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**Cardioprotection by remote ischemic conditioning: Mechanisms and clinical evidences**

Aimo A *et al*. Remote ischemic conditioning

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**Abstract**

In remote ischemic conditioning (RIC), several cycles of ischemia and reperfusion render distant organ and tissues more resistant to the ischemia-reperfusion injury. The intermittent ischemia can be applied before the ischemic insult in the target site (remote ischemic preconditioning), during the ischemic insult (remote ischemic perconditioning) or at the onset of reperfusion (remote ischemic postconditioning). The mechanisms of RIC have not been completely defined yet; however, these mechanisms must be represented by the release of humoral mediators and/or the activation of a neural reflex. RIC has been discovered in the heart, and has been arising great enthusiasm in the cardiovascular field. Its efficacy has been evaluated in many clinical trials, which provided controversial results. Our incomplete comprehension of the mechanisms underlying the RIC could be impairing the design of clinical trials and the interpretation of their results. In the present review we summarize current knowledge about RIC pathophysiology and the data about its cardioprotective efficacy.

**Key words**: Remote ischemic conditioning; Ischemic heart disease; Percutaneous coronary intervention; Cardiac surgery; Atherosclerosis

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**Core tip:** Remote ischemic conditioning (RIC) is a safe, non-invasive, and inexpensive technique that has the potential to protect the heart against the ischemia-reperfusion injury. Its cardioprotective efficacy is currently being evaluated, and diverging results are emerging. It is thus worth resuming current understanding of RIC pathophysiology and clinical efficacy.

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**INTRODUCTION**

The myocardium can tolerate brief periods (up to 15 min) of severe and even total ischemia. Such ischemic episodes occur in the settings of angina, coronary vasospasm, and balloon angioplasty, and are not associated with concomitant myocyte cell death. With increasing duration and severity of ischemia, greater myocardial damage, and the predisposition to further damage during reperfusion develop. The combined deleterious effects of coronary occlusion and revascularization configure the “ischemia-reperfusion (IR) injury”[1].

The counterintuitive idea to apply several brief episodes of IR cycles to protect the myocardium against IR injury was firstly advanced in 1986, when Murry *et al*[2] reported that the infarcted area following a 40-min coronary occlusion was reduced if preceded by four 5-min IR cycles. This phenomenon was called “ischemic preconditioning”. Its clinical application is hindered by the unpredictable timing of acute myocardial infarction (AMI), and by the necessity to intervene on coronary vessels[3]. However, several IR cycles were found to confer cardioprotection even when applied at the onset of coronary revascularization (ischemic postconditioning)[4,5], both in animals and in human patients undergoing primary percutaneous coronary intervention (PCI).

In 1993, it was demonstrated in anesthetized dogs that 4 episodes of 5-min ischemia and reperfusion in the left circumflex coronary territory, followed by a 1-h occlusion of the left anterior descending coronary artery, significantly reduced the infarct size[6]. The “remote ischemic conditioning (RIC)” paradigm has been progressively extended[7]. At present, RIC is defined as the phenomenon by which brief episodes of ischemia and reperfusion in one vascular bed, tissue, or organ render distant sites resistant to the ischemia-reperfusion injury[7,8]. The IR cycles are effective when applied before myocardial ischemia (remote ischemic preconditioning), during coronary occlusion (remote ischemic perconditioning), and during cardiac revascularization (remote ischemic postconditioning)[7-12].

The mechanisms conferring protection at distance have not been completely defined[7], yet their characterization would be relevant to achieve a full comprehension of the phenomenon, and to exploit its full potential in clinical practice. In fact, understanding whether humoral mediators, neural mechanisms, or their combination mediate remote ischemic conditioning would be crucial to determine the optimal number of IR cycles, the better site and timing of their application, to select the patients according to age, comorbidities, and medical treatment, and to optimize the overall therapeutic management of the patient.

