Remote Ischemic Preconditioning for Cardiac Surgery
Reflections on Evidence of Efficacy

Anweshan Samanta, Buddhadeb Dawn

Effect of remote ischemic preconditioning on clinical outcomes in patients undergoing coronary artery bypass graft surgery: the ERICCA Trial
Hausenloy et al
N Engl J Med. 2015;373:1408–1417.

A multi-center trial of remote ischemic preconditioning for heart surgery
Meybohm et al
N Engl J Med. 2015;373:1397–1407.

Ever since its discovery more than 2 decades ago, remote ischemic preconditioning (RIPC) has generated tremendous interest among scientists and clinicians alike. However, two recent large, well-conducted, randomized controlled trials (RCTs) have failed to identify any significant benefit of RIPC during cardiac surgery. A reconciliatory yet objective review of cumulative evidence with regard to cardiac surgery reveals that RIPC in preclinical studies reduced infarct size after experimental myocardial infarction (MI), which is different from cardiac surgery; improved release of biomarkers, but not hard clinical end points, in proof-of-concept clinical trials with discordant results; and failed to produce significant improvement in outcomes in meta-analyses. This difficult journey of RIPC across the valley of death underscores the importance of scientific rigor and exercise of caution in interpreting data at every step of the way until efficacy of a purported therapy is proven conclusively in large RCTs.

RIPC is a phenomenon, whereby brief episodes of ischemia in a distant vascular bed protect other organs in the body from subsequent ischemic injury. The concept that a noninvasive and simple procedure can protect organs during elective ischemic episodes has continued to generate tremendous interest among clinicians and scientists. Promising results from numerous basic studies led to many smaller clinical trials and meta-analyses, and then to two large, well-conducted RCTs. The recent results from Effect of Remote Ischaemic Preconditioning on Clinical Outcomes in CABG Surgery (ERICCA) and RIPHeart, however, have failed to identify any significant benefit of RIPC on hard clinical end points or surrogate markers of organ protection.[1,2] Because hindsight is often 20/20, it is important to interpret these latest findings in light of relevant data accumulated over the past 2 decades.

Reduction in Infarct Size in Preclinical Studies

In 1993, Przyklenk et al[3] first reported reduction in infarct size after left anterior descending coronary artery occlusion in dogs that underwent prior ischemia/reperfusion in left circumflex coronary artery territory. Subsequent studies showed that brief ischemia/reperfusion episodes in remote renal, mesenteric, cerebral, aortic, and femoral vascular beds could also afford protection against subsequent MI in rats, rabbits, pigs, and mice.[4] The RIPC-induced improvements in cardiac parameters were largely due to a major reduction in infarct size.[4] Although these studies in different species nearly unanimously indicated that RIPC imparts marked benefits, some reports did question its efficacy. In a study in rabbits, Nakano et al[5] found no significant infarct-sparing effect of regional coronary ischemia/reperfusion in distant myocardial segments. More recently, Schmidt et al[6] have reported worsening of infarct size and LV function with RIPC in neonatal rabbit hearts and lack of significant protection in neonatal pig hearts in the absence of concomitant metabolic intervention.[7]

In addition, a substantive amount of research effort has also been dedicated toward understanding the mechanisms of RIPC and identifying key molecules that trigger or mediate RIPC.[8] Many of these in vivo studies have established causal relationships of specific signaling pathways with protection offered by RIPC beyond reasonable doubt. The diversity of species, models, and protocols were perhaps no more than what would be inherent in any topic of investigation that involves in vivo experimentation.

Discordant Data From Proof-of-Concept Clinical Studies

The strength of preclinical evidence and the potentially negligible side effects of RIPC protocols quickly led to testing of safety and efficacy in humans. In 2000, Gunaydin et al[9] reported the first human data from a small randomized study with 4 patients who underwent RIPC in right arm with 2 cycles of 3-minute ischemia/2-minute reperfusion and 4 controls undergoing coronary artery bypass surgery (CABG). Five minutes after the release of aortic cross-clamp, lactate dehydrogenase levels were significantly higher in blood samples

The opinions expressed in this Commentary are not necessarily those of the editors or of the American Heart Association.

Commentaries serve as a forum in which experts highlight and discuss articles (published here and elsewhere) that the editors of *Circulation Research* feel are of particular significance to cardiovascular medicine.

Commentaries are edited by Aruni Bhatnagar & Ali J. Marian.

From the Division of Cardiovascular Diseases, Cardiovascular Research Institute, The Midwest Stem Cell Therapy Center, University of Kansas Medical Center and Hospital, Kansas City.

The online-only Data Supplement is available with this article at http://circres.ahajournals.org/lookup/suppl/doi:10.1161/CIRCRESAHA.116.308373/-/DC1.

Correspondence to Buddhadeb Dawn, MD, Division of Cardiovascular Diseases, University of Kansas Medical Center, 3901 Rainbow Blvd, 1001 Eaton, MS 3006, Kansas City, KS 66160. E-mail bdawn@kumc.edu

(*Circ Res*. 2016;118:1055-1058.
DOI: 10.1161/CIRCRESAHA.116.308373.)

***Circulation Research* is available at http://circres.ahajournals.org**
DOI: 10.1161/CIRCRESAHA.116.308373

from the coronary perfusion catheter in the RIPC group. In a subsequent study in children, 4 cycles of 5-minute ischemia/reperfusion in the lower limb before congenital heart surgery attenuated perioperative myocardial injury with lower postoperative troponin I and lower inotrope requirement at 3 and 6 hours after surgery.[10] A large number of smaller clinical trials have since been conducted to explore the utility of RIPC in the setting of cardiac surgery (Online Table I), elective percutaneous coronary intervention, and primary percutaneous coronary intervention after acute MI.[11] Among the clinical scenarios that might benefit from RIPC, cardiac surgery has been investigated in the largest number of clinical trials. A review of the literature reveals that several smaller trials in adult and pediatric patients undergoing CABG, valve replacement, or surgery for congenital heart diseases reported improvement in cardiac enzyme release in patients who underwent RIPC protocols (Online Table I). Importantly, RIPC failed to produce any significant improvement even in cardiac enzyme release in nearly half of these studies (Online Table I). Thus, the overall evidence in support of cardioprotection afforded by RIPC was discordant at best.[11,12]

Another important point to consider is the nature and basis of evidence in support of protection by RIPC. In the vast majority of clinical trials that showed cardioprotection by RIPC during cardiac surgery, this conclusion was based on assessment of myocardial injury using the surrogate end points of peak or area under the curve of serial cardiac troponin assays[11] (Online Table I). Although several trials did examine clinical parameters, including duration of mechanical ventilation, inotrope requirement, ICU stay, hospital stay, etc, RIPC was generally ineffective in improving these parameters (Online Table I). Furthermore, even fewer trials examined short- and long-term clinical outcomes during follow-up; and only one[13] reported improvement with RIPC in hard clinical outcomes after 1 year of follow-up (Online Table I). Therefore, and although cardiac enzyme release has been shown to correlate with outcomes, the evidence supporting the efficacy of RIPC in proof-of-concept clinical trials was indirect and remarkably weak.

