

RIPC Remains a Promising Technique for Protection of the Myocardium during Open Cardiac Surgery: A Meta-Analysis and Systematic Review

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ABSTRACT

Background: Remote ischemic preconditioning (RIPC) is the process of inducing brief ischemia in a tissue to prevent ischemic damage in another. This preconditioning can be induced simply by inflating a blood pressure cuff on a limb. Previous randomized controlled trials (RCT) have suggested that RIPC may infer myocardial protection during open cardiac surgery. One method of assessing the degree of myocardial damage incurred in these studies is to assay troponin concentration. Troponin is a cardiac enzyme released by damaged myocytes. With the recent publication of several large RCTs in this area, a meta-analysis of the evidence was undertaken.

Methods: A systematic search of PubMed, EMBASE, and clinicaltrials.gov.uk was conducted using MeSH terms “ischaemic preconditioning” and “cardiac surgery.” RCTs that examined post-surgery troponin concentrations were included in this review. The primary outcome investigated was troponin levels at six hours post-cardiac surgery. Secondary outcomes included six to eight hour and twenty-four hour troponin release.

Results: Thirteen RCTs, comprising 1398 participants, were identified for inclusion in this meta-analysis. Twelve hour postoperative troponin was significantly reduced by RIPC, standardized mean difference 1.29 (95% CI 0.34-2.24). Six to eight and twenty-four hour troponin were also significantly reduced, standardized mean differences 1.23 (95% CI 0.62-1.84) and 1.25 (95% CI 0.31-2.19) respectively.

Conclusion: The reduction in troponin concentration suggests that RIPC reduces myocardial damage during open cardiac surgery, however, the degree of bias in the studies assessed may have had a significant impact on this result.

INTRODUCTION

Remote ischemic preconditioning (RIPC) is the process of inducing brief ischemia in a tissue to prevent ischemic damage in another. This is commonly performed by inflation of a blood pressure cuff around the upper or lower limb. During cardiac surgery myocardial cells adapt to anaerobic

metabolism. A subsequent return of oxygen during reperfusion activates macrophages, which produce reactive oxygen species (ROS) that damage the myocardium and trigger an inflammatory response [Tapuria 2008]. Modification of this inflammatory response by RIPC may protect the myocardium [Lu 1997; Ates 2002; Waldow 2005], although the exact mechanism remains elusive. Certain studies have suggested a neuronal mechanism for RIPC [Tang 1999; Oxman 1997; Kharbanda 2002], whereas some propose a humoral response. Konstantinov et al found that RIPC was still beneficial in a denervated heart [Konstantinov 2005].

Several small randomized controlled trials have demonstrated a reduction in myocardial injury assessed by troponin concentration post cardiac surgery. Two previous reviews [Pilcher 2012] have concluded that these proof of concept trials are promising but larger scale double-blinded RCTs are required to assess the impact of RIPC accurately. In the review published by Pilcher et al, the beneficial effect of RIPC estimated by trials that were adequately blinded was non significant [Pilcher 2012]. Non and partially blinded studies produced a significant reduction in troponin following cardiac surgery.

Since the publication of this previous review in 2012 there have been seven articles published on the ability of RIPC to reduce troponin following open cardiac surgery. As such, this review is intended to update the previous evidence, summarize the current understanding in this promising area, and answer the question: Does RIPC reduce myocardial damage as indicated by troponin levels in patients undergoing open cardiac surgery?

METHODS

Literature Search Strategy

PubMed, clinicaltrials.gov.uk, and EMBASE were searched using MeSH terms “ischaemic preconditioning” and “cardiac surgery” up until September 2013. The search had the following limits: English, RCTs, and humans. Searches were conducted by R.P. and J.A. The reference lists of all studies included were subsequently screened for any further articles of relevance. All authors of articles included were contacted in an attempt to identify any unpublished data.

Eligibility Criteria

Initially search results were screened by title and abstract to identify articles for full text review. Inclusion criteria were: randomized controlled trials, articles written in English, adult

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patients undergoing any open cardiac surgery, studies comparing RIPC with sham RIPC in the control group, and outcomes needed to include postoperative troponin level.