In the first part of the present review, we analyze current knowledge of the mechanisms underlying RIC, comparing humoral and reflex-mediated mechanisms. In the second half of this work, we attempt a critical analysis of the available literature concerning the cardioprotective potential of RIC in different settings.

**THE “HUMORAL HYPOTHESIS” OF RIC, AND POTENTIAL CIRCULATING MEDIATORS**

The “humoral hypothesis” has been formulated in the setting of remote ischemic preconditioning (RIPC). It postulates that the IR cycles in a distant site cause the local accumulation of mediators which are then released into the bloodstream and finally reach the heart[7] (Figure 1).

Several data from animal models support this hypothesis. In particular, it has been demonstrated that the effluent from preconditioned hearts could transfer the protection to naïve recipients[13-15]; this protection seems to be mediated by small hydrophobic proteins whose molecular weight ranges between 3.5 and 15-30 kDa[16].

Since these humoral mediators must be effective in remote sites after dilution into the bloodstream, their release from the peripheral tissue has to be massive[16]. The identification of humoral mediators should therefore be relatively easy to perform in animals or humans undergoing a RIPC protocol[16]. Indeed, proteomic approaches have been attempted in both animals and humans, still they have yielded controversial results[17-19].

Among the proteins potentially involved, there are kallistatin, apolipoprotein A-I, and stromal-derived factor 1α (SDF-1α)[16].

Kallistatin is a serine protease which reduces inflammation, apoptosis, and oxidative stress in endothelial cells[20]. It has been recently characterized as a protective factor against renal ischemia-reperfusion injury in mice[21], and has been found to be increased in the plasma of healthy humans undergoing a RIPC protocol[16]. However, its role as a humoral mediator of RIPC has not been properly evaluated yet.

Apolipoprotein A-I has anti-inflammatory properties, which could prove useful in the protection against ischemia-reperfusion injury[18]. In humans, its circulating levels have been found to be either increased[18] or decreased[17,22] after a RIPC protocol; therefore, its exact role is still debated.

Finally, SDF-1α has been proposed to be an important, and possibly the main, mediator of RIPC[23]. In a study on rats, a 50% plasma increment was detected in rats subjected to a RIPC protocol compared to control animals (890 ± 70 pg/mL *vs* 590 ± 50 pg/mL; *n* = 8, *P* < 0.01)[23]. Nevertheless, the administration of a selective inhibitor of SDF-1α did not completely abrogate the reduction in infarct size following RIPC[24], suggesting the existence of other mechanisms of cardioprotection[24].

Several potential other mediators have been identified: among them, there are microRNAs (miRNAs), bradykinin, adenosine, and nitric oxide (NO).

miRNAs have been involved in both muscle ischemia[25] and protection against myocardial IR injury[26]. The circulating levels of miR-144 have been found to increase by 1.6 folds in healthy human subjects undergoing a RIPC protocol, even though the exact mechanism of its action is still unknown[27].

Bradykinin is released by damaged tissues and can activate afferent fibers (see paragraph 2.2), possibly contributing to a cardioprotective effect known as “remote preconditioning of trauma”[28]. A release of bradykinin from ischemic tissues into the bloodstream has been reported[29]; the involvement of bradykinin in the RIPC response has been postulated, but the data from an animal study were inconclusive[30].

Finally, both adenosine and NO have been extensively studied in the setting of ischemic preconditioning[31], and have been considered potential mediators of RIPC as well[7,32], although their extremely short half-life makes unlikely that they could exert a significant cardioprotective effect.

To summarize, it is quite established the existence of humoral mechanisms underlying RIPC, but the nature of the mediator(s) is currently unclear. Potential humoral mediators should be assessed with respect to their potential mechanism of action, the increase in their circulating levels following a conditioning protocol, and their half-life; in fact, all these parameters should be compatible with a cardioprotective role. Further studies are required to define the existence and the role of humoral mechanisms underlying RIPC, as well as the other forms of remote ischemic conditioning.

