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# Remote ischemic preconditioning versus standard myocardial protection in cardiac surgery: ten years of clinical trials. A systematic review and meta-analysis

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## Summary

**Objectives:** To systematically review and assess the existing evidence for the applicability of remote ischemic preconditioning (rIPC) in cardiac surgery.

**Material and methods:** Major biomedical databases: Medline, Cochrane, etc. were searched. All randomized controlled trials (RCTs) comparing rIPC and standard myocardial protection in patients submitted to cardiac surgery were included if they reported at least one of the outcomes of interest: myocardial injury markers, postoperative inotropic support, or length of ICU stay.

**Results:** 991 patients were included in the analysis. rIPC was shown to reduce myocardial injury markers postoperatively by –0.63 SMD [–0.99 to –0.28] and postoperative inotropic requirement by –0.40 SMD [–0.66 to –0.16] in the adult patients submitted to cardiac surgery. There has been significant, yet correctable, heterogeneity of the primary outcome of interest, and the available RCTs were small sample studies.

**Conclusions:** This meta-analysis provides evidence confirming that rIPC has potential benefits with regard to myocardial protection.

**Key words:** meta-analysis, remote ischemic preconditioning, myocardial protection, cardiac surgery.

## Streszczenie

**Celem** niniejszej metaanalizy jest systematyczny przegląd dowodów obrazujących wpływ odległego hartowania niedokrwiennego (rIPC) na mięsień serca pacjentów poddanych operacjom kardiochirurgicznym.

**Materiały i metody:** Przeglądu literatury dokonano na podstawie pełnotekstowych prac publikowanych w bazach danych Medline, Cochrane itp. Włączono badania kontrolowane z randomizacją, porównujące rIPC oraz standardową ochronę mięśnia serca u pacjentów poddanych zabiegom kardiochirurgicznym, jeżeli raportowały co najmniej jeden z wyników: markery uszkodzenia mięśnia sercowego, pooperacyjne zapotrzebowanie na leki wykazujące dodatni efekt inotropowy, czas hospitalizacji na oddziale intensywnej terapii.

**Wyniki:** Do metaanalizy włączono 991 pacjentów. W porównywanych badaniach rIPC zmniejszało istotnie statystycznie ilość uwalnianych pooperacyjnie markerów martwicy mięśnia sercowego o –0,63 SMD [–0,99 do –0,28] oraz pooperacyjne zapotrzebowanie na leki inotropowe o –0,40 SMD [–0,66 do –0,16] w populacji osób dorosłych. Badanie było obarczone korygowalnym statystycznie współczynnikiem heterogeniczności. Publikowane dane przygotowano na podstawie badań pilotażowych.

**Wnioski:** Poniższa metaanaliza wczesnych dowodów klinicznych potwierdza istnienie potencjalnych korzyści ze stosowania rIPC w celu zmniejszenia okołooperacyjnego uszkodzenia mięśnia sercowego.

**Słowa kluczowe:** metaanaliza, odległe hartowanie niedokrwienne, kardioprotekcja, kardiochirurgia.

## Introduction

A significant amount of research has been performed to provide a closer look at the ischemia-reperfusion phenomenon and at interventions that could overcome the associated injury. There is no other way to salvage the ischemic myocardium than to restore and maintain blood flow to

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the hypoxic tissue [1]. This well-known therapeutic paradigm has unfortunately been associated with additional injury mediated by free radicals generated during the transition from anaerobic to aerobic metabolism upon the restoration of blood flow [2]. Several mechanisms (such as intracellular calcium oscillation, opening of mitochondrial transition pores, or simply oxidative stress) are thought to play a role in the additional necrosis or myocardial stunning associated with reperfusion. Not surprisingly, during the 1990s, much scientific effort was devoted to these physiological phenomena, giving rise to various therapeutic approaches [3]. Inducing non-lethal and brief ischemia before the period of prolonged ischemia has been considered as a tool for increasing the heart's resistance to ischemia-reperfusion (I/R) injury, as tested in pre-clinical studies and in human volunteers [4, 5]. Subsequently, preconditioning the heart with ischemia was shown to maintain its cardioprotective abilities even if the non-lethal ischemic stimulus was applied not directly to the targeted tissue, but to any distant site of the organism – hence the idea of remote ischemic preconditioning (rIPC) [6]. In cardiac surgery, where the timing of global ischemia and reperfusion periods is predictable, the application of rIPC seemed a perfect solution [7]. It has been ten years since the first application of rIPC in CABG patients, and, so far, approximately one thousand patients have been submitted to cardiac surgery with or without rIPC. Over the decade, leading cardiovascular researchers have gone from great excitation to dramatic disappointment with the clinical application of rIPC [8, 9]. The frustration could not be overcome by the recent meta-analyses and narrative reviews, due to their low quality or lack of objective quantitative measures of the effect, respectively [10-13]. This review and meta-analysis provides the most up-to-date and in-depth quantitative analysis of rIPC in adult and pediatric cardiac surgery.

This generic study and literature review was performed to critically appraise the evidence for the effect of rIPC on myocardial protection against I/R injury. This was achieved by means of a quantitative analysis comparing the release of postoperative myocardial injury markers in the patients who received the intervention and those who did not. Inotropic support requirement was analyzed, as it correlates with the extent of myocardial stunning following heart surgery, a core effect of I/R. ICU length of stay was also assessed. Heterogeneity assessment and sensitivity analysis were undertaken in the case of discrepancies between contrary results.