No Suggestion of Improvement in Clinical Outcomes in Meta-Analyses

The discordant nature of the results from smaller trials of RIPC has resulted in repeated analyses of pooled data by several groups. In the first such effort, Takagi et al[14] (Online Table II) analyzed data from only 4 RCTs and reported improvement in cardiac enzyme release after cardiac surgery in patients who underwent RIPC. More than 20 meta-analyses have since included trials that examined children and adults undergoing cardiac surgery (Online Table II). A careful review of the results of these meta-analyses reveals that although RIPC was often associated with decreased cardiac enzyme release after cardiac surgery, these effects generally did not translate into improvements in patient outcomes. In fact, these enzymatic benefits did not even improve in-hospital clinical outcomes in most analyses. In contrast to results from meta-analyses that included cardiac surgery trials only, one meta-analysis that included patients undergoing percutaneous coronary intervention as well yielded more favorable effects with RIPC.[15] Interestingly, in a meta-analysis of RCTs that showed significantly reduced troponin levels with RIPC, this observation was most marked in trials that lacked full blinding.[16] The benefits lost significance in fully blinded trials, suggesting that lack of blinding was a significant confounding factor.[16]

Negative Results of Two Large RCTs

In a recent issue of *The New England Journal of Medicine*, two large multicenter phase III RCTs assessed the effects of RIPC on clinical end points after cardiac surgery. ERICCA enrolled 1612 high-risk patients (EuroSCORE 5 or higher) undergoing on-pump CABG (with or without valve surgery) at 30 centers across the United Kingdom.[1] Patients randomized to the RIPC group were subjected to 4 cycles of 5 minutes of ischemia and reperfusion of the upper arm after anesthesia and before surgical incision. RIPC did not significantly reduce the proportion of patients with a major cardiac or cerebral event, acute kidney injury within 72 hours, duration of hospital and ICU stays and area under the curve for troponin T. Patients who underwent RIPC walked a longer distance on the 6-minute walk test at 12 months, but only 360 of 1612 patients completed this test. Worryingly, RIPC showed a trend toward an increase in rate of death from cardiovascular causes, although the study was not sufficiently powered to detect this end point. RIPHeart enrolled 1403 patients undergoing elective cardiac surgery requiring cardiopulmonary bypass at 14 university hospitals in Germany.[2] Most patients underwent CABG alone, while others received mitral and aortic valve replacement/reconstruction or other surgeries, sometimes in combination. RIPHeart included lower risk (68.7% patients had a EuroSCORE of ≤5) and younger patients (mean age of patients in RIPHeart was ≈10 years less) compared with ERICCA. The RIPC protocol was similar to the one used in ERICCA. RIPC did not cause a significant reduction in the primary end point, which was a composite of death from any cause, nonfatal MI, new stroke, and acute renal failure. The RIPC arm showed a trend toward reduction of MI, although this did not reach significance. There was no significant difference in secondary end points: duration of ICU and hospital stay, duration of mechanical ventilation, levels of troponin T and I, creatinine level, new-onset atrial fibrillation, and incidence of postoperative delirium.

How Do We Reconcile These Results?

The results of these two large RCTs indicate that the strong promise from preclinical studies has failed to deliver measurable benefits in rigorous clinical trials. If we assume that RIPC indeed protects the heart in patients during cardiac surgery, its failure to do so in ERICCA and RIPHeart can be potentially attributable to several design issues. However, the validity of such an argument needs to be carefully judged in light of available evidence. First, the effects of various anesthetics on RIPC remain unclear. An earlier study reported that propofol inhibited RIPC by interfering with activation of the cardioprotective molecule STAT5.[17] However, when Hausenloy et al[18] used a targeted dose of propofol, RIPC was found to be cardioprotective. Kottenberg et al[19] further conducted a 4-arm trial, wherein patients undergoing CABG were randomized to receive isoflurane or propofol with or without RIPC. They reported that RIPC decreased

myocardial damage during isoflurane administration but not propofol. On the other hand, Lucchinetti et al[20] used isoflurane for anesthesia and found RIPC to be ineffective for cardiac surgery. These results suggested that RIPC could not confer additional benefits above and beyond those already provided by isoflurane.[20] It is important to note that ERICCA had ≈90% of its patients on either volatile anesthetics or propofol, whereas the RIPHeart protocol used propofol. Importantly, in detailed subanalyses, ERICCA showed that anesthetics had no significant effect on primary and secondary outcomes. Furthermore, if the protective effects induced by standard anesthetic agents are strong enough to mask those of RIPC, RIPC may not be necessary after all.

Second, these large RCTs used RIPC protocols that were not standardized rigorously. However, as shown in Online Table I, the clinical trials performed thus far, including those showing significant reduction in enzyme release, have generally used 3 or 4 cycles of 5 minutes of ischemia interspersed with reperfusion. A thorough review of basic and preclinical data would also reveal that nearly all types of protocols have produced benefits in diverse experimental models and species. So, it seems unlikely that simple optimization of clinical RIPC protocol would have been sufficient to turn these negative results into positive effects. Third, the potential roles played by patients' comorbidities and medications cannot be discounted. However, patients enrolled in ERICCA and RIPHeart do represent patients likely to be subjected to RIPC in the real world, if its benefits are proven. Candidates for cardiac surgery often have multiple comorbidities and as a result, are on many different medications before and after surgery. If the benefits of RIPC are not evident in these populations that are likely to undergo cardiac surgery, the strength of its effects as well as its clinical use for cardiac surgery may both be questionable.

The final potential explanation for these negative findings is that RIPC simply does not work, at least during cardiac surgery. If we critically review the available evidence stemming from basic studies (which largely measured infarct size after experimentally induced MI), small proof-of-concept trials (which showed benefits mostly with regard to enzyme release, if at all), and meta-analyses of cardiac surgery trials alone (which did not suggest improvement in clinical outcomes), this possibility cannot be ignored.

Lessons Learned and Future Perspectives

The results of two well-conducted large RCTs, ERICCA, and RIPHeart, have caused a major setback to the potential applicability of RIPC for cardiac surgery. They have provided rather conclusive evidence that RIPC does not confer any important benefit to patients undergoing cardiac surgery. Although disappointing, this may not signify the end of the road for RIPC. RIPC may still be able to meaningfully protect the heart before elective percutaneous coronary intervention or acute MI—a concept that remains to be proven in large RCTs. However, the history of RIPC underscores the importance of scientific rigor and how critical it is for translating findings, however exciting, from the basic laboratories to therapies in patients.[21] Indeed, before proceeding to large RCTs, a concept needs to be tested carefully in clinically relevant disease models using the most rigorous methodologies; the proof-of-concept trials should assess relevant clinical outcomes rather than biochemical and surrogate markers; investigators should remain blinded whenever possible; data from smaller trials failing to support the popular belief should not be simply dismissed as exploratory, but rather utilized to improve future trial design; the value of hypotheses from meta-analyses should be tempered with critical evaluation of their heterogeneity and other methodologies; and finally, the RCTs need to be adequately powered to assess hard clinical end points. Failure to follow these methodological best practices underlies the failure to translate into clinical therapies not only RIPC but also many other putative cardioprotective interventions.