Data Extraction

Data was extracted from the text, tables, and where necessary, from graphs using Plot Digitizer [Rohatgi 2013]. Three articles listed median values for troponin concentration, and in these cases the authors were contacted for mean values and standard deviations. Data extraction was performed by R.P. and validated by J.S. and J.A. Disagreements were resolved by consensus.

Outcomes

The primary outcome was 12 hour troponin concentration. Secondary outcomes included 6-8 and 24 hour troponin and total troponin release, expressed as area under the curve

at 72 hours. Other outcomes reported included ventilation duration, mortality at 30 days, and requirement for inotropic support. This data was not analyzed in the meta-analysis.

Statistical Analysis

Meta-analysis was performed using RevMan 5.0 [RevMan 2012]. Standardized mean difference with inverse variance weighting was calculated as varying assays, and units were used for troponin levels, and a random effects model was used where significant heterogeneity was present. This method enables all results to be compared. Homogeneity was calculated for all analyses performed. Publication bias was assessed through the use of funnel plots.

Blinding

Bias was assessed by J.A. and J.S. in accordance with the Cochrane Collaboration's tool for assessing the risk of bias in

Table 1. The Cochrane Collaboration's Tool for Assessing Risk of Bias

Domain	Support for judgement	Review authors' judgement
<i>Selection bias</i>		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during enrollment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
<i>Performance bias</i>		
Blinding of participants and personnel – Assessments should be made for each main outcome (or class of outcomes).	Describe all measures used, if any to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
<i>Detection bias</i>		
Blinding of outcomes assessment – Assessments should be made for each main outcome (or class of outcomes).	Describe all measures used, in any to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcomes assessors.
<i>Attrition bias</i>		
Incomplete outcome data – Assessments should be made for each main outcome (or class of outcomes).	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
<i>Reporting bias</i>		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
<i>Other bias</i>		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

Table 2.

Author	n	RIPC Technique	Anesthetic	Surgery	Bias	Significant effect found at any time?
Lomivorotov 2012	80	Right upper limb 3*5 min	Fentanyl, propofol and pipecuronium bromide. Isoflurane	CABG under CPB	U	No
Karup-pasamy 2011	54	Left upper limb 3*5 min After anesthesia induction	Midazolam, remifentanyl, propofol and atracurium. Isoflurane.	CABG	U	No
Thielmann 2010	53	Left upper limb 3*5 min After anesthesia induction	Sufentanil, etomidate and rocuronium. Isoflurane or propofol.	CABG under CPB	U	Yes
Xie 2012	73	Right upper limb 3*5 min After anesthesia induction	Sufentanil, etomidate, midazolam and rocuronium bromide. Sufentanil (when shallow anesthesia small amount of sevoflurane)	Heart valve surgery	H	Yes
Heusch 2012	23	Left upper limb 3*5 min After anesthesia induction	Sufentanil, etomidate and rocuronium. Isoflurane.	CABG under CPB	U	Yes
Venugopal 2009	45	Right upper limb 3*5 min After anesthesia induction	Midazolam, etomidate or propofol, fentanyl and pancuronium. Either halogenated anesthetic or propofol.	CABG with or without aortic valve replacement	H	Yes
Hausenloy 2007	57	Right upper limb 3*5 min After anesthesia induction	Temazepam. Midazolam, etomidate or propofol, fentanyl and pancuronium. Propofol	CABG under CPB	U	Yes
Kottenberg 2012	72	Left upper limb 3*5 min After anesthesia induction	Sufentanil, etomidate and rocuronium. Isoflurane or propofol infusion.	CABG	L	Yes
Hong 2010	130	Upper limb 4*5 min After anesthesia induction	Midazolam, sufentanil, vecuronium. Sevoflurane and remifentanyl.	Off pump CABG	L	No
Li 2010	81 (53 included in meta analysis)	Right lower limb 3*4 min After anesthesia induction	Midazolam, vecuronium bromide. Fentanyl, propofol and intermittent isoflurane.	Valve replacement	L	No
Young 2012	96	Upper limb 3*5 min With first surgical incision	Midazolam, fentanyl, vecuronium or rocuronium. Propofol and isoflurane.	Double/triple valve surgery, mitral valve surgery, CABG plus valve, CABG writ pre operative EF of <50%	L	No
Wu 2011	75 (50 included in meta analysis)	Right upper limb 3*5 min After anesthesia induction	Midazolam, fentanyl, vecuronium. Midazolam, sufentanyl and vecuronium.	Mitral valve replacement	U	No
Thielmann 2013	329	Left upper limb 3*5 min After anesthesia induction	Sufentanil, etomidate, rocuronium. Isoflurane or propofol.	CABG	L	Yes