## Material and methods

### *Literature search*

Major contemporary biomedical databases were searched in order to make the review as comprehensive as possible. The databases included: Medline/PubMed (1950 – August 2011), Google Scholar (1992 – August 2011), Web of Knowledge (1945 – August 2011), CINAHL (1980 – August 2011), EMBASE (1980 – August 2011), Cochrane Library/ Central Register of Controlled Trials (CENTRAL). The primary search employed the following key terms: "remote ischemic preconditioning" and/or "remote ischemic pre conditioning" and/or "remote ischemia" and "cardiac surgery". The 'related articles' function was used in order to ensure the broadest possible data retrieval. All relevant medical literature, regardless of the language of reporting and type of publication, were retrieved by the aforementioned search. Titles and abstracts of these publications were checked against predefined criteria for eligibility. These were as follows: (1) RCT design, (2) trials comparing rIPC versus controls (placebo with standard myocardial protection), (3) trials reporting at least one outcome of interest, (4) trials not duplicating results obtained from one study group, (5) trials published in peer-reviewed journals. These criteria excluded 'grey literature' and papers that duplicated findings derived from one study group; when the latter was the issue, the most representative report was included for further assessment. The search strategy is presented in Fig. 1.

### *Data extraction*

A pre-designed form was used in order to provide the medium for data extraction. Two independent searches and data extractions were made by two different authors: JM and TP. There was unequivocal agreement between

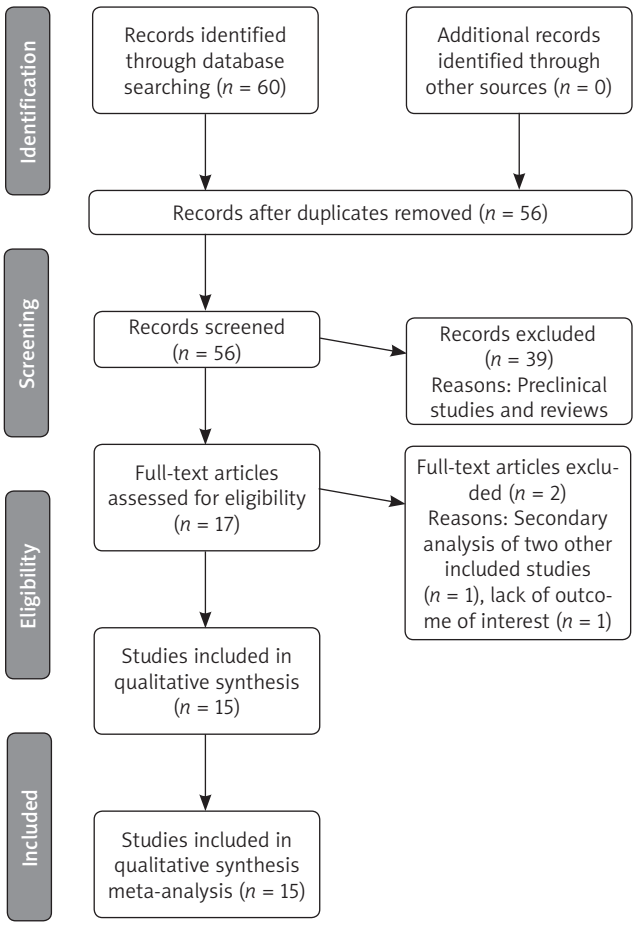


**Fig. 1.** PRISMA flow diagram

the authors as to which papers should be included, given the proposed criteria. Both authors used the same form to assess the three major points of systematic review: eligibility criteria, outcomes of interest, and the risk of bias associated with individual papers using the Cochrane Collaboration criteria and the Jadad score [14]. Any disagreement during the process was resolved by consensus. If data were missing from a report, the following algorithm was applied: the authors of the report were contacted and requested to provide the missing data. If that did not suffice, the missing data were assessed and, if feasible, computed from other data available in the paper (missing variance or inappropriate variance format). Only one case required the application of this second step: the missing variance value was replaced by the result of variance calculation using the algorithm for interquartile range assessment of variance [15].

### *Definitions of outcomes of interest*

Our study had one primary and two secondary outcomes of interest. The primary outcome was the release of myocardial injury markers following a cardiac procedure, while the secondary outcomes were inotropic support requirement and ICU length of stay. The data were insufficient to construct an analysis based on hard clinical endpoints, such as peri-procedural myocardial infarction (PMI) or in-hospital mortality; therefore, the review was based on surrogate outcomes.

### *Statistical analysis*

The report was written in accordance with the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and the Cochrane Collaboration recommendations [16, 17]. The meta-analysis was performed using Cochrane Collaboration Software – Review Manager [18]. The magnitude and the direction of effects computed from continuous data were presented as the standardized mean difference (SMD). When the outcome was reported consistently on the same scale, the result was presented as mean difference (MD). All outcomes are presented with appropriate 95% confidence intervals. Statistical significance was assumed at $p < 0.05$.

**Tab. I.** Methodological quality assessment (Jadad score)

| |
|---|
| **Generation of allocation sequence:**<br>2: computer-generated random numbers<br>1: not described |
| **Allocation concealment:**<br>3: central randomization<br>2: sealed envelopes or similar<br>1: not described or inadequate |
| **Investigator blindness:**<br>2: identical placebo tablets or similar<br>1: inadequate or not described<br>0: no double-blinding |
| **Description of withdrawals and drop-outs:**<br>1: numbers and reasons are described<br>0: numbers and reasons are not described |
| **Efficacy of randomization:**<br>2: pretreatment variables in tabular form<br>1: balance of pretreatment variables mentioned but not in tabular form<br>0: no information reported |

### *Assessment of data validity and heterogeneity*

Validity, heterogeneity, and the risk of bias were approached in both a graphical and a quantitative manner. A random effect model was preferred when significant heterogeneity was the issue, as it allows for a larger margin of variance between individual studies. A fixed effect model was applied when heterogeneity was low ($I^2 < 25\%$). Heterogeneity was assessed with standard $\chi^2$ calculation and the $I^2$ statistic. The $I^2$ statistic allows for the assessment of the observed variation between studies, which can be assigned as having a low (< 25%), moderate (25-75%), or high (> 75%) degree of heterogeneity [19].

