperfusion. The control group had a deflated cuff placed on the upper arm for 30 mins. Serum troponin T was measured pre-operatively and at 6, 12, 24, 48 and 72 hrs after surgery and the area under the
curve (AUC at 72 hrs) calculated. Remote ischemic pre-conditioning reduced absolute serum troponin T release by 42.4 % (mean (S.D.) AUC at 72 hrs: 31.53 (24.04) microg/L 72 hrs in controls versus 18.16 (6.67) microg/L 72 hrs in RIPC; 95 % confidence interval [CI]: 2.4 to 24.3; p = 0.019). The authors concluded that RIPC induced by brief ischemia and reperfusion of the arm reduces myocardial injury in CABG surgery patients undergoing cold-blood cardioplegia.

Ali et al (2010) examined the role of RIPC on myocardium, against ischemia reperfusion injury in patients undergoing CABG surgery by measuring creatine kinase-myocardial band (CK-MB) levels. A total of 100 patients with double and triple vessels coronary artery disease were randomized in 2 groups of 50 each. Protocol of RIPC consisted of 3 cycles of 5-min fore-arm ischemia, induced by a BP cuff inflated to 200 mmHg, with an intervening 5 mins of reperfusion, during which the cuff was deflated. Patients in the control group were not subjected to limb ischemia. The protocol of induced ischemia was completed before placing patients on extracorporeal bypass circuit. At the end of surgery, serum CK-MB levels were measured and compared at 8, 16, 24 and 48 hrs from both the groups. Remote ischemic pre-conditioning significantly reduced CK-MB levels at 8, 16, 24 and 48 hrs after surgery with p-values of 0.026, 0.021, 0.052 and 0.003, respectively. There was mean reduction of 3 International Units/L in CK-MB levels, in patients who underwent RIPC protocol prior to CABG surgery, compared to control group. The authors concluded that these findings showed a significant reduction of enzyme marker CK-MB in patients subjected to RIPC prior to CABG surgery. This suggests lesser degree of myocardial damage compared to control group in CABG patients.

Hong et al (2010) noted that in several recent clinical trials on cardiac surgery patients, RIPC showed a powerful myocardial protective effect. However the effect of RIPC has not been studied in patients undergoing off-pump CABG surgery. These investigators evaluated if RIPC could induce myocardial protection in off-pump CABG surgery patients. Patients undergoing elective off-pump CABG surgery were randomly allocated to the RIPC (n = 65) or control group (n = 65). After induction of anesthesia, RIPC was induced by 4 cycles of 5-min ischemia and reperfusion on the upper limb using a pneumatic cuff. Anesthesia was maintained with sevoflurane, remifentanil and vecuronium. Myocardial injury was assessed by troponin I before surgery and 1, 6, 12, 24, 48 and 72 hrs after surgery. There were no statistical differences in troponin I levels between RIPC and control groups (p = 0.172). Although RIPC reduced the total amount of troponin I (area under the curve of troponin increase) by 26 %, it did not reach statistical significance (RIPC group 53.2 +/- 72.9 hrs x ng/ml versus control group 67.4 +/- 97.7 hrs x ng/ml, p = 0.281). In this study, RIPC by upper limb ischemia reduced the post-operative myocardial enzyme elevation in off-pump CABG surgery patients, but this did not reach statistical significance. The authors concluded that further study with a larger number of patients are needed to fully evaluate the clinical effect of RIPC in off-pump CABG surgery patients.