randomized trials. Disagreements were resolved by consensus. The risk of bias tool evaluates six areas of bias: selection bias (which is split into random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias, and any other bias.

Within each area, assessments are undertaken and a judgment of high, low, and unclear risk of bias made. Each publication was critiqued in detail in conjunction with the tool's criteria given in Table 1. All publications deemed to have a high risk of bias in any area were scrutinized further.

It was arbitrarily determined that a publication would be considered at low risk of bias if at least six of the seven areas were scored at low risk without a high risk component. A publication was deemed as high risk if it contained one or more high risk components or unclear risk of bias if more than one component was uncertain and no areas were recorded as high risk.

RESULTS

Quantity of Evidence

The search described produced 163 results, and after applying the selection criteria, thirteen of these remained for inclusion in the meta-analysis (Table 2). No further studies were found through screening reference lists. This resulted in 1398 participants included in the meta-analysis.

Basic Demographics

Eight of the articles described the use of RIPC in elective isolated coronary artery bypass grafting (CABG) [Lomivorotov 2012; Karuppasamy 2011; Thielmann 2010; Heusch 2012; Hausenloy 2007; Kottenberg 2012; Hong 2010; Thielmann 2013]. Of these, one investigated off-pump CABG (OPCABG) [Hong 2010] with the remaining seven investigating CABG with bypass. Three studies investigated its impact on valve surgery [Xie 2012; Li 2010; Wu 2011], two included CABG with or without valve surgery [Venugopal 2009; Young 2012].

Most studies excluded participants with evidence of recent cardiac ischemia, however, this varied with recent ischemic events within 7 days, 4 weeks, and 30 days prior to surgery being excluded. All participants included had baseline troponin measurements. Authors did not report that any results indicated acute coronary syndrome preoperatively. Patients with diabetes, pulmonary, and hepatic disease were excluded from the majority of studies. Cardioprotection included cold blood cardioplegia, crystalloid cardioplegia, and cross clamp fibrillation. Peripheral vascular disease present in the limb of RIPC was also an exclusion criterion, as restricting blood flow to the limb in these patients would be contraindicated.

RIPC was performed in the upper limb in the majority of studies, however, one group reported using the lower limb [Li 2010]. In twelve articles, RIPC was undertaken following anesthesia prior to skin incision, and in one RIPC was initiated with the first skin incision [Young 2012].

Overall, five studies were concluded to have a low risk of bias, six were uncertain risk, and two were at high risk of bias; details can be found in Figure 1.

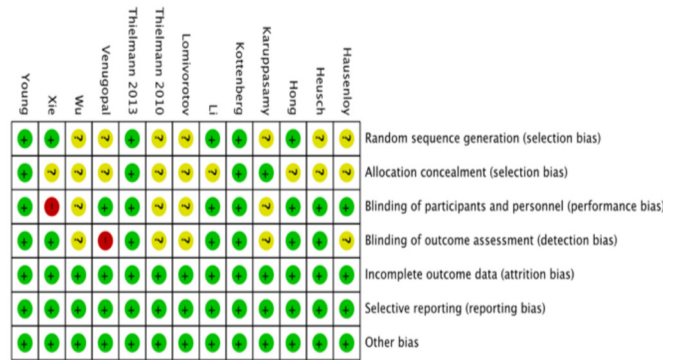


Figure 1.