Acknowledgments

This publication was supported, in part, by the National Institutes of Health grant R01 HL-117730.

Disclosures

None.

References

1. Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, Knight R, Kunst G, Laing C, Nicholas J, Pepper J, Robertson S, Xenou M, Clayton T, Yellon DM; ERICCA Trial Investigators. Remote Ischemic Preconditioning and Outcomes of Cardiac Surgery. *N Engl J Med*. 2015;373:1408–1417. doi: 10.1056/NEJMoa1413534.
2. Meybohm P, Bein B, Brosteanu O, et al; RIPHeart Study Collaborators. A Multicenter Trial of Remote Ischemic Preconditioning for Heart Surgery. *N Engl J Med*. 2015;373:1397–1407. doi: 10.1056/NEJMoa1413579.
3. Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation*. 1993;87:893–899.
4. Hausenloy DJ, Yellon DM. Remote ischaemic preconditioning: underlying mechanisms and clinical application. *Cardiovasc Res*. 2008;79:377–386. doi: 10.1093/cvr/cvn114.
5. Nakano A, Heusch G, Cohen MV, Downey JM. Preconditioning one myocardial region does not neccessarily precondition the whole rabbit heart. *Basic Res Cardiol*. 2002;97:35–39.
6. Schmidt MR, Støttrup NB, Michelsen MM, Contractor H, Sørensen KE, Kharbanda RK, Redington AN, Bøtker HE. Remote ischemic preconditioning impairs ventricular function and increases infarct size after prolonged ischemia in the isolated neonatal rabbit heart. *J Thorac Cardiovasc Surg*. 2014;147:1049–1055. doi: 10.1016/j.jtcvs.2013.05.022.
7. Schmidt MR, Støttrup NB, Contractor H, Hyldebrandt JA, Johannsen M, Pedersen CM, Birkler R, Ashrafian H, Sørensen KE, Kharbanda RK, Redington AN, Bøtker HE. Remote ischemic preconditioning with–but not without–metabolic support protects the neonatal porcine heart against ischemia-reperfusion injury. *Int J Cardiol*. 2014;170:388–393. doi: 10.1016/j.ijcard.2013.11.020.
8. Gill R, Kuriakose R, Gertz ZM, Salloum FN, Xi L, Kukreja RC. Remote ischemic preconditioning for myocardial protection: update on mechanisms and clinical relevance. *Mol Cell Biochem*. 2015;402:41–49. doi: 10.1007/s11010-014-2312-z.
9. Günaydin B, Cakici I, Soncul H, Kalaycioglu S, Cevik C, Sancak B, Kanzik I, Karadenizli Y. Does remote organ ischaemia trigger cardiac preconditioning during coronary artery surgery? *Pharmacol Res*. 2000;41:493–496. doi: 10.1006/phrs.1999.0611.
10. Cheung MM, Kharbanda RK, Konstantinov IE, Shimizu M, Frndova H, Li J, Holtby HM, Cox PN, Smallhorn JF, Van Arsdell GS, Redington AN. Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: first clinical application in humans. *J Am Coll Cardiol*. 2006;47:2277–2282. doi: 10.1016/j.jacc.2006.01.066.
11. Heusch G, Bøtker HE, Przyklenk K, Redington A, Yellon D. Remote ischemic conditioning. *J Am Coll Cardiol*. 2015;65:177–195. doi: 10.1016/j.jacc.2014.10.031.
12. Sabbagh S, Henry Salzman MM, Kloner RA, Simkhovich BZ, Rezkalla SH. Remote ischemic preconditioning for coronary artery bypass

graft operations. *Ann Thorac Surg*. 2013;96:727–736. doi: 10.1016/j.athoracsur.2013.02.049.
13. Thielmann M, Kottenberg E, Kleinbongard P, Wendt D, Gedik N, Pasa S, Price V, Tsagakis K, Neuhäuser M, Peters J, Jakob H, Heusch G. Cardioprotective and prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial. *Lancet*. 2013;382:597–604. doi: 10.1016/S0140-6736(13)61450-6.
14. Takagi H, Manabe H, Kawai N, Goto SN, Umemoto T. Review and meta-analysis of randomized controlled clinical trials of remote ischemic preconditioning in cardiovascular surgery. *Am J Cardiol*. 2008;102:1487–1488.
15. Le Page S, Bejan-Angoulvant T, Angoulvant D, Prunier F. Remote ischemic conditioning and cardioprotection: a systematic review and meta-analysis of randomized clinical trials. *Basic Res Cardiol*. 2015;110:11. doi: 10.1007/s00395-015-0467-8.
16. Pilcher JM, Young P, Weatherall M, Rahman I, Bonser RS, Beasley RW. A systematic review and meta-analysis of the cardioprotective effects of remote ischaemic preconditioning in open cardiac surgery. *J R Soc Med*. 2012;105:436–445. doi: 10.1258/jrsm.2012.120049.
17. Kottenberg E, Musiolik J, Thielmann M, Jakob H, Peters J, Heusch G. Interference of propofol with signal transducer and activator of transcription 5 activation and cardioprotection by remote ischemic preconditioning during coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2014;147:376–382. doi: 10.1016/j.jtcvs.2013.01.005.
18. Hausenloy DJ, Mwamure PK, Venugopal V, Harris J, Barnard M, Grundy E, Ashley E, Vichare S, Di Salvo C, Kolvekar S, Hayward M, Keogh B, MacAllister RJ, Yellon DM. Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial. *Lancet*. 2007;370:575–579. doi: 10.1016/S0140-6736(07)61296-3.
19. Kottenberg E, Thielmann M, Bergmann L, Heine T, Jakob H, Heusch G, Peters J. Protection by remote ischemic preconditioning during coronary artery bypass graft surgery with isoflurane but not propofol - a clinical trial. *Acta Anaesthesiol Scand*. 2012;56:30–38. doi: 10.1111/j.1399-6576.2011.02585.x.
20. Lucchinetti E, Bestmann L, Feng J, Freidank H, Clanachan AS, Finegan BA, Zaugg M. Remote ischemic preconditioning applied during isoflurane inhalation provides no benefit to the myocardium of patients undergoing on-pump coronary artery bypass graft surgery: lack of synergy or evidence of antagonism in cardioprotection? *Anesthesiology*. 2012;116:296–310. doi: 10.1097/ALN.0b013e318242349a.
21. Jones SP, Tang XL, Guo Y, et al. The NHLBI-sponsored Consortium for preclinicAl assESsment of cARdioprotective therapies (CAESAR): a new paradigm for rigorous, accurate, and reproducible evaluation of putative infarct-sparing interventions in mice, rabbits, and pigs. *Circ Res*. 2015;116:572–586. doi: 10.1161/CIRCRESAHA.116.305462.