Bøtker et al (2010) tested the hypothesis that RIPC during evolving ST-elevation MI (STEMI), and done before primary PCI (pPCI), increases myocardial salvage. A total of 333 consecutive adult patients with a suspected first acute MI were randomly assigned in a 1:1 ratio to receive pPCI with (n = 166) versus without (n = 167) remote conditioning (intermittent arm ischemia through 4 cycles of 5-min inflation and 5-min deflation of a BP cuff). Patients received remote conditioning during transport to
hospital, and pPCI in hospital. The primary end point was myocardial salvage index at 30 days after pPCI, measured by myocardial perfusion imaging as the proportion of the area at risk (AAR) salvaged by treatment; analysis was per protocol. A total of 82 patients were excluded on arrival at hospital because they did not meet inclusion criteria, 32 were lost to follow-up, and 77 did not complete the follow-up with data for salvage index. Median salvage index was 0.75 (inter-quartile range of 0.50 to 0.93, n = 73) in the remote conditioning group versus 0.55 (0.35 to 0.88, n = 69) in the control group, with median difference of 0.10 (95 % CI: 0.01 to 0.22; p = 0.0333); mean salvage index was 0.69 (SD 0.27) versus 0.57 (0.26), with mean difference of 0.12 (95 % CI: 0.01 to 0.21; p = 0.0333). Major adverse coronary events were death (n = 3 per group), re-infarction (n = 1 per group), and heart failure (n = 3 per group). The authors concluded that ischemic conditioning before hospital admission increases myocardial salvage, and has a favorable safety profile. They stated that these findings merit a larger trial to establish the effect of remote conditioning on clinical outcomes.

Munk et al (2010) evaluated the short-term effects of RIC on LV function. Patients with a first STEMI were randomized to RIC (4 cycles of 5-min upper-limb ischemia) during transfer to pPCI (n = 123) versus pPCI alone (n = 119). Ejection fraction, LV volumes, (2D and 3D echocardiography and myocardial perfusion imaging), and speckle-tracking global longitudinal strain were compared between treatment groups. There was no significant difference in LV function at day 1 (EF-2D, 0.51 +/- 0.10 versus 0.49 +/- 0.10; p = 0.22) and after 30 days (EF-2D, 0.54 +/- 0.08 versus 0.53 +/- 0.10) between the RIC and the pPCI-alone groups. In patients with extensive AAR greater than or equal to 35 % of LV (n = 53), EF after 30 days was higher after RIC than after pPCI alone (EF-2D, 0.51 +/- 0.07 versus 0.46 +/- 0.09; p = 0.05). In patients with anterior infarction (n = 97), RIC preserved LV function on day 1 (EF-2D, 0.51 +/- 0.11 versus 0.46 +/- 0.11; p = 0.03) and persistently after 30 days (EF-2D, 0.55 +/- 0.08 versus 0.50 +/- 0.11; p = 0.04; EF-myocardial perfusion imaging, 0.55 +/- 0.10 versus 0.49 +/- 0.12; p = 0.02). These patients had similar AAR, whereas RIC reduced infarct size from 16 % to 7 % of LV (p = 0.01). The authors concluded that although no significant overall effect was observed, RIC seemed to result in modest improvement in LV function in high-risk patients prone to develop large myocardial infarcts. They stated that these results need to be confirmed in larger trials.

Venugopal and colleagues (2010) examined the effect of RIPC on acute kidney injury in non-diabetic patients undergoing CABG surgery. A total of 78 consenting selected subjects were included in this study -- RIPC consisted of 3 cycles of 5-min right forearm ischemia, induced by inflating a BP cuff on the upper arm to 200 mmHg, with an intervening 5 mins of reperfusion, during which time the cuff was deflated. The control consisted of placing an uninflated cuff on the arm for 30 mins. Major outcomes assessed were acute kidney injury (AKI) measured using Acute Kidney Injury Network (AKIN) criteria, duration of hospital stay, in-hospital and 30-day mortality. Numbers of participants with AKI stages 1, 2, and 3 were 1 (3 %), 3 (8 %), and 0 in the intervention group compared with 10 (25 %), 0, and 0 in the control group, respectively (p = 0.005). The decrease in AKI was independent of the effect of concomitant aortic valve replacement and cross-clamp times, which were distributed unevenly between the 2 groups. The limitations of this study were: (i) retrospective analysis of data, and (ii) more patients in the RIPC group underwent concomitant aortic valve replacement with CABG; although the authors had corrected statistically for this imbalance, it remains an important confounding variable. The authors
concluded that RIPC induced using transient forearm ischemia decreased the incidence of AKI in non-diabetic patients undergoing elective CABG surgery in this retrospective analysis. Moreover, they stated that a large prospective clinical trial is needed to study this effect and clinical outcomes in patients undergoing cardiac surgery.