**NEURALLY-MEDIATED CARDIOPROTECTION**

***Neural control of the heart***

The autonomic nervous system consists of an afferent pathway, integrating centers located into the central nervous system, and two efferent limbs, the sympathetic and the parasympathetic nervous systems[33]. In the heart, sensory innervation is provided by afferent neurons located into the nodose and dorsal root ganglia, and projecting to brainstem areas controlling the activity of both sympathetic and parasympathetic nuclei[33]. Sympathetic efferent fibers innervate the sinoatrial and atrioventricular nodes, the atria, and the ventricles[33]. Parasympathetic efferent fibers are traditionally believed to control exclusively the nodal tissue and the atria[33]. Nevertheless, the presence of cholinergic innervations have been detected in both ventricles, and it has been demonstrated that vagal activation decreases the force of ventricular contraction irrespective of its effect on heart rate, in both animals and humans[33].

***The “neural hypothesis” of RIPC, and potential role of the sympathetic system***

The “neural hypothesis” of remote ischemic preconditioning (RIPC) postulates that ischemia-reperfusion (IR) cycles in peripheral sites might activate a neural reflex resulting in myocardial protection against a subsequent myocardial insult[34] (Figure 1).

In animals, cycles of occlusion and reopening of the renal artery, mesenteric artery, or femoral artery resulted in significant cardioprotection; in all these cases, the resection of the afferent fibers projecting to the ischemized territories abolished the cardioprotective effect[35-37]. In rats, IR cycles in the mesenteric artery conferred a cardioprotection similar in entity to that provided by ischemic preconditioning (*i.e.*, IR cycles of the coronary vessel before sustained occlusion); the systemic administration of hexametonium, a blocker of both sympathetic and parasympathetic ganglia, abolished this effect[38].

Conflicting results have been provided by Kingma *et al*[39], who reported that, in dogs anesthetized with isoflurane, a RIPC protocol conferred robust myocardial protection against a subsequent ischemic injury even during autonomic blockade or surgical denervation of the heart[39]. It should be noted that in this study the animals were anesthetized with isoflurane[39], whichis *per se* a powerful preconditioning agent (see paragraph 4).

The activation of neural afferents during RIPC has been ascribed to local accumulation of mediators such as calcitonin-gene related peptide (CGRP), adenosine, and bradykinin[40]. Interestingly, the accumulation of adenosine[41,42], bradykinin[43], and other mediators[44,45] in the exercising muscle has been implied as a determinant of the metaboreflex[46], which is a neural mechanism coupling sympathetic tone to exercise requirements[47,48]. It could then be speculated that the IR cycles of a conditioning protocol cause metaboreflex activation. The subsequent increase in sympathetic outflow could confer myocardial protection through the activation of β1 and/or β2 adrenergic receptors; this phenomenon has been discovered in animal hearts perfused with β-agonists, and has been named “β-adrenergic preconditioning”[49-51].

***Evidences of vagal activation following RIPC***

As discussed above, a theoretical framework could be provided for sympathetic outflow as the final mediator of RIPC. Nevertheless, a growing body of evidences points to RIPC as a vagal reflex.

The possibility to precondition the heart by the infusion of acetylcholine (ACh) was demonstrated in 1993 by Yao *et al*[52] The preconditioning potential of ACh has been confirmed by several other studies[53-55]. It has been demonstrated that cardioprotection by RIPC is suppressed by spinal cord section, bilateral vagotomy or the systemic administration of the muscarinic receptor antagonist atropine, while vagal stimulation closely recapitulates the effects of RIPC[56,57].

Using a viral transfer gene approach in rats, Mastitskaya *et al*[58]confirmed that an intact parasympathetic outflow is crucial for myocardial protection by RIPC. The neurons in the dorsal motor nucleus of the vagus nerve were selectively silenced, thus abolishing the cardioprotective effect of a RIPC protocol[58]. The selective activation of the same neurons closely recapitulated the cardioprotective effect of RIPC; this response was suppressed by atropine[58]. Again in rats, Basalay *et al*[59]reported that IR cycles in the limb conferred cardioprotection when applied 25 min prior to myocardial ischemia. The authors then found that the cardioprotective effect was abolished by the denervation of the peripheral ischemic organ or bilateral vagotomy[59].