Circulation Research
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Remote Ischemic Preconditioning for Cardiac Surgery: Reflections on Evidence of Efficacy

Anweshan Samanta and Buddhadeb Dawn

Circ Res. 2016;118:1055-1058
doi: 10.1161/CIRCRESAHA.116.308373
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7330. Online ISSN: 1524-4571

Online Table I. Proof-of-concept clinical trials of remote ischemic preconditioning in patients undergoing cardiac surgery

Study	Patients (control, RIPC)	Surgery	RIPC Protocol	Laboratory Results with RIPC	In-hospital and Short-term Clinical Outcomes with RIPC	Longer-term Clinical Outcomes with RIPC
Gunaydin et al., 2000[1]	4, 4	CABG (blood cardioplegia)	Upper limb: 2 cycles I/R (3/2 min)	Increased LDH release	NR	NR
Cheung et al., 2006[2]	20, 17	Pediatric congenital cardiac surgery (blood cardioplegia)	Lower limb: 4 cycles I/R (5/5 min)	Reduced TnI release	Reduced inotrope score at 3 and 6 h; reduced airway resistance at 6 h. No significant difference in duration of mechanical ventilation and ICU stay.	NR
Hausenloy et al., 2007[3]	30, 27	CABG (cold blood cardioplegia or intermittent cross-clamp fibrillation)	Upper limb: 3 cycles I/R (5/5 min)	Reduced TnT release	NR	NR
Venugopal et al., 2009[4]	22, 23	CABG (cold blood cardioplegia)	Upper limb: 3 cycles I/R (5/5 min)	Reduced TnT release	NR	NR
Ali et al., 2010[5]	50, 50	CABG (warm blood hyperkalemic cardioplegia)	Upper limb: 3 cycles I/R (5/5 min)	Reduced CK-MB release	NR	NR
Hong et al., 2010[6]	65, 65	CABG (off pump)	Upper limb: 4 cycles I/R (5/5 min)	No significant change in TnI release	No significant impact on duration of mechanical ventilation, ICU stay and hospital stay	NR
Li et al., 2010[7]	27, 26	Elective valve replacement (cold crystalloid-blood cardioplegia)	Lower limb: 3 cycles I/R (4/4 min)	No effect on TnI release	No significant decrease in duration of mechanical ventilation, ICU stay, hospital stay, and inotrope score at 24 h	NR
Rahman et al., 2010[8]	82, 80	CABG (cold blood cardioplegia)	Upper limb: 3 cycles I/R (5/5 min)	No effect on TnT release	No significant impact on new onset LBBB, Q wave, postoperative intraaortic balloon pump usage, inotrope usage, extubation time, duration of ICU stay, hospital stay and dialysis requirement. No significant improvement in LVEF, LVESVI	NR

					at 5-7 days after surgery.	
Thielmann et al., 2010[9]	26, 27	CABG (cold crystalloid cardioplegic arrest)	Upper limb: 3 cycles I/R (5/5 min)	Reduced TnI release	No decrease in duration of mechanical ventilation, ICU stay, hospital stay, inotrope score. No change in postoperative eGFR, hemodialysis requirement and serum creatinine concentrations.	No effect on mortality at 30 days.
Wagner et al., 2010[10]	34, 32	CABG with or without aortic valve replacement (cold crystalloid cardioplegia)	Upper limb: 3 cycles I/R (5/5 min) 18 h prior to surgery	Reduced TnI release	NR	NR
Zhou et al., 2010[11]	30, 30	Pediatric cardiac surgery (ventricular septal defect)	Upper limb: 3 cycles I/R (5/5 min) 24 h and 1 h prior to surgery	Reduced CK-MB and inflammatory biomarkers	No significant change in duration of mechanical ventilation and ICU stay.	NR
Karuppasamy et al., 2011[12]	27, 27	CABG with or without valve/aortic surgery	Upper limb: 3 cycles I/R (5/5 min)	No significant effect on CK-MB, TnI and BNP release	No significant change in postoperative inotrope requirements, duration of postoperative ventilation, ICU stay and hospital stay	NR
Luo et al., 2011[13]	20, 20	Pediatric cardiac surgery (ventricular septal defect)	Lower limb: 3 cycles I/R (5/5 min)	Reduced peak CK-MB and TnI	NR	NR
Wu et al., 2011[14]	25, 25, 25	Elective mitral valve replacement (cold blood cardioplegia)	Group I: Upper limb: 3 cycles I/R (5/5 min); Group II: Upper limb: 3 cycles I/R (5/5 min) + lower limb 2 cycles I/R (10/10 min)	Reduced TnI release in group II but not group I	No significant effect on duration of ICU stay and hospital stay	NR
Heusch et al., 2012[15]	12, 12	CABG (cold crystalloid cardioplegia)	Upper limb: 3 cycles I/R (5/5 min)	Reduced TnI release	NR	NR
Hong et al., 2012[16]	35, 35	CABG (off pump)	Lower limb: 8 cycles I/R (5/5 min) - 4 cycles before and 4 after anastomoses	Reduced TnI release	No significant decrease in duration of mechanical ventilation, ICU stay and hospital stay. No significant impact on renal and pulmonary function.	NR

Kottenberg et al., 2012[17]	19, 20	CABG (cold crystalloid cardioplegia)	Upper limb: 3 cycles I/R (5/5 min)	Reduced TnI release under isoflurane, but not under propofol	NR	NR
Lee et al., 2012[18]	28, 27	Pulmonary hypertensive infants receiving ventricular septal defect repair	Lower limb: 4 cycles I/R (5/5 min)	No significant decrease in TnI release	No significant decrease in duration of mechanical ventilation and ICU stay	NR
Lomivorotov et al., 2012[19]	40, 40	CABG (cold-crystalloid cardioplegia)	Upper limb: 3 cycles I/R (5/5 min)	No significant effect on CK-MB and TnI release	No significant decrease in duration of ventilation time and ICU stay	NR
Lucchinetti et al., 2012[20]	28, 27	CABG (cold blood cardioplegia)	Lower limb: 4 cycles I/R (5/5 min)	No significant effect on TnT and NT-proBNP release	No decrease in new myocardial infarction and atrial fibrillation at 3 days. The incidence for postoperative composite endpoint combining new arrhythmias and new myocardial infarctions was higher in RIPC group.	No decrease in death or clinical outcomes (heart failure, renal failure and new atrial fibrillation) at 6 months
Pavione et al., 2012[21]	10, 12	Pediatric congenital cardiac surgery (cold blood cardioplegia)	Lower limb: 4 cycles I/R (5/5 min)	Reduced NT-proBNP levels but no effect on TnI release	No impact on incidence of arrhythmia, inotropic score, duration of mechanical ventilation, PICU stay and hospital stay. No improvement of pediatric logistic organ dysfunction (PELOD) score at 24 h and 2 days.	NR
Xie et al., 2012[22]	35, 38	Elective valve replacement (cold blood cardioplegia)	Upper limb: 3 cycles I/R (5/5 min)	Reduced TnI release	NR	RIPC group had greater improvement in NYHA class and LVEF at 3 months
Young et al., 2012[23]	48, 48	High risk cardiac surgery (CABG or valve surgery or both) (blood cardioplegia)	Upper limb: 3 cycles I/R (5/5 min)	No decrease in TnT release	RIPC increased post-operative duration of noradrenaline support and mechanical ventilation. No effect on incidence of AKI.	No decrease in mortality at 30 days
Jones et al., 2013[24]	19, 20	Neonatal cardiac surgery (transposition of	Lower limb: 4 cycles I/R (5/5 min)	No significant effect on TnI release and markers of renal	No significant decrease in duration of mechanical ventilation	NR