Hu and colleagues (2010) examined if a large clinical trial testing the effect of RIPC on neurological outcomes in patients undergoing spine surgery is warranted. A total of 40 adult cervical spondylotic myelopathy patients undergoing elective decompression surgery were randomly assigned to either the RIPC group (n = 20) or the control group (n = 20). Limb RIPC consisted of 3 cycles of 5-min upper right limb ischemia with intervening 5-min periods of reperfusion. Neuron-specific enolase and S-100B levels were measured in serum at set time points. Median nerve somatosensory-evoked potentials (SEPs) were also recorded. Neurological recovery rate was evaluated using a Japanese Orthopedic Association scale. Remote ischemic preconditioning significantly reduced serum S-100B release at 6 hrs and 1 day after surgery, and reduced neuron-specific enolase release at 6 hrs, and then at 1, 3, and 5 days after surgery. No differences were observed in SEP measurements or the incidence of SEP changes during surgery between the control and RIPC groups. Recovery rate at 7 days, and at 1 and 3 months after surgery was higher in the RIPC group than in the control group (p < 0.05). The authors concluded that these findings for markers of neuronal ischemic injury and rate of recovery suggest that a clinical trial with sufficient statistical power to detect an effect of RIPC on the incidence of neurological complications (e.g., paresis, palsy, etc) due to spinal cord ischemia-reperfusion injury after spine surgery is warranted.

Bein and Meybohm (2010) stated that recent demographical developments challenge anesthesiologists with an increasing number of elderly patients with cardiovascular co-morbidities undergoing major surgery. Interventions that are capable to increase tissue tolerance against ischemia are of paramount importance. In this context, conditioning is defined as a mechanism that fosters tissue by specific adaptive processes to develop tolerance against a subsequent ischemia. Dependent upon the temporal relationship between the intervention and the index ischemia, preconditioning is differentiated from post-conditioning. Ischemia induced in tissue remote from the target organ is called remote pre-conditioning. Both brief periods of ischemia as well as volatile anesthetics and opioids are able to trigger conditioning. On a cellular level, ATP-dependent potassium channels and the mitochondrial permeability transition pore are thought to be key effectors. Effective conditioning has been demonstrated for various tissues in animal experiments. Clinical trials in patients undergoing cardiac surgery have provided evidence for organ protection by conditioning. The authors stated that large scale multi-center randomized trials, however, are still needed.

In the position paper from the Working Group of Cellular Biology of the Heart of the European Society of Cardiology on “Post-conditioning and protection from reperfusion injury”, Ovize et al (2010) noted that ischemic post-conditioning (brief periods of ischemia alternating with brief periods of reflow applied at the onset of reperfusion following sustained ischemia) effectively reduces size of MI in all species tested so far, including humans. Ischemic post-conditioning is a simple and safe maneuver, but because reperfusion injury is initiated within minutes of reflow, post-conditioning must be applied at the onset of reperfusion. The mechanisms of protection by post-
conditioning include: formation and release of several autacoids and cytokines; maintained acidosis during early reperfusion; activation of protein kinases; preservation of mitochondrial function, most strikingly the attenuation of opening of the mitochondrial permeability transition pore (MPTP). Exogenous recruitment of some of the identified signaling steps can induce cardio-protection when applied at the time of reperfusion in animal experiments, but more recently cardio-protection was also observed in a proof-of-concept clinical trial. Indeed, studies in patients with an acute MI showed a reduction of infarct size and improved LV function when they underwent ischemic post-conditioning or pharmacological inhibition of MPTP opening during interventional reperfusion. The authors stated that further animal studies and large-scale human studies are needed to determine whether patients with different co-morbidities and co-medications respond equally to protection by post-conditioning. Also, the underlying mechanisms must be better understood to develop new therapeutic strategies to be applied at reperfusion with the ultimate aim of limiting the burden of ischemic heart disease and potentially providing protection for other organs at risk of reperfusion injury, such as brain and kidney.