***Autonomic function in RIPC: what happens in humans?***

To our knowledge, only two studies have evaluated the consequences of a RIPC protocol on the autonomic function in humans. In 2005, Loukogeorgakis *et al*[60]evaluated the possibility to protect against endothelial ischemia-reperfusion injury by RIPC. A cuff inflation to 200 mmHg for 20 min in the non-dominant arm was used as the ischemic insult; the subsequent endothelial damage was denoted by reduced flow-mediated dilation (FMD)[60]. When arm ischemia was preceded by a RIPC protocol in the dominant arm, the ischemic insult in the other arm caused no significant reduction in FMD compared to baseline, suggesting endothelial protection by RIPC[60]. Such response was abolished by the autonomic ganglion blocker trimetaphan[60]. These results suggested an autonomic activation underlying the endothelial protection by RIPC; however, being trimetaphan an aspecific autonomic blocker, it was not possible to ascertain if either the sympathetic or the parasympathetic system accounted for the protection by RIPC[60].

Parasympathetic activation was detected as the underlying mechanism by Enko *et al*[61]in 2011. After 3 cycles of 5 min ischemia and 5 min reperfusion in the left arm, a significant dilation of the right brachial artery was observed; in the power spectral analysis of heart rate, the high frequency domain displayed a simultaneous increase, denoting increased parasympathetic outflow[61].

***Remote ischemic perconditioning and postconditioning: does vagal activation play a role?***

The first demonstration of remote ischemic perconditioning was provided in 2007: in pigs, four 5-min cycles of lower limb ischemia during a 40-min left anterior descending coronary artery occlusion caused a significant reduction in infarct size, improved indexes of systolic and diastolic function, and less arrhythmic events during the reperfusion phase[11]. With respect to remote ischemic postconditioning, a cardioprotective effect of IR cycles at the beginning of reperfusion was demonstrated for the first time in 2005[12], and subsequently corroborated by other animal studies[62,63].

To our knowledge, only Basalay *et al*[59] assessed the pathophysiology of remote ischemic perconditioning and postconditioning. These authors reported that deafferenting the site of IR cycles or cutting both vagus nerves abolished the preconditioning and perconditioning responses in rats, but did not alter the postconditioning effect[59]. These results suggest that remote ischemic perconditioning relies on neural mechanisms, while remote ischemic postconditioning is mediated by humoral mediators[59].

Further studies are required to assess this hypothesis. However, it should be noted that neural mechanisms are more qualified than humoral mechanisms to protect the ischemic myocardium in the setting of remote ischemic perconditioning, at least when the coronary flow is completely blocked. In the same setting, an activation of the parasympathetic system would probably be more effective than a sympathetic response.

Excessive concentrations of catecholamines have been detected in the ischemic area during an acute myocardial infarction[64]. Increased cardiac sympathetic outflow is due to pain, anxiety, and a fall of cardiac output or arterial blood pressure; a further release of catecholamines is promoted by the ischemic damage of nerve endings[64]. As a result, extracellular norepinephrine reaches up to 100-1000 times its normal plasma concentrations within 30 min of coronary occlusion[64]. Far from being protective, local concentrations of this magnitude are capable of producing myocardial necrosis even in nonischemic myocardium, and might promote malignant arrhythmias[64]. This mechanism accounts for the positive effects of early administration of β-blockers during acute myocardial infarction[65,66], and probably excludes increased sympathetic outflow as the final mediator of cardioprotection by remote ischemic perconditioning.