Studies Excluded

Cheung et al found a significant effect of RIPC on troponin release in pediatric cardiac surgery [Cheung 2006]; this was excluded due to differences in pediatric and adult physiology. Three of the studies [Rahman 2010; Wagner 2010; Lucchinetti 2012] identified in the literature search reported median troponin values after surgery. Authors were contacted to obtain mean values but unfortunately no response was received. As such, these studies could not be included in the meta-analysis. To summarize, Wagner et al demonstrated a significant reduction in troponin I release at 8 hours after the operation caused by RIPC administered 18 hours prior to surgery [Wagner 2010]; Rahman et al found no significant improvement in troponin release in a double blind trial of 162 patients [Rahman 2010]; Lucchinetti also found no improvement in troponin release following RIPC in patients undergoing on-pump CABG surgery [Lucchinetti 2012].

Potential confounding factors were not assessed in the meta-analysis as individual data was unavailable. The duration of cardiopulmonary bypass is one possible confounding factor that may affect troponin concentration. The use of certain anesthetic agents such as isoflurane are postulated to have an impact on the efficacy of RIPC [Karuppasamy 2011].

Primary Outcomes

When considering data from all studies, 12 hour postoperative troponin was significantly reduced by RIPC, standardized mean difference 1.29 (95% CI 0.34-2.24). There was significant heterogeneity amongst studies; I-squared was 97%. Heterogeneity was not explained by the overall bias of the paper or operation type. The funnel plot suggests evidence of publication bias. In analyses of low and uncertain bias studies, troponin was also reduced at 12 hours; standardized mean difference was 1.08 (95% CI 0.02-2.15). However, in the low risk of bias studies RIPC did not reduce troponin concentration, standardized mean difference 0.79 (95% CI -0.80-2.39). Again, significant heterogeneity was present in both these analyses, I-squared values were 98% and 99% respectively.

Secondary Outcomes

RIPC significantly reduced the troponin concentration at 6-8 hours and 24 hours. Standardized mean differences were 1.23

(95% CI 0.62-1.84) and 1.25 (95% CI 0.31-2.19) respectively. Significant heterogeneity was again detected, I-squared was 95% in the 6-8 hour analysis and 97% in the 24 hour analysis.

In the low and uncertain risk of bias group of studies the effect was reduced at 6-8 hours, standardized mean difference 1.11 (95% CI 0.43-1.80); no significant effect was found in these studies at 24 hours or in the area under the curve at 72 hours.

In the seven studies deemed low risk of bias, there was no significant reduction of troponin at 6-8 hours, 12 hours, 24 hours or the total troponin (AUC at 72 hours).

DISCUSSION

This meta-analysis demonstrated that RIPC resulted in a significant reduction in troponin post open cardiac surgery in adult patients. This effect was present at 6-8, 12, and 24 hours after surgery. Similarly, the total troponin release was also significantly reduced. The reduction was only present at 6-8 hours and 12 hours when studies with a high risk of bias were excluded. When studies with a low risk of bias were analyzed, the effect was not present at any time point after surgery. This is similar to the results of a previous review [Pilcher 2012], which concluded with the need for further adequately powered and well-blinded studies to enable accurate assessment of this method. Since then, seven new studies [Lomivorotov 2012; Heusch 2012; Kottenberg 2012; Thielmann 2013; Xie 2012; Young 2012; Lucchinetti 2012] have been undertaken and six included in this paper. Lucchinetti et al was excluded due to the use of median values [Lucchinetti 2012]. Of these new trials, three were deemed low, two unclear, and one at high risk of bias.

One study found there was no benefit of RIPC in low-risk patients undergoing CABG in terms of troponin release [Lomivorotov 2012]. The group did however identify that RIPC improved cardiac function in the short term in these patients. Another study included a further sub-analysis of those patients deemed at higher risk (patients with a longer bypass time or high EuroSCORE) with no benefit [Karuppusamy 2011]. One trial that recruited high-risk cardiac patients also failed to show any improvement with RIPC [Young 2012].

The optimal RIPC protocol is yet to be established, with variables including the limb used, the number and duration of cycles, and its relationship to surgery requiring clarification. A trial that compared two RIPC protocols [Wu 2011] demonstrated that a longer period of RIPC was more beneficial, supporting the theory that a minimum duration of RIPC is required before any cardioprotective effect is seen.