The estimation of publication bias and the risk of bias was conducted in compliance with the Cochrane Collaboration guidelines [17]. Publication bias was evaluated by funnel plot asymmetry assessment. Studies lying outside of the 95% CI were considered causative of asymmetry. The risk of bias was assessed in a standard Cochrane manner with regard to six domains representing different items which might be responsible for systematic deviation from true results, i.e. selection, performance, detection, attrition, reporting, and other bias. Additionally, the Jadad score was calculated for every paper to provide more data concerning the risk of bias associated with individual papers (Table I). Sensitivity analysis was conducted in order to compare the fixed effect and random effect models. Both models were applied in order to assess the differences in their possible impact on the meta-analytical results. Subgroup analysis was managed by analyzing adult CABG trials, adult valve trials, and pediatric cardiac trials separately. Individual analysis was also performed on studies of high or low risk of bias, studies using different sites of RIPC application (lower or upper extremity), and studies including both diabetic and non-diabetic patients.

## Results

### *Literature search and study characteristics*

Using the reported search, sixty papers were found, of which fifteen were in agreement with the inclusion criteria. References of these articles were cross-searched to reveal any documents missing from the review. Finally, fifteen papers were found to present the best available evidence. These studies pertained to: adult coronary bypass grafting surgery with or without AVR [9, 12-27], adult valvular surgery [28-30], and pediatric cardiac surgery [31-33]. All the available papers were designed as prospective randomized controlled trials. The characteristics and outcomes of the investigated studies are presented in Table II and Table III.

The meta-analysis involved a total of 991 patients, with 491 receiving rIPC and 500 in the control group. The mean

**Tab. II.** Characteristics of investigated trials

| Study/year | Participants RIPC/Controls | Gender-male RIPC/Controls | Age RIPC/Controls | Type of surgical procedure | Means of reporting outcomes | RIPC protocol Ischemia/Reperfusion (min) |
|---|---|---|---|---|---|---|
| Cheung, 2006 [31] | 17/20 | – | 0.9 (±0.9)/2.2 (±3.4), years (±SD) | VSD mainly ASD and TGA or ToF | Troponin I | 5/5 min, 4 cycles (lower extremity) |
| Zhou, 2010 [32] | 30/30 | 16/18 | 160.83 (±58.39)/154.13 (±55.82), days (±SD) | VSD closure (elective) | Troponin I, CK MB and LDH | 5/5 min, 2 cycles (upper extremity) |
| Wagner, 2010 [22] | 32/34 | 24/23 | 67 years/71 years | CABG ± AVR (elective) | Troponin I $C_{max}$ within 24 hours | 5/5 min, 3 cycles (upper extremity) |
| Choi, 2011 [29] | 38/38 | 15/15 | 57 (±12)/60 (±13), years (±SD) | AVR/MVR/DVR and Bentall procedures ± CABG | CK-MB at $12^{th}$ and $24^{th}$ hour | 10/10 min, 3 cycles (lower extremity) |
| Li, 2010 [28] | 26/27 | 9/13 | 45.8 (±11.2)/42.3 (±10.6), years (±SD) | AVR/MVR and DVR (elective) | Troponin I AUC over 72 hours | 5/5 min, 3 cycles (lower extremity) |
| Hausenloy, 2007 [9] | 27/30 | 21/24 | 67 (±11.8)/67 (±9.4), years (±SD) | CABG (elective) | Troponin T AUC over 72 hours | 5/5 min, 3 cycles (upper extremity) |
| Rahman, 2010 [19] | 80/82 | 72/71 | 65 years/63 years | CABG (urgent and elective) | Troponin T AUC over 48 hours | 5/5 min, 3 cycles (upper extremity) |
| Ali, 2010 [21] | 50/50 | 47/42 | 56.0 (±8.2)/51.6 (±9.6), years (±SD) | CABG (elective) ± CEA | CK-MB $C_{max}$ within 48 hours | 5/5 min, 3 cycles (upper extremity) |
| Thielmann, 2010 [25] | 27/26 | 23/22 | 64.1/63.4 years | CABG (elective) | Troponin I $C_{max}$ within 24 hours | 5/5 min, 3 cycles (upper extremity) |
| Venugopal, 2009 [24] | 23/22 | 19/19 | 62 (±9.7)/64 (±9.0), years (±SD) | CABG ± AVR (elective) | Troponin I AUC over 72 hours | 5/5 min, 3 cycles (upper extremity) |
| Gunaydin, 2000 [26] | 4/4 | 4/4 | 62.2 (±6.2)/60 (±10.7), years (±SD) | CABG (elective) | CK-MB, LDH and CPK | 3/2 min, 2 cycles (upper extremity) |
| Wu, 2011 [27] | 25/25 | 9/7 | 44.9 (±14.4)/43.6 (±14.3), years (±SD) | MVR (elective) | Troponin I $C_{max}$ within 72 hours | 5/5 min, 3 cycles (upper extremity) and 10/10 min, 2 cycles (lower extremity) |
| Hong, 2010 [20] | 65/65 | 46/44 | 65.7 (±7.5)/65.1 (±9.0), years (±SD) | OPCABG (elective) | Troponin I AUC after 72 hours | 5/5 min, 4 cycles (upper extremity) |
| Luo, 2011 [30] | 20/20 | 13/8 | 2.8 (±1.0)/2.7 (±0.9), years (±SD) | VSD closure (elective) | Troponin I, CK-MB | 5/5 min, 3 cycles (lower extremity) |
| Karuppasamy, 2011 [23] | 27/27 | 22/23 | 66.9 (±11.2)/67.3 (±10.3), years (±SD) | CABG ± AVR (elective) | Troponin I AUC after 48 hours | 5/5 min, 3 cycles (upper extremity) |