		great arteries and hypoplastic left heart syndrome)		and cerebral injury		
Kleinbongard et al., 2013[25]	75, 65	CABG	Upper limb: 3 cycles I/R (5/5 min)	Reduced TnI release	NR	NR
Pepe et al., 2013[26]	20, 20	Pediatric cardiac surgery (tetralogy of Fallot)	Lower limb: 4 cycles I/R (5/5 min)	No effect on TnI release and other markers for apoptosis and autophagy	No significant decrease in duration of ventilation time, ICU stay and hospital stay	NR
Thielmann et al., 2013[27]	167, 162	CABG (cold crystalloid cardioplegia)	Upper limb: 3 cycles I/R (5/5 min)	Reduced TnI release	Reduced perioperative MI. No significant decrease in duration of mechanical ventilation, ICU and hospital stay.	Reduced all-cause mortality, MACCE, and MI at 1 year. Trend toward reduced cardiac death. No significant decrease in incidence of stroke and repeat vascularization.
Ahmad et al., 2014[28]	32, 35	CABG (on pump)	NA	No effect on CK-MB release	No significant impact on in-hospital mortality	No significant impact on mortality at 1 year
Bautin et al., 2014[29]	12, 12	Aortic valve replacement	Lower limb: 3 cycles I/R (5/5 min) simultaneously on both sides	Reduced TnI release under sevoflurane, but not under propofol	Reduced incidence of paroxysmal atrial fibrillation	NR
Gedik et al., 2014[30]	10, 10	CABG (cold crystalloid cardioplegia)	Upper limb: 3 cycles I/R (5/5 min)	Reduced TnI release	NR	NR
Holmberg et al., 2014[31]	23, 23	Elective cardiac surgery (on pump with cold blood cardioplegia)	Upper limb: 3 cycles I/R (5/5 min)	No significant decrease in TnT and CK-MB release	No decrease in duration of ICU stay and hospital stay. No significant decrease in episodes of atrial fibrillation at ICU.	NR
Hong et al., 2014[32]	636, 644	Elective cardiac surgery (off pump and on pump with cold blood cardioplegia)	Upper limb: 4 cycles I/R (5/5 min) - 2 cycles before and 2 after anastomoses	NR	No decrease in rate of primary end-points (composite of major adverse outcomes including death, MI, arrhythmia, stoke, coma, renal failure or dysfunction, respiratory failure, cardiogenic shock, gastrointestinal complication and	NR

					multiorgan failure). No significant impact on any of the individual outcomes. No significant decrease in duration of mechanical ventilation, ICU stay and hospital stay.	
Kottenberg et al., 2014[33]	12, 12	CABG	Upper limb: 3 cycles I/R (5/5 min)	No significant effect on TnI release	NR	NR
Kottenberg et al., 2014[34]	130, 100	CABG	Upper limb: 3 cycles I/R (5/5 min)	Reduced TnI release in non-diabetic patients but not in sulphonylurea-treated diabetics	NR	NR
McCrindle et al., 2014[35]	151, 148	Pediatric cardiac surgery	Lower limb: 4 cycles I/R (5/5 min)	No significant impact on TnI release or markers of hematologic, hepatic and renal dysfunction	Decrease in incidence of arrhythmia. No decrease in duration of mechanical ventilation, ICU stay and hospital stay.	NR
Slagsvold et al., 2014[36]	30, 30	CABG (crystalloid or blood cardioplegia)	Upper limb: 3 cycles I/R (5/5 min)	No significant decrease in TnT, CK-MB and NT-proBNP release. Preserved mitochondrial function.	Reduced postoperative atrial fibrillation. No significant decrease in duration of ICU stay.	NR
Candilio et al., 2015[37]	90, 90	CABG and/or valve surgery	Upper and lower limb: 2 cycles I/R (5/5 min)	Reduced TnT release	Reduced incidence of new onset atrial fibrillation and duration of ICU stay	Trend toward reduced AKI, duration of hospital stay and death at 6 weeks. No significant decrease in incidence of MI and stroke at 6 weeks.

Abbreviations: AKI, acute kidney injury; BNP, brain natriuretic peptide; CABG, coronary artery bypass surgery; CK-MB, creatine kinase-MB isoform; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; I/R, ischemia/reperfusion; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVESVI, LV end-systolic volume index; MACCE, major adverse cardiac and cerebrovascular event; MI, myocardial infarction; NA, not available; NR, not reported; NT-proBNP, n-terminal-proBNP; NYHA, New York heart association; TnI, troponin I; TnT, troponin T

Online Table II. Meta-analyses of clinical trials examining the effects of remote ischemic preconditioning in patients undergoing cardiac surgery

Study	No. of Trials	Patient Population	Patients (total)	Surgical Procedures	Laboratory Results with RIPC	Clinical Outcomes with RIPC
Takagi et al., 2008[38]	4	Children, adults	184	Pediatric cardiac surgery, adult cardiac surgery, adult vascular surgery	Reduced release of biomarkers of myocardial injury	NR
Takagi et al., 2011[39]	9	Children, adults	482	Pediatric cardiac surgery, adult cardiac surgery, adult vascular surgery	Reduced troponin release	No significant effect on early mortality and perioperative MI
Alreja et al., 2012[40]	17	Adults	1371	Adult cardiac surgery, PCI, vascular surgery	Reduced release of biomarkers of myocardial injury	Reduced incidence of perioperative MI. Reduced renal injury in patients undergoing abdominal aortic aneurysm repair.
Brevoord et al., 2012[41]	23	Children, adults	1878	Pediatric cardiac surgery, adult cardiac surgery, PCI, adult vascular surgery	Reduced troponin release	Reduced incidence of MI. No significant impact on mortality, MACCE, atrial fibrillation, kidney injury, duration of ICU and hospital stay.
D'Ascenzo et al., 2012[42]	9	Adults	704	CABG	Reduced troponin release	No decrease in duration of hospital stay
Pilcher et al., 2012[43]	10	Children, adults	693	Pediatric cardiac surgery, adult cardiac surgery	Reduced troponin release in unblinded trials but did not significantly reduce in fully blinded trials	NR
Yetgin et al., 2012[44]	13	Adults	891	Adult cardiac surgery	Reduced release of biomarkers of myocardial injury in the absence of inhaled anesthetics	NR
Li et al., 2013[45]	10	Adults	924	Adult cardiac surgery, PCI, vascular surgery	Reduced incidence of AKI using fixed-effects model but not random-effects. No significant effect on renal biomarkers.	No significant effect on renal replacement therapy requirement, mortality, duration of ICU stay and hospital stay
Zhou et al., 2013[46]	15	Adults	1155	Adult cardiac surgery	Reduced release of biomarkers of myocardial injury after valve surgery, but did not significantly	No significant reduction in mortality, duration of mechanical ventilation, ICU stay and hospital stay