**PROTECTING THE HEART IN THE SETTING OF PCI**

Stable coronary artery disease (SCAD) is associated with impaired quality of life, reduced physical endurance, recurrent hospitalizations and outpatient visits[67]. Revascularization by either elective PCI or CABG can relieve symptoms, reduce the use of anti-ischemic drugs, improve exercise capacity and quality of life, compared to medical therapy alone[67]. The efficacy of elective PCI in addition to medical therapy in patients with SCAD has been demonstrated in a large number of randomized controlled trials, meta-analyses, and large-scale registries[67].

Albeit elective PCI is becoming increasingly safe, balloon inflation during PCI often causes transient ischemia[68]. Myocardial injury with necrosis may derive from recognizable peri-procedural events such as coronary dissection, occlusion of a major coronary artery or a side-branch, disruption of collateral flow, slow flow or no-reflow, distal embolization, and microvascular plugging; alternatively, the ischemic insult can have no detectable cause[68]. Myocardial ischemia is attested by a rise and fall of cardiac biomarkers after the procedure, with values rising five or more folds over the 99th percentile being indicative of peri-procedural myocardial infarction (PMI)[68].

Four recent meta-analyses have demonstrated that RIPC is effective in reducing PMIs in patients undergoing elective PCI[69-72]. For example, in the meta-analysis by Zografos *et al*[71], PMI occurred in 40.3% of patients in the RIPC group and in 51.3% of patients in the control group (odds ratio 0.57).

Several trials have assessed the long-term outcomes after elective PCI. An improvement in prognosis was not found by Prasad *et al*[73]over 1 year follow-up. By contrast, in the Cardiac Remote Ischemic Preconditioning in Coronary Stenting study, a significant reduction of major adverse cardiac and cerebral events (MACCE; a composite of all-cause mortality, myocardial infarction, readmission for heart failure, and ischemic stroke or transient ischemic attack) was found at 6 mo[74]. A recent follow-up study evaluating the same cohort demonstrated that the MACCE rate at 6 years remained lower in the RIPC group[75].

The significant heterogeneity of the study protocols could be hindering a careful assessment of RIPC efficacy in the setting of elective PCI.For example, the studies assessed in the meta-analysis by Zografos *et al*[71] differed with regard to the RIPC procedure (number of IR cycles, duration of the IR periods, site of application of the IR cycles), the percentage of patients with multivessel disease, and the positivity or the negativity of cardiac troponin I (cTnI) before PCI[71]. By contrast, in all the studies evaluated in this meta-analyis the IR cycles were performed immediately before elective PCI[74-80], so that a different time span between the IR cycles and the angioplasty procedure cannot be regarded as a potential confounding factor.

On the whole, a protective role for RIPC in the setting of elective PCI is emerging, even though its efficacy seems to be lower than in primary PCI. Nevertheless, only one long-term follow-up study has been published so far[75]; the prognostic role of RIPC should therefore receive extensive evaluation, as well as the optimal RIPC protocol to achieve effective cardioprotection.

Remote ischemic perconditioning refers to the application of ischemia-reperfusion cycles in a distant site shortly before revascularization. The first evidences of a protective role of remote ischemic perconditioning in human patients was provided in 2010 by Bøtker *et al*[81], who assessed 333 patients with suspected first ST-elevation myocardial infarction (STEMI). The primary endpoint was myocardial salvage index (MSI), quantified as the proportion of the area at risk preserved by the treatment, 30 d after primary PCI. MSI was significant higher in the conditioning group than in controls; the protective effect of remote ischemic perconditioning seemed to be strongest in patients with more severe infarctions, *i.e*., presenting with occluded vessels or infarcts in the left anterior descending artery[81].

The long-term outcome of remote ischemic perconditioning was assessed in the same study population[82]. A significant reduction of MACCE and all cause mortality was observed in the conditioning group over a median follow-up of 3.8 years. There was also a trend toward reduced myocardial reinfarction, readmission for heart failure, and ischemic stroke or transient ischemic attack[82].