In a health technology assessment on RIC, the Canadian Agency for Drugs and Technologies in Health (CADTH, 2010) identified 1 systematic review and meta-analysis that included 4 RCTs and 8 additional RCTs that met the inclusion criteria. Remote ischemic conditioning has been studied mostly in a pre-operative setting when the risk of experiencing an ischemic event is high. Only 2 studies were found that applied remote conditioning induced with limb ischemia in patients experiencing an acute MI. Mostly surrogate outcomes were measured. In the pre-conditioning studies, only 2 studies reported morbidity outcomes. The cardiac remote ischemic pre-conditioning in coronary stenting (CRISP Stent) study (Hoole et al, 2009b) showed that RIPC patients had statistically significantly less chest pain during stenting, and that the rate of major adverse cardiac and cerebral events were statistically significant lower at 6 months. The study by Walsh et al (2009) showed no statistically significant differences in cardiac outcomes between groups. Similarly, a per-conditioning study (Bøtker et al, 2010) reported no statistically significant differences in cardiac outcomes between groups. The CADTH concluded that more studies measuring short-term as well as long-term morbidity and mortality are needed to ascertain the clinical effectiveness of remote conditioning in any clinical setting.

Ingenix Health Technology Pipeline’s review on RIC (2010) stated that this approach has the potential for broad organ protection and is under investigation for diverse indications such as cognitive protection during CABG, renal or pulmonary protection during bypass surgery, and effects on survival after organ transplantation. Many clinical studies are underway to determine whether RIC provides myocardial protection in various circumstances, including CABG and PCI.

Lavi and Lavi (2011) noted that ischemic pre-conditioning was demonstrated in animals more than 20 years ago, and subsequent studies in humans showed a dramatic protective effect on the heart. This method did not translate into clinical practice partially due to difficulty in application of conditioning. At the same time, multiple drugs were assessed, but none proved to be beneficial in large-scale studies for myocardial protection. Although multi-center RCTs are still lacking, it was recently demonstrated in reasonable sized studies that in patients undergoing PCI or suffering from myocardial infarction, RIC has beneficial protective effect. The authors noted that with more studies one may see translation into clinical practice in the near future.
The American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines' report on "Coronary artery bypass graft surgery" (Hillis et al, 2011) noted that (i) remote ischemic pre-conditioning strategies using peripheral-extremity occlusion/reperfusion might be considered to attenuate the adverse consequences of myocardial re-perfusion injury (Class IIb Recommendation; Level of Evidence: B [recommendation's usefulness/efficacy less well-established; greater conflicting evidence from single randomized trial or non-randomized studies]); and (ii) the effectiveness of post-conditioning strategies to attenuate the adverse consequences of myocardial re-perfusion injury is uncertain (Class IIb Recommendation; Level of Evidence: C [recommendation's usefulness/efficacy less well-established; only diverging expert opinion, case studies, or standard of care]).

Hahn and colleagues (2012) examined if remote ischemic per-conditioning may provide neuroprotection in a clinically relevant rat model of acute ischemic stroke. Remote ischemic conditioning by transient limb ischemia was used in a rat transient middle cerebral artery occlusion model of acute stroke. A total of 39 P60 rats were randomly allocated to receive pre-conditioning, per-conditioning, or sham conditioning. Cerebral ischemia was maintained for 120 mins followed by reperfusion. The resulting infarct size at 24 hours was quantified using computerized image analysis of 2-3-5-triphenyl tetrazolium chloride-stained brain sections. Compared with control, both pre- and per-conditioning significantly reduced brain infarct size with the more clinically relevant per-conditioning stimulus being superior to pre-conditioning. The authors concluded that remote per-conditioning by transient limb ischemia is a facile, clinically relevant stimulus that provides potent neuroprotection in a model of regional brain ischemia-reperfusion injury. They stated that further studies are needed to better understand the mechanisms and biology of this response before translation to RCTs of remote per-conditioning for acute ischemic stroke.