					reduce after CABG	
Healy et al., 2014[47]	23	Adults	2200	Adult cardiac surgery, vascular surgery	NR	No significant effect on death, perioperative MI, renal failure, stroke, mesenteric ischemia, new-onset arrhythmias, duration of ICU stay and hospital stay
Tie et al., 2014[48]	7	Children	359	Pediatric cardiac surgery	No significant decrease in TnI release	Reduced duration of ICU stay. No significant reduction in duration of mechanical ventilation and hospital stay.
Yang L et al., 2014[49]	19	Children, adults	1235	Pediatric cardiac surgery, adult cardiac surgery	Reduced TnI release	No significant reduction in death, incidence of MI, renal failure and atrial fibrillation. No decrease in duration of mechanical ventilation, ICU stay and hospital stay.
Yang Y et al., 2014[50]	13	Adults	1334	Adult cardiac surgery, PCI, vascular surgery	No significant decrease in incidence of AKI and biomarkers of renal function	No significant impact on renal replacement therapy requirement, in-hospital mortality, duration of ICU stay and hospital stay
Yasin et al., 2014[51]	25	Children, adults	N/A	Pediatric cardiac surgery, adult cardiac surgery	Reduced release of biomarkers of myocardial injury	No evidence of renal or pulmonary protection. No effect on duration of mechanical ventilation, ICU stay and hospital stay. No significant reduction in mortality at 30 days.
Zhang et al., 2014[52]	8	Adults	960	CABG	NR	No significant effect on duration of mechanical ventilation and ICU stay and mortality at 30 days
Deng et al., 2015[53]	11	Adults	1062	Adult cardiac surgery	Reduced release of biomarkers of myocardial injury	No significant effect on incidence of MI, arrhythmias and renal injury. No significant effect on duration of mechanical ventilation, ICU stay and hospital stay.
Page et al., 2015[54]	44	Children, adults	5317	Pediatric cardiac surgery, adult cardiac surgery, PCI, adult vascular surgery	Reduced troponin and CK-MB release	Reduced incidence of myocardial infarction. Reduced MACCE and all-cause mortality at > 1 year. Non-significant reduction in MACCE and all-cause mortality at < 1 year.
Payne et al., 2015[55]	13	N/A	1398	NA	Reduced troponin release	NR
Tie et al., 2015[56]	9	Children	697	Pediatric cardiac surgery	No significant decrease in TnI release	No significant decrease in duration of mechanical ventilation, ICU stay and hospital stay
Zangrillo et al., 2015[57]	55	N/A	6921	NA	NR	The use of volatile agents and combination of volatile agents with RIPC were associated with a reduction in mortality when compared with total intravenous anesthesia

Zhao et al., 2016[58]	15	Children, adults	4770	Pediatric cardiac surgery, adult cardiac surgery, adult vascular surgery	Trend toward decrease in risk of AKI	NR

Abbreviations: AKI, acute kidney injury; CABG, coronary artery bypass surgery; CK-MB, creatine kinase-MB isoform; ICU, intensive care unit; MACCE, major adverse cardiac and cerebrovascular event; MI, myocardial infarction; NA, not available; NR, not reported; TnI, troponin I

REFERENCES

1. Gunaydin B, Cakici I, Soncul H, Kalaycioglu S, Cevik C, Sancak B, Kanzik I, Karadenizli Y. Does remote organ ischaemia trigger cardiac preconditioning during coronary artery surgery? *Pharmacol Res*. 2000;41:493-496
2. Cheung MM, Kharbanda RK, Konstantinov IE, Shimizu M, Frndova H, Li J, Holtby HM, Cox PN, Smallhorn JF, Van Arsdell GS, Redington AN. Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: first clinical application in humans. *J Am Coll Cardiol*. 2006;47:2277-2282
3. Hausenloy DJ, Mwamure PK, Venugopal V, Harris J, Barnard M, Grundy E, Ashley E, Vichare S, Di Salvo C, Kolvekar S, Hayward M, Keogh B, MacAllister RJ, Yellon DM. Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial. *Lancet*. 2007;370:575-579
4. Venugopal V, Hausenloy DJ, Ludman A, Di Salvo C, Kolvekar S, Yap J, Lawrence D, Bognolo J, Yellon DM. Remote ischaemic preconditioning reduces myocardial injury in patients undergoing cardiac surgery with cold-blood cardioplegia: a randomised controlled trial. *Heart*. 2009;95:1567-1571
5. Ali N, Rizwi F, Iqbal A, Rashid A. Induced remote ischemic pre-conditioning on ischemia-reperfusion injury in patients undergoing coronary artery bypass. *J Coll Physicians Surg Pak*. 2010;20:427-431
6. Hong DM, Mint JJ, Kim JH, Sohn IS, Lim TW, Lim YJ, Bahk JH, Jeon Y. The effect of remote ischaemic preconditioning on myocardial injury in patients undergoing off-pump coronary artery bypass graft surgery. *Anaesth Intensive Care*. 2010;38:924-929
7. Li L, Luo W, Huang L, Zhang W, Gao Y, Jiang H, Zhang C, Long L, Chen S. Remote perconditioning reduces myocardial injury in adult valve replacement: a randomized controlled trial. *J Surg Res*. 2010;164:e21-26
8. Rahman IA, Mascaro JG, Steeds RP, Frenneaux MP, Nightingale P, Gosling P, Townsend P, Townend JN, Green D, Bonser RS. Remote ischemic preconditioning in human coronary artery bypass surgery: from promise to disappointment? *Circulation*. 2010;122:S53-59
9. Thielmann M, Kottenberg E, Boengler K, Raffelsieper C, Neuhaeuser M, Peters J, Jakob H, Heusch G. Remote ischemic preconditioning reduces myocardial injury after coronary artery bypass surgery with crystalloid cardioplegic arrest. *Basic Res Cardiol*. 2010;105:657-664
10. Wagner R, Piler P, Bedanova H, Adamek P, Grodecka L, Freiberger T. Myocardial injury is decreased by late remote ischaemic preconditioning and aggravated by tramadol in patients undergoing cardiac surgery: a randomised controlled trial. *Interact Cardiovasc Thorac Surg*. 2010;11:758-762
11. Zhou W, Zeng D, Chen R, Liu J, Yang G, Liu P, Zhou X. Limb ischemic preconditioning reduces heart and lung injury after an open heart operation in infants. *Pediatr Cardiol*. 2010;31:22-29
12. Karuppasamy P, Chaubey S, Dew T, Musto R, Sherwood R, Desai J, John L, Shah AM, Marber MS, Kunst G. Remote intermittent ischemia before coronary artery bypass graft