*CEA – carotid endarterectomy, AUC – area under the curve, RIPC – remote ischemic preconditioning, AVR – aortic valve replacement, MVR – mitral valve replacement, DVR – double valve replacement, ASD – atrial septal defect, VSD – ventricular septal defect, TGA – transposition of great vessels, ToF – tetralogy of Fallot, CK-MB – creatine kinase-myocardial band, CPK – creatine phosphokinase, LDH – lactate dehydrogenase*

age of patients ranged from 160.83 (±58.39) days to 67 (±12) years in the rIPC group and from 154 (±56) days to 67 (±9) years among the controls. Male gender proportion ranged from 35% to 100% in the rIPC group and from 28% to 100% among the controls. The majority of patients were operated on due to coronary artery disease (335 in the rIPC group and 340 in the control group) [9, 20-27]. The analysis of rIPC in pediatric patients undergoing cardiac surgery included 67 patients in the rIPC study groups and 70 in the control groups [31-33], whereas 89 and 90 patients were submitted to isolated valvular surgery with or without rIPC, respectively [28-30]. All studies were proof-of-concept trials with small sample sizes, and only three included more than 100 patients [20-22]. Diabetic subjects were partially included in six trials [9, 21-24, 30]. Time from rIPC to global ischemia (e.g. cross-clamping of the aorta) was clearly stated in ten trials and equivocally in five. Two trials used the 'second window' of protection

**Table III.** Characteristics of investigated trials

| Study/year/type | Exclusion/inclusion criteria | Cross-clamp time (min) | Time from RIPC to reperfusion | Preoperative LVEF (%) RIPC/Controls | Myocardial protection | Jadad Score – (max. 10 pts) |
|---|---|---|---|---|---|---|
| Cheung, 2006<br>PRCT<br>Single-blinded [31] | **Excluded:** isolated ASD, Fontan completion, ToF, chromosomal defect, airway and parenchymal lung disease, immunodeficiency and "blood disorders" | 55 (13)/59 (13) | Time from RIPC to bypass: '5-10 minutes'. | – | Blood cardioplegia | 4 points |
| Zhou, 2010<br>PRCT<br>Single-blinded [32] | **Included:** patients with pulmonary hypertension, VSD, weight < 7 kg; **Excluded:** heart failure, pneumonia, history of other systemic diseases, limb trauma, or acidosis | 24.13 (9.83)/24.17 (8.21) | Repeated twice: 24 hours and 1 hour prior to surgery | 65.27 (5.85)/64.80 (6.21) | Cardioplegic arrest | 3 points |
| Wagner, 2010<br>PRCT<br>Single-blinded [22] | **Excluded:** age > 80 years, UA, LVEF < 30%, CRF sCr > 220 mmol/l, bilirubin > 30 mmol/l, pulmonary disease, recent systemic infection | 45/51 | 18(2) hours prior to surgery | < 50% - 20/21 patients | Cold crystalloid cardioplegia (St. Thomas solution) | 7 points |
| Choi, 2011<br>PRCT<br>Single-blinded [29] | **Excluded:** age > 80 years, LM (LCA) stenosis > 50%, hepatic or pulmonary disease, active infective endocarditis, LVEF < 30%, AMI within 3 weeks, sCr > 1.4 (female) or 1.6 (male) mg/dl, PDA | 98 (27)/108 (29) | At least 10 minutes | 63 (9)/60 (12) | Blood cardioplegia | 6 points |
| Li, 2010<br>PRCT<br>Single-blinded [28] | **Excluded:** age > 65 years, non-rheumatic heart valve disease, infective endocarditis, previous cardiac surgery, diabetes mellitus, CAD, PDA, arterial hypertension, ASA, ACE inhibitors or corticosteroids or statins | 47.3 (17.9)/47.4 (17.3) | After the induction of anesthesia | < 55% – 7/6 | Cold blood cardioplegia | 5 points |
| Hausenloy, 2007<br>PRCT<br>Single-blinded [9] | **Excluded:** age > 80 years, UA, LM (LCA) stenosis, hepatic, renal, pulmonary disease, PDA of upper limbs or on oral hypoglycemics | 36 (17)/45 (22) | Not more than 45 minutes before aortic cross-clamping | < 55% – 5/10 | Cardioplegic arrest and intermittent cross-clamp fibrillation | 7 points |
| Rahman, 2010<br>PRCT<br>Double-blinded [19] | **Included:** elective and urgent patients; **Excluded:** UA within 48 hours, AMI within 30 days, pregnancy, DM, dialysis, other than CABG, radial artery usage | 76 (21)/71 (18) | 74 (16) min | 58.5 (13.3)/61.6 (13.4) | Intermittent cold blood cardioplegia | 9 points |
| Ali, 2010<br>PRCT<br>Single-blinded [21] | **Excluded:** significant renal and hepatic disease, hemodynamic instability, UA, AMI within 4 weeks or ongoing | 33.4 (10.6)/33.7 (8.5) | Before placing the patient on bypass | < 55% – 46%/27% | Warm blood cardioplegia | 5 points |
| Thielmann, 2010<br>PRCT<br>Single-blinded [25] | **Excluded:** DM, renal failure, PDA of upper extremities, hemodynamic instability, AMI within the previous 2 weeks, emergency, combined or redo surgery | 54 (14)/53 (11) | 54 (14) min | < 55% – 19%/23% | Cold crystalloid cardioplegia | 6 points |
| Venugopal, 2009<br>PRCT<br>Single-blinded [24] | **Excluded:** age > 80 years, UA, DM, hepatic, renal or pulmonary disease, PDA of upper limbs | 53 (14)/65 (30) | 60 minutes before aortic cross-clamping | < 55% – 3%/1% | Cold blood cardioplegia | 7 points |