Anesthetic choice may explain the lack of effect observed in some groups [Karuppusamy 2011; Rahman 2010]. Volatile anesthetics have previously been demonstrated to offer cardioprotection during cardiac surgery via the KATP channel [Kersten 1997; Zaugg 2002]. There is evidence that a ceiling to the cardioprotection gained by isoflurane and sevoflurane at approximately 1.5 MAC [Zaugg 2002] exists. This limit may negate the effect of RIPC in patients anesthetized in this way. A comparison of RIPC with isoflurane,

RIPC with propofol and two control groups, one with each anesthetic, showed a reduction in troponin in the RIPC isoflurane group compared to the isoflurane control. This effect was not present in the corresponding propofol groups [Kottenberg 2012].

It is possible that RIPC has more of an effect in certain types of cardiac surgery. Troponin I was reduced by 26% in patients undergoing OPCABG in one study [Hong 2010], however, this result was not statistically significant. It is hypothesized that the lack of effect observed in this case may be due to the more variable level of myocardial damage that occurs during OPCABG when compared with CABG under bypass. A greater number of participants would have been needed to power a study with this reduced effect size.

This meta-analysis used troponin as a marker of myocardial damage. However, the source of troponin during cardiac surgery is a subject of debate. While some argue that troponin is released from damaged cardiac myocytes, it has been suggested that increased permeability of the cell wall causes leaking of troponin from the cytosol [White 2011]. If the latter is the source of significant troponin release, its use as a proxy for myocardial damage should be called into question. Regardless of the source, previous work has identified that higher levels of troponin are associated with worse morbidity and mortality following cardiac surgery [Lehrke 2004].

While this meta-analysis has focused on the benefits of RIPC, Iliodromitis et al found that RIPC increased troponin release after PCI [Iliodromitis 2006]. Similar detrimental effects of RIPC were found by Lucchinetti et al after cardiac surgery [Lucchinetti 2012].

Other outcomes that could be assessed might include cardiac function, morbidity, and mortality. These would obviously require larger studies and longer follow-up periods; the majority of studies in this meta-analysis were not adequately powered to detect these changes. RIPC did not improve left ventricular ejection fraction assessed by echocardiography [Rahman 2010]. However, one group did demonstrate an improvement in cardiac index following RIPC [Lomivorotov 2012]. Another large study [Thielmann 2013] found a significant reduction in all cause mortality at 1 year. Major adverse cardiac and cerebrovascular events were also reduced at the end of follow up, more than 4 years after surgery. However, when sepsis as a cause of death was excluded, this result was no longer significant. While RIPC does have a systemic effect, it is a tenuous link that relates this method to a reduced rate of sepsis.

Conclusion

The previous systematic review by Pilcher et al [Pilcher 2012] concluded with the need for further double-blind randomized controlled trials (RCTs). Taking into account data published since, this meta-analysis concludes that RIPC remains a promising technique. However, this analysis is limited in that it does not take into account clinical outcomes, and the additional studies included are relatively small, with bias remaining a significant issue.

However, the ideal RIPC protocol has not yet been established and may need adjusting in order to achieve maximum effect, offering a potential avenue for further research.

We suggest further studies be undertaken to investigate the effects of RIPC. In order to definitively establish the effects of RIPC on clinical and biochemical outcomes, further large, double-blinded RCTs with longer follow-up periods are required. Outcome measures, including clinical outcome measures, might include: MACCE, cardiac index, ejection fraction, exercise tolerance, quality of life score, and mortality. In order to demonstrate clinical significance, large double-blind RCTs would be required. Given that the SYNTAX trial [Serruys 2009] quotes an MACCE rate of 12.4% at 12 months following CABG, a study including 4498 patients would be required to demonstrate a reduction in this rate by 25%, with a power of 0.8 and a P value of .05.

Obtaining reliable data might be complicated due to the lack of consensus on the ideal RIPC protocol. Adjustment to this may be necessary in order to achieve maximum effect, offering a potential avenue for further research.

Hopefully the forthcoming ERICCA trial [Hausenloy 2012], due to conclude in 2016, will be adequately powered to determine whether RIPC is of clinical benefit, at which point there may be more evidence to suggest long-term benefits of RIPC.

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