surgery: a strategy to reduce injury and inflammation? *Basic Res Cardiol*. 2011;106:511-519
13. Luo W, Zhu M, Huang R, Zhang Y. A comparison of cardiac post-conditioning and remote pre-conditioning in paediatric cardiac surgery. *Cardiol Young*. 2011;21:266-270
14. Wu Q, Gui P, Wu J, Ding D, Purusram G, Dong N, Yao S. Effect of limb ischemic preconditioning on myocardial injury in patients undergoing mitral valve replacement surgery. -A randomized controlled trial. *Circ J*. 2011;75:1885-1889
15. Heusch G, Musiolik J, Kottenberg E, Peters J, Jakob H, Thielmann M. STAT5 activation and cardioprotection by remote ischemic preconditioning in humans: short communication. *Circ Res*. 2012;110:111-115
16. Hong DM, Jeon Y, Lee CS, Kim HJ, Lee JM, Bahk JH, Kim KB, Hwang HY. Effects of remote ischemic preconditioning with postconditioning in patients undergoing off-pump coronary artery bypass surgery--randomized controlled trial. *Circ J*. 2012;76:884-890
17. Kottenberg E, Thielmann M, Bergmann L, Heine T, Jakob H, Heusch G, Peters J. Protection by remote ischemic preconditioning during coronary artery bypass graft surgery with isoflurane but not propofol - a clinical trial. *Acta Anaesthesiol Scand*. 2012;56:30-38
18. Lee JH, Park YH, Byon HJ, Kim HS, Kim CS, Kim JT. Effect of remote ischaemic preconditioning on ischaemic-reperfusion injury in pulmonary hypertensive infants receiving ventricular septal defect repair. *Br J Anaesth*. 2012;108:223-228
19. Lomivorotov VV, Shmyrev VA, Nepomnyaschih VA, Ponomarev DN, Knyazkova LG, Lomivorotov VN, Karaskov AM. Remote ischaemic preconditioning does not protect the heart in patients undergoing coronary artery bypass grafting. *Interact Cardiovasc Thorac Surg*. 2012;15:18-22
20. Lucchinetti E, Bestmann L, Feng J, Freidank H, Clanachan AS, Finegan BA, Zaugg M. Remote ischemic preconditioning applied during isoflurane inhalation provides no benefit to the myocardium of patients undergoing on-pump coronary artery bypass graft surgery: lack of synergy or evidence of antagonism in cardioprotection? *Anesthesiology*. 2012;116:296-310
21. Pavione MA, Carmona F, de Castro M, Carlotti AP. Late remote ischemic preconditioning in children undergoing cardiopulmonary bypass: a randomized controlled trial. *J Thorac Cardiovasc Surg*. 2012;144:178-183
22. Xie JJ, Liao XL, Chen WG, Huang DD, Chang FJ, Chen W, Luo ZL, Wang ZP, Ou JS. Remote ischaemic preconditioning reduces myocardial injury in patients undergoing heart valve surgery: randomised controlled trial. *Heart*. 2012;98:384-388
23. Young PJ, Dalley P, Garden A, Horrocks C, La Flamme A, Mahon B, Miller J, Pilcher J, Weatherall M, Williams J, Young W, Beasley R. A pilot study investigating the effects of remote ischemic preconditioning in high-risk cardiac surgery using a randomised controlled double-blind protocol. *Basic Res Cardiol*. 2012;107:256
24. Jones BO, Pepe S, Sheeran FL, Donath S, Hardy P, Shekerdemian L, Penny DJ, McKenzie I, Horton S, Brizard CP, d'Udekem Y, Konstantinov IE, Cheung MM. Remote ischemic preconditioning in cyanosed neonates undergoing cardiopulmonary bypass: a randomized controlled trial. *J Thorac Cardiovasc Surg*. 2013;146:1334-1340

25. Kleinbongard P, Thielmann M, Jakob H, Peters J, Heusch G, Kottenberg E. Nitroglycerin does not interfere with protection by remote ischemic preconditioning in patients with surgical coronary revascularization under isoflurane anesthesia. *Cardiovasc Drugs Ther*. 2013;27:359-361
26. Pepe S, Liaw NY, Hepponstall M, Sheeran FL, Yong MS, d'Udekem Y, Cheung MM, Konstantinov IE. Effect of remote ischemic preconditioning on phosphorylated protein signaling in children undergoing tetralogy of Fallot repair: a randomized controlled trial. *J Am Heart Assoc*. 2013;2:e000095
27. Thielmann M, Kottenberg E, Kleinbongard P, Wendt D, Gedik N, Pasa S, Price V, Tsagakis K, Neuhauser M, Peters J, Jakob H, Heusch G. Cardioprotective and prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial. *Lancet*. 2013;382:597-604
28. Ahmad AM, Ali GS, Tariq W. Remote ischemic preconditioning is a safe adjuvant technique to myocardial protection but adds no clinical benefit after on-pump coronary artery bypass grafting. *Heart Surg Forum*. 2014;17:E220-223
29. Bautin AE, Galagudza MM, Datsenko SV, Tashkhanov DM, Marichev AO, Bakanov A, Malaia E, Naimushin AV, Rubinchik VE, Gordeev ML. [Effects of remote ischemic preconditioning on perioperative period in elective aortic valve replacement]. *Anesteziol Reanimatol*. 2014:11-17
30. Gedik N, Thielmann M, Kottenberg E, Peters J, Jakob H, Heusch G, Kleinbongard P. No evidence for activated autophagy in left ventricular myocardium at early reperfusion with protection by remote ischemic preconditioning in patients undergoing coronary artery bypass grafting. *PLoS One*. 2014;9:e96567
31. Holmberg FE, Ottas KA, Andreasen C, Perko MJ, Moller CH, Engstrom T, Steinbruchel DA. Conditioning techniques and ischemic reperfusion injury in relation to on-pump cardiac surgery. *Scand Cardiovasc J*. 2014;48:241-248
32. Hong DM, Lee EH, Kim HJ, Min JJ, Chin JH, Choi DK, Bahk JH, Sim JY, Choi IC, Jeon Y. Does remote ischaemic preconditioning with postconditioning improve clinical outcomes of patients undergoing cardiac surgery? Remote Ischaemic Preconditioning with Postconditioning Outcome Trial. *Eur Heart J*. 2014;35:176-183
33. Kottenberg E, Musiolik J, Thielmann M, Jakob H, Peters J, Heusch G. Interference of propofol with signal transducer and activator of transcription 5 activation and cardioprotection by remote ischemic preconditioning during coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2014;147:376-382
34. Kottenberg E, Thielmann M, Kleinbongard P, Frey UH, Heine T, Jakob H, Heusch G, Peters J. Myocardial protection by remote ischaemic pre-conditioning is abolished in sulphonylurea-treated diabetics undergoing coronary revascularisation. *Acta Anaesthesiol Scand*. 2014;58:453-462
35. McCrindle BW, Clarizia NA, Khaikin S, Holtby HM, Manlhiot C, Schwartz SM, Caldarone CA, Coles JG, Van Arsdell GS, Scherer SW, Redington AN. Remote ischemic preconditioning in children undergoing cardiac surgery with cardiopulmonary bypass: a single-center double-blinded randomized trial. *J Am Heart Assoc*. 2014;3