**Table III.** Cont.

| Study/year/type | Exclusion/inclusion criteria | Cross-clamp time (min) | Time from RIPC to reperfusion | Preoperative LVEF (%) RIPC/Controls | Myocardial protection | Jadad Score – (max. 10 pts) |
|---|---|---|---|---|---|---|
| Gunaydin, 2000<br>PRCT<br>Single-blinded [26] | **Excluded:** UA, DM, LV aneurysm, LVEF < 40% | 37.8 (27.0)/28.5 (11.4) | 2 minutes before aortic cross-clamping | Not lower than 40% | Blood cardioplegia | 3 points |
| Wu, 2011<br>PRCT<br>Single-blinded [27] | **Excluded:** concomitant heart abnormalities, NYHA 4, history of respiratory infection, asthma or previous cardiac surgery, hepatic, renal, pulmonary disease. PDA and usage of oral hypoglycemics | 63.5 (19.8)/51.7 (7.4) | After the induction of anesthesia | 61.1 (8.0)/63.4 (7.0) | Cold blood cardioplegia | 5 points |
| Hong, 2010<br>PRCT<br>Double-blinded [20] | **Excluded:** age > 80 years, UA, heart failure requiring mechanical or inotropic support, combined surgery, sever renal, liver or pulmonary disease, LVEF < 30%, AMI or sepsis/infection within 7 days, Nicorandil usage, PDA, or amputation | - | 19.2 (10.8) min | 56.6 (10)/53.5 (12.2) | Intra-coronary shunt | 10 points |
| Luo, 2011<br>PRCT<br>Single-blinded [30] | **Included:** elective surgery, aged 1 to 5 years old; **Excluded:** concomitant surgery, infective endocarditis, preoperative medications usage, hepatic or renal malfunctioning | 36.1 (15.8)/32.7 (12.4) | Immediately after the induction of anesthesia | – | Cold blood cardioplegia | 4 points |
| Karuppasamy, 2011<br>Single-blinded [23] | **Excluded:** age > 85 years, UA, hepatic, pulmonary, renal disease, PDA affecting upper limbs, receiving oral hypoglycemics | 43.4 (15.2)/56.6 (27.1) | After the induction of anesthesia | 54.0 (12.1)/54.4 (1.5) | Intermittent aortic cross-clamping and intermittent cold blood cardioplegia | 7 points |

*CEA – carotid endarterectomy, AUC – area under the curve, RIPC – remote ischemic preconditioning, AVR – aortic valve replacement, MVR – mitral valve replacement, DVR – double valve replacement, VSD – ventricular septal defect, PAD – peripheral artery disease, DM – diabetes mellitus, PRCT – prospective randomized clinical trial, AMI – acute myocardial infarction, UA – unstable angina, LVEF – left ventricular ejection fraction, NYHA – New York Health Association, sCr – serum creatinine, LM – main stem of left coronary artery*

(rIPC performed > 24 hours before the ischemic insult), whereas the rest used the 'immediate window' of protection (around 60 minutes from the insult).

### Meta-analysis of RCTs according to outcomes of interest

#### *Postoperative release of myocardial injury markers*

Our analysis found that rIPC was associated with the reduction of myocardial injury markers by –0.63 SMD (–0.63, 95% CI: –0.99 to –0.28; $p < 0.0005$) in the adult patients and by –1.19 SMD (–1.19, 95% CI: –1.56 to –0.82; $p < 0.00001$) in the pediatric population. The degree of heterogeneity was exceptionally high ($I^2 = 83\%$) for the adult group and extremely low for the pediatric population ($I^2 = 0\%$). The analysis included 424 adult and 67 pediatric patients in the rIPC group. This model was assessed for the whole population of adult cardiac surgery patients, including coronary and valvular disease. Separate analysis was performed for pediatric cardiac procedures (Fig. 2). The analysis of bias was performed by means of funnel plot asymmetry assessment, as presented in Fig. 3.

#### *Perioperative inotropic support requirement*

Adult patients receiving rIPC benefited from lower inotropic support requirement following cardiac surgery, as shown by the negative SMD (–0.40, 95% CI: –0.66 to –0.14; $p < 0.002$). This effect was even more pronounced in children undergoing heart surgery and rIPC (–0.83, 95% CI: –1.18 to –0.48; $p < 0.00001$). This analysis included 116 adult and 67 pediatric patients in the rIPC group with the exceptionally low heterogeneity of 0% (Fig. 4).