Veighey and Macallister (2012) stated that ischemia-reperfusion injury is a composite of damage accumulated during reduced perfusion of an organ or tissue and the additional insult sustained during reperfusion. Such injury occurs in a wide variety of clinically important syndromes, such as ischemic heart disease and stroke, which are responsible for a high degree of morbidity and mortality worldwide. Basic research has identified a number of interventions that stimulate innate resistance of tissues to ischemia-reperfusion injury. These researchers summarized the experimental and clinical trial data under-pinning one of these "conditioning" strategies, the phenomenon of remote ischemic pre-conditioning.

Brevoord et al (2012) performed a systematic review and meta-analysis to investigate whether RIC reduces mortality, major adverse cardiovascular events, length of stay in hospital and in the intensive care unit and biomarker release in patients who suffer from or are at risk for ischemia re-perfusion injury. Medline, EMBASE and Cochrane databases were searched for RCTs comparing RIC, regardless of timing, with no conditioning. Two investigators independently selected suitable trials, assessed trial quality and extracted data. A total of 23 studies in patients undergoing cardiac surgery (15 studies), PCI (4 studies) and vascular surgery (4 studies), comprising in total 1,878 patients, were included in this review. Compared to no conditioning, RIC did not reduce mortality (odds ratio 1.22 [95% CI: 0.48 to 3.07]) or major adverse cardiovascular events (0.65 [0.38 to 1.14]). However, the incidence of MI was
reduced with RIC (0.50 [0.31 to 0.82]), as was peak troponin release (standardized mean difference -0.28 [-0.47 to 0.09]). The authors concluded that there is no evidence that RIC reduces mortality associated with ischemic events; nor does it reduce major adverse cardiovascular events. However, RIC did reduce the incidence of peri-procedural MI, as well as the release of troponin.

Alreja and colleagues (2012) evaluated the effect of RIPC on the incidence of myocardial and renal injury in patients undergoing cardiovascular interventions as measured by biomarkers. Clinical data were pooled to evaluate the usefulness of RIPC to benefit clinical outcomes. Systematic review and meta-analysis of prospective RCTs of patients undergoing cardiovascular interventions who received RIPC versus control were performed. Two independent reviewers selected articles from MEDLINE, EMBASE, SCOPUS, Cochrane, ISI Web of Science, and BIREME, and through hand search of relevant reviews and meeting abstracts upon agreement.

Surrogate markers of myocardial (troponin T or I and CK-MB) and renal (serum creatinine) injury for primary outcomes were abstracted. Final pooled analysis from 17 clinical trials showed significant heterogeneity of results and no relevant publication bias. Patients receiving RIPC had lower levels of markers of myocardial injury in the first few days after surgery (standardized mean difference [SMD], 0.54; 95 % CI: -1.01 to -0.08; p = 0.01) with highly heterogeneous results (I² = 93 %). A lower incidence of peri-operative MI (7.9 % RIPC versus 13.9 % placebo; RR, 0.56; 95 % CI: 0.37 to 0.84; p = 0.005; I² = 0 %) was also noted. In patients undergoing abdominal aortic aneurysm repair, RIPC when compared to control also decreased renal injury (SMD, 0.28; 95 % CI: -0.49 to -0.08; p = 0.007; I² = 51 %). The authors concluded that RIPC appears to be associated with a favorable effect on serological markers of myocardial and renal injury during cardiovascular interventions. Moreover, they stated that larger trials should be conducted to substantiate this initial impression.