In 2013, remote ischemic postconditioning was assessed on 232 patients undergoing elective PCI[83]. In the conditioning group, the patients underwent three 5-min cycles of cuff inflation in the nondominant arm just after the end of the angioplasty. No significant difference was found between the conditioning group and the control group in terms of peak troponin I levels, PMI rate, recurrence of myocardial ischemia[83]. In another study, the incidence of PMIs was similar between all groups, and no difference was remarked with respect to the creatine kinase (CK) levels or the incidence of acute kidney failure[84]. In other studies, significant reductions in the incidence of acute kidney failure were observed; the prevention of acute kidney failure is currently regarded as the most promising perspective for the application of remote ischemic postconditioning during PCI[85,86].

For the details of the studies cited in the present paragraph, see Table 1.

**REMOTE ISCHEMIC PRECONDITIONING BEFORE ELECTIVE CARDIAC SURGERY**

Elective coronary artery bypass surgery (CABG) stands as an alternative to elective PCI for the management of SCAD[87]. The safety and efficacy of both techniques are similar, as well as the incidence of PMIs[87].

In 2007, a randomized controlled study enrolled 57 adult patients undergoing elective CABG surgery[88]. In the RIPC group, three IR cycles were performed after the induction of anesthesia, resulting in a 43% reduction in the 72 h area under the curve (AUC) of cTnT compared with the control group[88]. Other randomized trials confirmed a cardioprotective role of RIPC, in terms of reduced cTnT[89], cTnI[90], and CK isoenzyme MB[91] levels. By contrast, several studies failed to detect significant differences among the RIPC group and the control group[92-95]; the use of volatile anesthetics with preconditioning potential (isoflurane, enflurane, sevoflurane) possibly accounts for discrepant results[96-98].

In a meta-analysis, D’Ascenzo *et al*[99]reported a significant reduction in cTnI and cTnT levels in the RIPC group after elective CABG surgery. Such difference persisted after excluding the trials with potentially confounding factors (among them, the use of isoflurane)[99]. It has been suggested that the cardioprotective effect of RIPC could be masked by the administration of volatile anesthetics and blunted by the perioperative administration of β-blockers[99,100]. Indeed, previous studies on animals or isolated human atrial trabeculae had demonstrated that β-blockers could attenuate ischemic preconditioning–induced cardioprotection[100,101], perhaps since even the activation of β-adrenergic receptor is protective against ischemia-reperfusion injury (β-adrenergic preconditioning; see paragraph The “neural hypothesis” of RIPC, and potential role of the sympathetic system).

Two studies evaluating the long-term efficacy of RIPC provided diverging results. Lucchinetti *et al*[94]did not find any difference at 6 mo in terms of deaths or revascularizations, whereas Thielmann *et al*[102]found significantly lower mortality rates in the RIPC group than in controls over a mean 1.54 year follow-up.

With respect to the settings of elective valve replacement surgery and congenital cardiac surgery, a recent metanalysis detected a significant cardioprotective role for RIPC[103]. Nevertheless, the small number of studies, and the high heterogeneity among them[103] might undermine the reliability of these conclusions. Another recent meta-analysis considered cumulatively CABG, valve replacement surgery, and congenital cardiac surgery, and detected a significant reduction in the post-operative cTnI levels among the patients undergoing RIPC[104]. No subgroup analysis was performed, and the heterogeneity among studies assessing non-CABG surgery was marked[104]. A third meta-analysis took into consideration the studies evaluating RIPC efficacy in adult patients undergoing “major elective or emergency cardiac or vascular surgery”[105]. In such a broad and mixed setting, no significant efficacy of RIPC was detected with regard to several outcomes: perioperative death, myocardial infarction, new-onset cardiac arrhythmias requiring treatment, cerebrovascular accidents, renal failure requiring renal replacement therapy, mesenteric ischemia, length of hospital stay and intensive care unit stay[105].