#### *Postoperative ICU stay*

No benefit was found for either adult or pediatric patients receiving rIPC with regard to ICU length of stay. This

| Study or Subgroup | RIPC Mean | RIPC SD | RIPC Total | Control Mean | Control SD | Control Total | Weight | Std. Mean Difference IV, Random, 96% CI |
|---|---|---|---|---|---|---|---|---|
| **1.1.1 Adult Cardiac Surgery** | | | | | | | | |
| Gunaydin 2000 | 310 | 100 | 4 | 520 | 100 | 4 | 2.3% | –1.83 (–3.70, 0.04) |
| Wu 2011 | 3.424 | 0.839 | 25 | 9.723 | 1.248 | 25 | 5.6% | –.035 (–3.89, –2.22) |
| Venugopal 2009 | 18.16 | 6.67 | 23 | 31.53 | 24.4 | 22 | 6.7% | –0.75 (–1.36, –0.15) |
| Thielmann 2010 | 259 | 176 | 27 | 477 | 388 | 26 | 6.9% | –0.72 (–1.27, –0.16) |
| Li 2010 | 10.05 | 4.4 | 26 | 11.67 | 4.48 | 27 | 7.0% | –0.36 (–0.90, 0.18) |
| Hausenloy 2007 | 20.58 | 9.58 | 27 | 36.12 | 26.08 | 30 | 7.0% | –0.76 (–1.30, –0.22) |
| Karuppasamy 2011 | 189.4 | 183.6 | 27 | 183 | 155.2 | 27 | 7.0% | 0.04 (–0.50, 0.57) |
| Wagner 2010 | 2.47 | 0.85 | 32 | 3.4 | 1.59 | 34 | 7.2% | –0.71 (–1.21, –0.22) |
| Choi 2011 | 23.4 | 9.1 | 38 | 32 | 19.1 | 38 | 7.4% | –0.57 (–1.03, –0.11) |
| Ali 2010 | 33.3 | 9.45 | 50 | 37.2 | 7.07 | 50 | 7.7% | –0.46 (–0.86, –0.07) |
| Hong 2010 | 53.2 | 72.9 | 65 | 67.4 | 97.7 | 65 | 7.9% | –0.16 (–0.51, 0.18) |
| Rahman 2010 | 30.1 | 11.78 | 80 | 27.7 | 14.89 | 82 | 8.0% | 0.18 (–0.13, 0.49) |
| **Subtotal (95% CI)** | | | **424** | | | **430** | **80.7%** | **–0.63 (–0.99, –0.28)** |
| Heterogeneity: Tau$^2$ = 0.31; $\chi^2$ = 65.40, df = 11 ($P$ < 0.00001); I$^2$ = 83% | | | | | | | | |
| Test for overall effect: $Z$ = 3.48 ($P$ = 0.0005) | | | | | | | | |
| **1.1.2 Paediatric Cardiac Surgery** | | | | | | | | |
| Cheung 2006 | 16.7 | 3.3 | 17 | 21.6 | 4.1 | 20 | 6.1% | –1.28 (–1.99, –0.56) |
| Luo 2011 | 0.26 | 0.09 | 20 | 0.49 | 0.19 | 20 | 6.2% | –1.52 (–2.23, –0.80) |
| Zhou 2010 | 2.1 | 0.32 | 30 | 2.41 | 0.32 | 30 | 7.0% | –0.96 (–1.49, –0.42) |
| **Subtotal (95% CI)** | | | **67** | | | **70** | **19.3%** | **–1.19 (–1.56, –0.82)** |
| Heterogeneity: Tau$^2$ = 0.00; $\chi^2$ = 1.59, df = 2 ($P$ = 0.45); I$^2$ = 0% | | | | | | | | |
| Test for overall effect: $Z$ = 6.35 ($P$ < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **491** | | | **500** | **100.0%** | **–0.75 (–1.09, –0.42)** |
| Heterogeneity: Tau$^2$ = 0.33; $\chi^2$ = 82.38, df = 14 ($P$ < 0.00001); I$^2$ = 83% | | | | | | | | |
| Test for overall effect: $Z$ = 4.47 ($P$ < 0.00001) | | | | | | | | |
| Test for subgroup differences: $\chi^2$ = 4.50, df = 1 ($P$ = 0.03); I$^2$ = 77.8% | | | | | | | | |

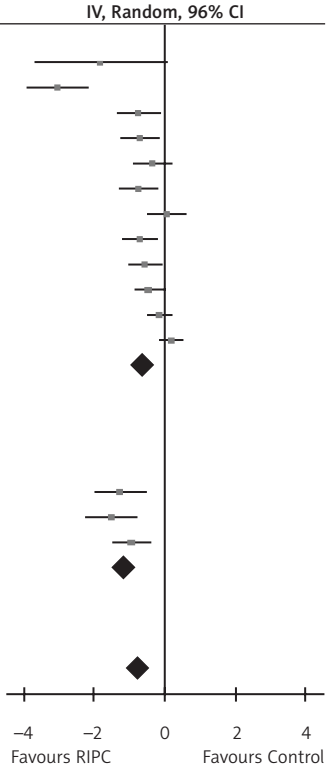


**Fig. 2.** Myocardial injury markers

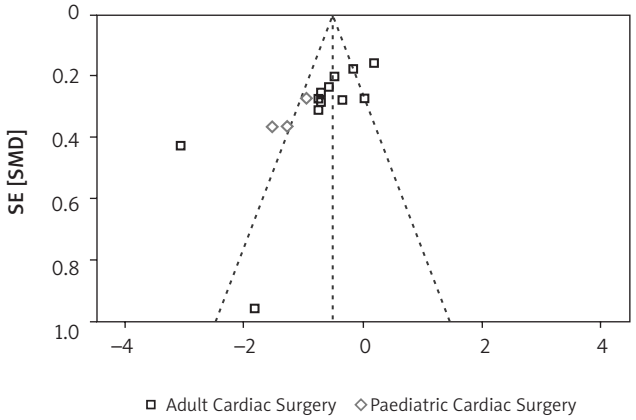


**Fig. 3.** Funnel plot – studies included in myocardial injury markers analysis

end-point was burdened with moderate heterogeneity (I$^2$ = 40%). The MD in the adults (–0.63 hour 95% CI: –4.60 to 3.34; $p$ = 0.76) and in the pediatric group (–0.59 hour 95% CI: –7.29 to 6.10; $p$ = 0.86) did not favor rIPC (Fig. 5).