Yetgin et al (2012) stated that although RIC by transient limb ischemia in PCI and CABG has shown favorable effects on myocardial (ischemia-reperfusion) injury, recent trials provided inconsistent results. These investigators assessed the effect of RIC in PCI or CABG. Medline/Embase/conference reports were searched for randomized RIC trials and were included if they reported on biomarkers of myocardial injury (CK-MB/troponin T/I), after which, standardized mean differences (SMDs) were calculated (Hedges g statistic). Meta-analysis of 4 studies on PCI, involving 557 patients, indicated reduced biomarkers for myocardial injury with RIC compared to control (random effects model: SMD, -0.21; 95 % CI: -0.66 to 0.24). Analysis of primary PCI studies, involving 314 patients, indicated a highly significant positive effect of RIC on myocardial injury (SMD, -0.55; 95 % CI: -0.77 to -0.32). The 13 CABG studies taken together, involving 891 patients, indicated a significant effect of RIC on myocardial injury (SMD, -0.34; 95 % CI: -0.59 to -0.08). The statistical tests indicated moderate-to-high heterogeneity across the studies (Q-statistic: PCI, p = 0.0006, I(2) = 83 %; CABG, p < 0.0001, I(2) = 69 %). The authors concluded that in patients undergoing PCI or CABG, RIC with transient episodes of limb ischemia is associated with lower biomarkers of myocardial injury compared to control, but this effect failed to reach statistical significance in the overall PCI analysis.

Young et al (2012) stated that the effectiveness of RIPC in high-risk cardiac surgery is uncertain. In a pilot study, 96 adults undergoing high-risk cardiac surgery were randomized to RIPC (3 cycles of 5 mins of upper-limb ischemia induced by inflating a BP cuff to 200 mmHg with 5 mins of re-perfusion) or control. Main end-points were
plasma high-sensitivity troponin T (hsTNT) levels at 6 and 12 hrs, worst post-operative AKI based on RIFLE criteria, and noradrenaline duration. High-sensitivity TNT levels were log-normally distributed and higher with RIPC than control at 6-hr post cross-clamp removal [810 ng/ml (IQR 527 to 1,724) versus 634 ng/ml (429 to 1,012); ratio of means 1.41 (99.17 % CI: 0.92 to 2.17); p = 0.04] and 12 hrs [742 ng/ml (IQR 427 to 1,700) versus 514 ng/ml (IQR 356 to 833); ratio of means 1.56 (99.17 % CI: 0.97 to 2.53); p = 0.01]. After adjustment for baseline confounders, the ratio of means of hsTNT at 6 hrs was 1.23 (99.17 % CI: 0.88 to 1.72; p = 0.10) and at 12 hrs was 1.30 (99.17 % CI: 0.92 to 1.84; p = 0.05). In the RIPC group, 35/48 (72.9 %) had no AKI, 5/48 (10.4 %) had AKI risk, and 8/48 (16.7 %) had either renal injury or failure compared to the control group where 34/48 (70.8 %) had no AKI, 7/48 (14.6 %) had AKI risk, and 7/48 (14.6 %) had renal injury or failure (Chi-squared 0.41; 2 degrees of freedom; p = 0.82). Remote ischemic pre-conditioning increased post-operative duration of noradrenaline support [21 hrs (IQR 7 to 45) versus 9 hrs (IQR 3 to 19); ratio of means 1.70 (99.17 % CI: 0.86 to 3.34); p = 0.04]. The authors concluded that RIPC does not reduce hsTNT, AKI, or ICU-support requirements in high-risk cardiac surgery.