The few studies evaluating the effects of RIPC in the sole setting of valve replacement yielded conflicting results. For example, Wu *et al*[106] did not find a significant effect of a standard RIPC protocol on cTnI release after mitral valve replacement surgery, whereas Xie *et al*[107]reported a significant reduction of the 72 h cTnI-AUC in patients undergoing mitral valve, aortic valve or tricuspid valve surgery.

On the whole, RIPC seems to exert a protective role against PMIs caused by elective CABG surgery, while its long term effects are still uncertain. Furthermore, no definite statement can be made about the RIPC efficacy in other forms of elective cardiac surgery, namely valve replacement surgery and congenital cardiac surgery (Table 2). Finally, volatile anesthetics and beta-blockers are emerging as potential confounding factors, although the mechanisms are still unclear.

**CONCLUSION**

Remote ischemic conditioning (RIC) has been proposed as a “non-invasive, simple, safe, and cheap”[108] strategy to protect the heart against ischemic insults. A great research effort has been performed in order to verify the existence of a myocardial protection by RIC, and to evaluate the extent of such protection. Nevertheless, clinical studies have provided conflicting results. A deeper comprehension of the mechanisms underlying RIC is advisable in order to correctly assess the cardioprotective potential of RIC, and to guide future clinical research.

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**Figure 1 Mechanisms of remote ischemic conditioning.** The cardioprotective effects of several ischemia/reperfusion cycles applied in a distant site (most commonly the upper limb) have been ascribed to the activation of humoral and/or neural pathways. The pathogenesis of remote ischemic conditioning is incompletely known, however it is possible that both humoral and neural mechanisms underlie this response.

**Table 1 Clinical studies on remote ischemic conditioning in percutaneous coronary intervention**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Patients n (CTRLS/RIPC)** | **ST or LT outcome** | **Conditioning protocol** | **Primary endpoint** | **Results** |
|  |  |  | I/R cycles | Cuff pressure | Limb |  | *RIPC* | *CTRLS* | *p* |
| **Remote ischemic preconditioning**  |
| Prasad *et al*[76], 2013 | 48/47 | ST | 3x3’ | 200 mmHg | upper | Post-PCI myonecrosis (cTnT >= 0.03 ng/dL) | 40% | 47% | 0.42 |
| Ahmed *et al*[79], 2013 | 72/77 | ST | 3x5’ | 200 mmHg | upper | cTnT 16 h post-PCI | 0.02 ng/mL | 0.047 ng/mL | 0.047 |
| Ghaemian *et al*[80], 2010 | 40/40 | ST | 2x5’ | Above systolic | lower | TnT 24 h post-PCI | 12.5% | 40% | 0.01 |
| Hoole *et al*[77], 200977 | 117/125 | ST | 3x5’ | 200 mmHg | upper | cTnI 24 h post-PCI | 0.06 ng/mL | 0.16 ng/mL | 0.04 |
| Luo *e et al*[81],2013= | 104/101 | ST | 3x5’ | 200 mmHg | upper | hs-cTnI 16 h post-PCI | 0.11 ng/mL | 0.21 ng/mL | <0.01 |
| Xu *et al*[82], 2014 | 98/102 | ST | 3x5’ | 200 mmHg | upper | hs-cTnI 16 h post-PCI | 0.29 ng/mL | 0.38 ng/mL | 0.256 |
| Davies *et al*[78],2013 | 117/125 | LT | 3x5’ | 200 mmHg | upper | MACCE (6 years follow up) | 23 | 36 | 0.039 |
| Bøtker *et al*[84], 2010 | 167/166 | ST | 4x5’ | 200 mmHg | upper  | MSI after 30 d | 0.75 | 0.55 | 0.033 |
| Sloth *et al*[85], 2014 | 167/166 | LT | 4x5’ | 200 mmHg | upper  | MACCE rates (5 year follow-up) | 25.6% | 13.5% | 0.018 |
| Carrasco-Chinchilla *et al*[86],2013 | 114/118 | ST | 3x5’ | 200 mmHg | upper  | TnI 24 h post-PCI | 0.476 ng/mL | 0.478 ng/mL | 0.378 |