### *Bias and heterogeneity assessment*

#### *Degree of bias*

All studies which were found eligible for the review were in fact of prospective randomized design, which is known to provide the most trustworthy evidence. Among these studies, we found discrepancies in the quality of reporting and methodological design. Firstly, all studies but two were single-blind, as it was extremely difficult to provide satisfactory logistics for a double-blind study with rIPC. Only Rahman *et al.* and Hong *et al.* managed to provide such an environment for their true double-blind studies. Secondly, this meta-analysis gathered its evidence from proof-of-concept trials, which are, by definition, limited in terms of the number of participants. Funnel plot analysis was employed to find evidence of asymmetry, and four studies were indeed found to lie outside the 95% confidence interval, with one additional study located on its border [20, 21, 24, 28, 31] (Fig. 3). The risk of bias is presented as percentages across all studies in Fig. 6, whereas individual domain-based assessment is provided in Fig. 7. Jadad score calculation stratified the studies into two groups with high and low risk of bias, with a clear cut-off point of 5 points and above for low risk studies. Table I provides data on individual Jadad scoring.

#### *Sensitivity analysis*

The application of a fixed effect model did not change the results significantly, but the effect of rIPC on the lowering of postoperative myocardial necrosis markers appeared smaller in the adult group (SMD –0.40; 95% CI: –0.54 to –0.27; $p$ = 0.00001). Subgroup analysis of the studies reporting outcomes of CABG with or without AVR showed results consistent with the general trend (SMD –0.42; 95% CI: –0.70 to –0.13, $p$ = 0.005) and I$^2$ = 67% [9, 20-27]. Studies concerning isolated valvular surgery did not confirm the protective result of rIPC; however, heterogeneity (I$^2$ = 94%) was essentially influencing the outcome effect under the random