Lomivorotov et al (2012) examined if RIPC reduces myocardial injury in CABG patients. A total of 80 patients were assigned to RIPC or control treatment. Ischemic preconditioning was induced by 3 cycles (5 mins each) of upper limb ischemia and re-perfusion after anesthesia induction. Hemodynamic and markers of myocardial damage were analyzed pre-operatively and over 48 hrs post-operatively. The cardiac index was higher immediately after RIPC in the main group. There were no differences in other hemodynamic, troponin I and CK-MB concentrations at any time point between groups. The authors concluded that short-term RIPC improved hemodynamics and did not reduce myocardial injury after CABG. Moreover, they stated that further studies of high-risk patients are needed to fully evaluate the clinical effect of RIPC.

Ovize et al (2013) provided a critical summary of the progress toward, opportunities for, and caveats to, the successful clinical translation of RIPC and RIC, the 2 conditioning strategies considered to have the broadest applicability for real-world patient care. In the majority of phase II studies published to date, post-conditioning evoked an approximately 35 % reduction of infarct size in ST-segment-elevation MI patients. Essential criteria for the successful implementation of post-conditioning include the appropriate choice of patients (i.e., those with large risk regions and negligible collateral flow), timely application of the post-conditioning stimulus (immediately on re-perfusion), together with proper choice of end-points (infarct size, with concomitant assessment of risk region). Remote conditioning has been applied in planned ischemic events (including cardiac surgery and ePCI) and in ST-segment-elevation MI patients during hospital transport. Controversies with regard to effectiveness have emerged, particularly among surgical trials. These disparate outcomes in all likelihood reflect the remarkable heterogeneity within and among studies, together with a deficit in the understanding of the impact of these variations on the infarct-sparing effect of remote conditioning. The author concluded that ongoing phase III trials will provide critical insight into the future role of RIPC and RIC as clinically relevant cardio-protective strategies.

Liu and colleagues (2013) stated that ischemic conditioning, the application of a mild ischemic stimulus to an ischemia-sensitive structure like the heart or brain either
before (pre-conditioning) or after (post-conditioning) its exposure to a lethal ischemic insult, is known to switch on endogenous protective mechanisms. However, most studies of its neuro-protective effect in the central nervous system (CNS) have focused on ischemic damage or related conditions like hypoxia, while its potential in treating other neural diseases remains uncertain. In particular, the recent discovery of RIPC whereby mild ischemia applied to a region remote from the target after the main ischemic insult also confers protection offers an attractive paradigm to study its potential in other types of neural injury. Retinal ganglion cells damaged by optic nerve transection undergo extensive cell death. However, application of a series of mild ischemic/re-perfusion cycles to the hind-limb (limb RIPC) at 10 mins or 6 hrs after optic nerve cut was found to promote ganglion cell survival at 7 days post-injury, with the 10-min post-conditioning still exerting protection at 14 days post-injury. Concomitant with the increased ganglion cell survival, 51% more ganglion cells expressed the small heat shock protein HSP27, when RIPC was performed at 10 mins post-injury, as compared to the sham conditioning group. The authors concluded that these findings high-lighted the potential of using RIPC as a non-invasive neuro-protective strategy in different CNS disorders like spinal cord injury and traumatic brain injury.

In a phase I clinical trial, Gonzalez et al (2014) evaluated the feasibility and safety of RIC for aneurysmal subarachnoid hemorrhage (aSAH). Consecutive patients hospitalized for treatment of an aSAH who met the inclusion/exclusion criteria were approached for consent. Enrolled patients received up to 4 RIC sessions on non-consecutive days. Primary end-points were (i) the development of a symptomatic deep venous thrombosis (DVT), bruising or injury to the limb and, (ii) request to stop by the patient or surrogate. The secondary end-points were the development of new neurological deficits or cerebral infarct, demonstrated by brain imaging after enrollment, and neurological deficit and condition at follow-up. A total of 20 patients were enrolled and underwent 76 RIC sessions, 75 of which were completed successfully. One session was discontinued when the patient became confused. No patient developed a DVT or injury to the pre-conditioned limb. No patient developed delayed ischemic neurological deficit during their enrollment. At follow-up, median modified Rankin Scale was 1 and Glasgow Outcome Score was 5. The authors concluded that the RIC procedure was well-tolerated and did not cause any injury. They stated that RIC for aSAH warrants investigation in a subsequent pivotal clinical trial.