36. Slagsvold KH, Rognmo O, Hoydal M, Wisloff U, Wahba A. Remote ischemic preconditioning preserves mitochondrial function and influences myocardial microRNA expression in atrial myocardium during coronary bypass surgery. *Circ Res*. 2014;114:851-859
37. Candilio L, Malik A, Ariti C, Barnard M, Di Salvo C, Lawrence D, Hayward M, Yap J, Roberts N, Sheikh A, Kolvekar S, Hausenloy DJ, Yellon DM. Effect of remote ischaemic preconditioning on clinical outcomes in patients undergoing cardiac bypass surgery: a randomised controlled clinical trial. *Heart*. 2015;101:185-192
38. Takagi H, Manabe H, Kawai N, Goto SN, Umemoto T. Review and meta-analysis of randomized controlled clinical trials of remote ischemic preconditioning in cardiovascular surgery. *Am J Cardiol*. 2008;102:1487-1488
39. Takagi H, Umemoto T. Remote ischemic preconditioning for cardiovascular surgery: an updated meta-analysis of randomized trials. *Vasc Endovascular Surg*. 2011;45:511-513
40. Alreja G, Bugano D, Lotfi A. Effect of remote ischemic preconditioning on myocardial and renal injury: meta-analysis of randomized controlled trials. *J Invasive Cardiol*. 2012;24:42-48
41. Brevoord D, Kranke P, Kuijpers M, Weber N, Hollmann M, Preckel B. Remote ischemic conditioning to protect against ischemia-reperfusion injury: a systematic review and meta-analysis. *PLoS One*. 2012;7:e42179
42. D'Ascenzo F, Cavallero E, Moretti C, Omede P, Sciuto F, Rahman IA, Bonser RS, Yunseok J, Wagner R, Freiberger T, Kunst G, Marber MS, Thielmann M, Ji B, Amr YM, Modena MG, Zoccai GB, Sheiban I, Gaita F. Remote ischaemic preconditioning in coronary artery bypass surgery: a meta-analysis. *Heart*. 2012;98:1267-1271
43. Pilcher JM, Young P, Weatherall M, Rahman I, Bonser RS, Beasley RW. A systematic review and meta-analysis of the cardioprotective effects of remote ischaemic preconditioning in open cardiac surgery. *J R Soc Med*. 2012;105:436-445
44. Yetgin T, Manintveld OC, Boersma E, Kappetein AP, van Geuns RJ, Zijlstra F, Duncker DJ, van der Giessen WJ. Remote ischemic conditioning in percutaneous coronary intervention and coronary artery bypass grafting. *Circ J*. 2012;76:2392-2404
45. Li L, Li G, Yu C, Li Y. The role of remote ischemic preconditioning on postoperative kidney injury in patients undergoing cardiac and vascular interventions: a meta-analysis. *J Cardiothorac Surg*. 2013;8:43
46. Zhou C, Liu Y, Yao Y, Zhou S, Fang N, Wang W, Li L. beta-blockers and volatile anesthetics may attenuate cardioprotection by remote preconditioning in adult cardiac surgery: a meta-analysis of 15 randomized trials. *J Cardiothorac Vasc Anesth*. 2013;27:305-311
47. Healy DA, Khan WA, Wong CS, Moloney MC, Grace PA, Coffey JC, Dunne C, Walsh SR, Sadat U, Gaunt ME, Chen S, Tehrani S, Hausenloy DJ, Yellon DM, Kramer RS, Zimmerman RF, Lomivorotov VV, Shmyrev VA, Ponomarev DN, Rahman IA, Mascaro JG, Bonser RS, Jeon Y, Hong DM, Wagner R, Thielmann M, Heusch G, Zacharowski K, Meybohm P, Bein B, Tang TY. Remote preconditioning and major clinical complications following adult cardiovascular surgery: systematic review and meta-analysis. *Int J Cardiol*. 2014;176:20-31

48. Tie HT, Luo MZ, Li ZH, Wang Q, Wu QC. Remote ischemic preconditioning for pediatric patients undergoing congenital cardiac surgery: a meta-analysis. *Int J Cardiol*. 2014;177:551-553
49. Yang L, Wang G, Du Y, Ji B, Zheng Z. Remote ischemic preconditioning reduces cardiac troponin I release in cardiac surgery: a meta-analysis. *J Cardiothorac Vasc Anesth*. 2014;28:682-689
50. Yang Y, Lang XB, Zhang P, Lv R, Wang YF, Chen JH. Remote ischemic preconditioning for prevention of acute kidney injury: a meta-analysis of randomized controlled trials. *Am J Kidney Dis*. 2014;64:574-583
51. Haji Mohd Yasin NA, Herbison P, Saxena P, Praporski S, Konstantinov IE. The role of remote ischemic preconditioning in organ protection after cardiac surgery: a meta-analysis. *J Surg Res*. 2014;186:207-216
52. Zhang B, Zhou J, Li H, Zhou M, Chen A, Zhao Q. Remote ischemic preconditioning does not improve the clinical outcomes in patients undergoing coronary artery bypass grafting: a meta-analysis of randomized controlled trials. *Int J Cardiol*. 2014;172:e36-38
53. Deng QW, Xia ZQ, Qiu YX, Wu Y, Liu JX, Li C, Liu KX. Clinical benefits of aortic cross-clamping versus limb remote ischemic preconditioning in coronary artery bypass grafting with cardiopulmonary bypass: a meta-analysis of randomized controlled trials. *J Surg Res*. 2015;193:52-68
54. Le Page S, Bejan-Angoulvant T, Angoulvant D, Prunier F. Remote ischemic conditioning and cardioprotection: a systematic review and meta-analysis of randomized clinical trials. *Basic Res Cardiol*. 2015;110:11
55. Payne RE, Aldwinckle J, Storrow J, Kong RS, Lewis ME. RIPC Remains a Promising Technique for Protection of the Myocardium during Open Cardiac Surgery: A Meta-Analysis and Systematic Review. *Heart Surg Forum*. 2015;18:E074-080
56. Tie HT, Luo MZ, Li ZH, Wang Q, Wu QC, Li Q, Zhang M. Remote Ischemic Preconditioning Fails to Benefit Pediatric Patients Undergoing Congenital Cardiac Surgery: A Meta-Analysis of Randomized Controlled Trials. *Medicine (Baltimore)*. 2015;94:e1895
57. Zangrillo A, Musu M, Greco T, Di Prima AL, Matteazzi A, Testa V, Nardelli P, Febres D, Monaco F, Calabro MG, Ma J, Finco G, Landoni G. Additive Effect on Survival of Anaesthetic Cardiac Protection and Remote Ischemic Preconditioning in Cardiac Surgery: A Bayesian Network Meta-Analysis of Randomized Trials. *PLoS One*. 2015;10:e0134264
58. Zhao BC, Deng WT, Li BC, Deng QW, Xia ZQ, Li YY, Liu KX. Remote ischemic preconditioning for preventing acute kidney injury following cardiovascular surgery: A meta-analysis with trial sequential analysis. *Int J Cardiol*. 2016;203:842-844