ACE: Adverse cardiovascular events; AUC: Area under the curve; AVS: Aortic valve surgery; CABG: Coronary artery bypass graft; cTnI: Cardiac troponin I; cTnT: Cardiac Troponin T; CTRLS: Controls; hs-cTnT: High sensitivity cardiac troponin T; I/R: Ischemia/reperfusion; MACCE: Major adverse cardiac and cerebral events; NS: Not specified; RIPC: Remote ischemic preconditioning; ST: Short term; LT: Long term.

**Table 2 Clinical studies on remote ischemic preconditioning before elective coronary artery bypass graft surgery**

|  |
| --- |
| **Short terms results** |
| Ref. | Patients n (CTRLS/RIPC) | RIPC protocol | Primary endpoint | Results | Notes |
| I/R cycles | Cuff pressure | Limb | RIPC | CTRLS | *P* | β- blockers | Isoflurane, desflurane |
| Hausenloy *et al*[91], 2007 | 30/27 | 3 × 5 min | 200 mmHg | Upper  | cTnT at 6 h12 h24 h48 h72 h | 0.31 mcg/L0.37mcg/L0.30 mcg/L0.30 mcg/L0.25 mcg/L | 0.59 mcg/L0.69 mcg/L0.52 mcg/L0.52 mcg/L0.48 mcg/L | 0.0390.0020.0030.0360.111 | + | + |
| Wagner *et al*[93],2010 | 35/33 | 3 × 5 min | 40 mmHg above systolic pressure | Upper  | cTnI at 8 h | 2.54 mcg/L | 2.90 mcg/L | 0.043 | - | - |
| Ali *et al*[94], 2010 | 50/50 | 3 × 5 min | 200 mmHg | upper  | CK-MB at 8 h16 h24 h48 h | 27.22 IU/L33.3 IU/L22.74 IU/L17.20 IU/L | 30.24 IU/L37.2 IU/L25.22 IU/L19.72 IU/L | 0.0260.0210.0520.003 | + | NS |
| Lomivorotov *et al*[96], 2012 | 40/40 | 3 × 5 min | 200 mmHg | Upper  | 48 h cTnI AUC  | 54.4 ng/mL | 53.3 ng/mL | >0.05 | + | + |
| Thielmann *et al*[105], 2013 | 167/162 | 3 × 5 min | 200 mmHg | Upper  | 72 h cTnI AUC | 266 ng/mL | 321 ng/mL | 0.022 | + | + |
| Rahman *et al*[98],2010 | 55 | 3 × 5 min | 200 mmHg | Upper  | 48 h cTnT AUC  | 30 ng/mL | 28 ng/mL | 0.721 | + | + |
| Lucchinetti *et al*[87], 2012 | 28/27 | 4 × 5 min | 400 mmHg | Lower  | 72 h hs-cTnT AUC | 11708 pg/mL | 9574 pg/mL | 0.33 | + | + |
| **Long term results** |
| Thielmann *et al*[105], 2013 | 167/162 | 3 × 5 min | 200 mmHg | Upper  | ACE at 1.54 yr Death MACCE |  3 8 |  11 23 |  0.046 0.005 | + | + |
| Lucchinetti *et al*[97], 2012 | 28/27 | 4 × 5 min | 400 mmHg | Lower  | ACE at 6 mo Death Rehospitalization |  0 3 |  1 3 |  1.00 1.00 | + | + |

AUC: Area under the curve; cTnI: Cardiac troponin I; cTnT: Cardiac Troponin T; CTRLS: Controls; hs-cTnT: High sensitivity cardiac troponin T; I/R: Ischemia/reperfusion; MACCE: Major adverse cardiac and cerebral events; NS: Not specified; RIPC: Remote ischemic preconditioning.