In a RCT, Wu and colleagues (2014) examined if RIC can attenuate ischemic reperfusion injury (IRI) in recipients after kidney transplantation using donation after cardiac death. A total of 48 recipients referred for kidney transplantation were recruited. The paired recipients who received the kidneys from the same donor were randomly assigned (1 received RIC and the other did not). Remote ischemic conditioning was induced by three 5-min cycles of brief repetitive ischemia and reperfusion by clamping the exposed external iliac artery. Blood samples were withdrawn at hour 2, hour 12, days 1 to 7, day 14, and day 30 to measure serum creatinine level and estimated glomerular filtration rate (GFR) after transplantation. Urine samples were collected at hours 2, 12, 24, and 48 to measure urine neutrophil gelatinase-associated lipocalin after transplantation. Renal tissues were obtained at 30 mins for histologic changes after transplantation. There were no significant differences in clinical characteristics of the recipients and donors between RIC and control groups. The serum creatinine level was lower in the RIC group compared with
that of the control group (12 hrs, days 1 to 14, p < 0.05; other p > 0.05); the estimated GFR was higher in the RIC group compared with that of the control group (12 hrs, days 1 to 14, p < 0.05; other p > 0.05); urine neutrophil gelatinase-associated lipocalin, an early marker of IRI, was lower in the RIC group at hours 2, 12, 24, and 48 (2 hrs, 48 hrs, p > 0.05; 12 hrs, 24 hrs, p < 0.05) compared with that of the control group. The graft pathology showed no differences between RIC and control groups. The authors concluded that RIC enhanced the early recovery of renal function in recipients after kidney transplantation. They stated that these findings provided a novel potential approach to attenuate transplantation-associated IRI.

In a pilot study, Lin and colleagues (2014) stated that primary graft dysfunction (PGD) remains a significant problem after lung transplantation. Data from animal and clinical studies suggested that RIC may reduce ischemia-reperfusion injury in solid organ transplantation. A RCT of 60 patients undergoing bilateral sequential lung transplantation assessed the utility of RIC in attenuating PGD. Treated recipients underwent 3 cycles of lower limb ischemic conditioning before allograft reperfusion. The primary outcome measure was a comparison of the partial pressure of arterial oxygen/fraction of inspired oxygen ratio (P/F ratio) between treatment groups. No adverse effects of tourniquet application were observed. The mean lowest P/F ratio during the first 24 hours after transplantation was 271.3 mm Hg in the treatment arm versus 256.1 mm Hg in the control arm (p = 0.46). Primary graft dysfunction grade and severity and the rate of acute rejection also showed a tendency to favor the treatment arm. Sub-group analysis demonstrated a significant benefit of treatment in patients with a primary diagnosis of restrictive lung disease, a group at high risk for the development of PGD. Remote ischemic conditioning was not accompanied by systemic release of high-molecular-weight group. Levels of cytokines, high-molecular-weight group, and endogenous secretory receptor for advanced glycation end products peaked within 2 hours after reperfusion and likely reflected donor organ quality rather than an effect of RIC. The authors concluded that RIC did not significantly improve P/F ratios or PGD in this RCT. However, encouraging results in this small study warrant a large multi-center trial of RIC in lung transplantation.

CPT Codes / HCPCS Codes / ICD-9 Codes

*There are no specific codes for remote ischemic conditioning:*

**ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):**

- 410.00 - 414.9  Ischemic heart disease
- 434.00 - Cerebral artery occlusion, unspecified, with cerebral infarction
- 434.91  [stroke]
- 854.00 - Intracranial injury [traumatic brain injury]
- 854.09
- 952.00 - Spinal cord injury
- 952.99

The above policy is based on the following references:


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