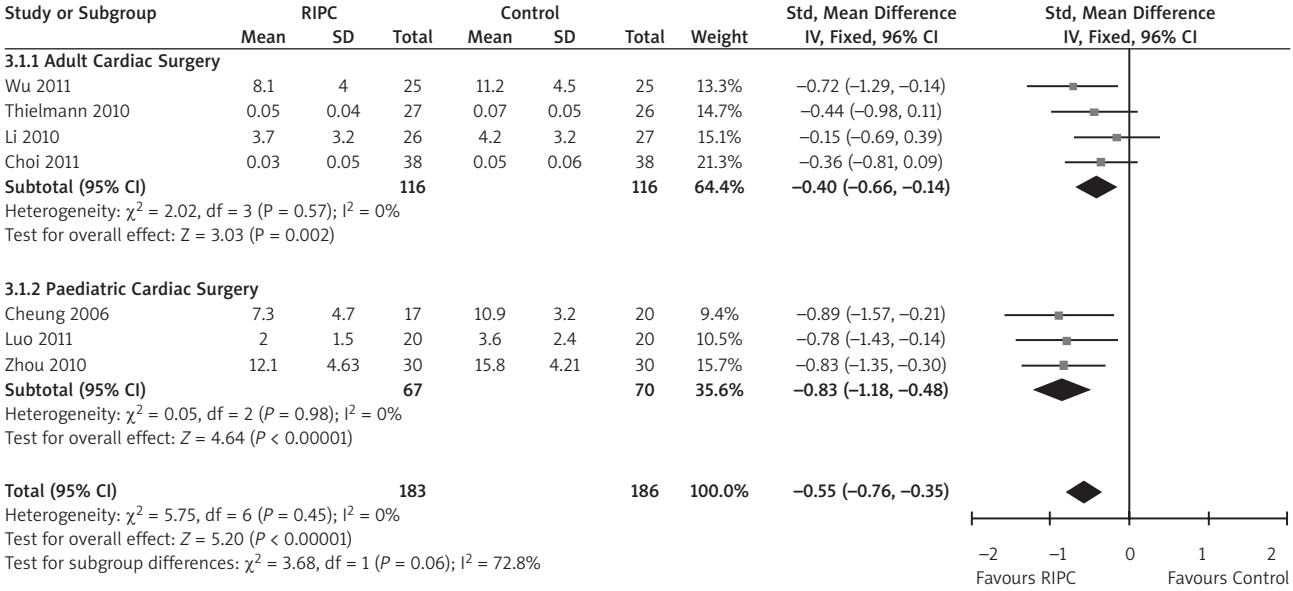


**Fig. 4.** Inotropic support requirements

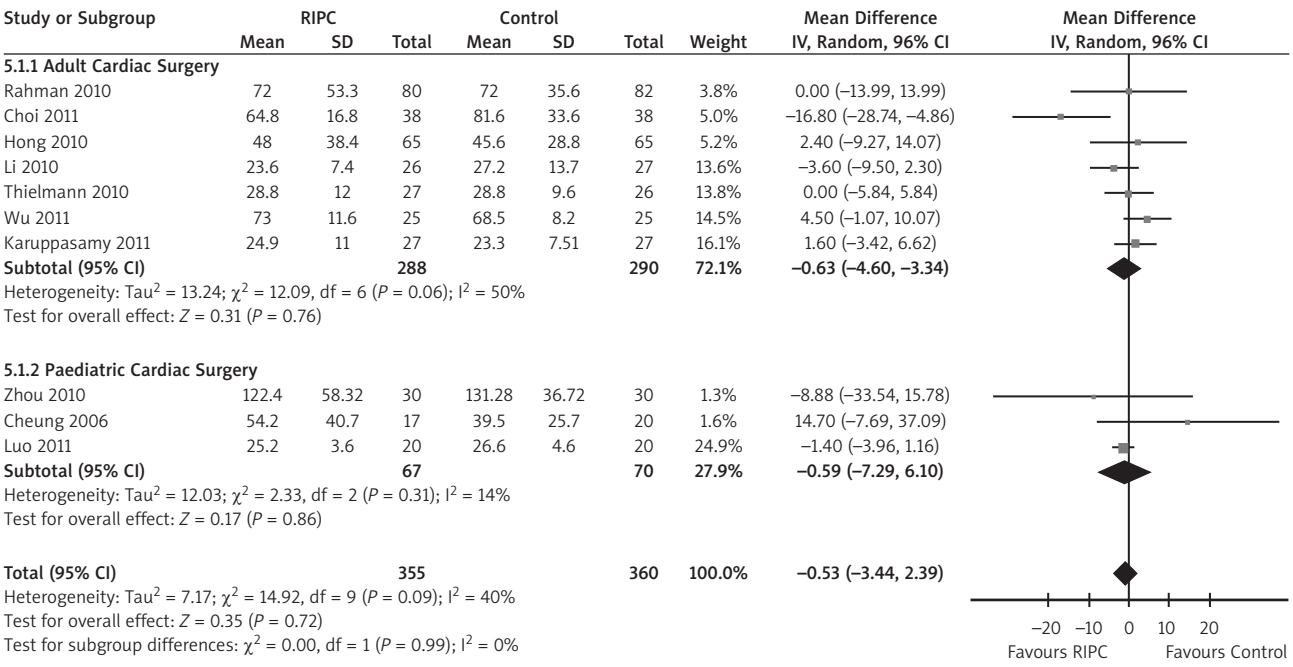


**Fig. 5.** Length of ICU stay in the postoperative period

model (SMD –1.28; 95% CI: –2.63 to 0.07; $p = 0.06$), and it changed when a fixed model was used (SMD –0.87; 95% CI: –1.19 to –0.54; $p < 0.00001$) [28-30]. Relevant outcomes associated with rIPC were found in patients undergoing pediatric cardiac surgery without heterogeneity ($I^2 = 0\%$) (SMD –1.19; 95% CI: –1.56 to –0.82; $p = 0.00001$) [30-32]. When the rIPC protocol was performed in the anatomic region of the lower extremities, the result was significant (SMD –1.31; 95% CI: 2.14 to 0.48; $p = 0.002$) with peaked heterogeneity ($I^2 = 88\%$). When rIPC was applied to an upper extremity, the effect appeared smaller, but still significant (SMD –0.54; 95% CI: –0.84 to –0.23; $p = 0.0006$), and $I^2$ was 71%. In order to correct for the high heterogeneity in the whole population, we restricted the analysis to studies lying inside the 95% CI on the funnel plot, excluding five studies [20, 21, 24, 28, 31]. This correction changed the heterogeneity from 83% to 0% and the effect was still highly significant (SMD –0.69; 95% CI: –0.86 to –0.51; $p = 0.00001$). With regard to studies scoring > 5 points on the Jadad scale, the meta-analysis showed a significant reduction of necrosis markers, although the effect was smaller than the effect for the whole population (SMD –0.40; 95% CI: –0.69 to –0.11; $p = 0.005$) [9, 20, 21, 23-26, 30]. We analyzed the effect of rIPC on diabetic patients separately, and compared it with trials in which

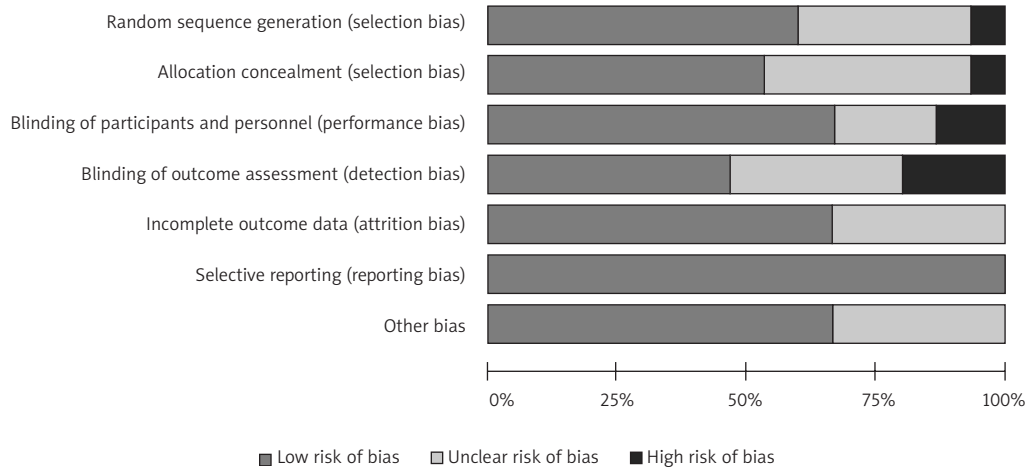


**Fig. 6.** Risk of bias assessment. Six domains used for the individual judging

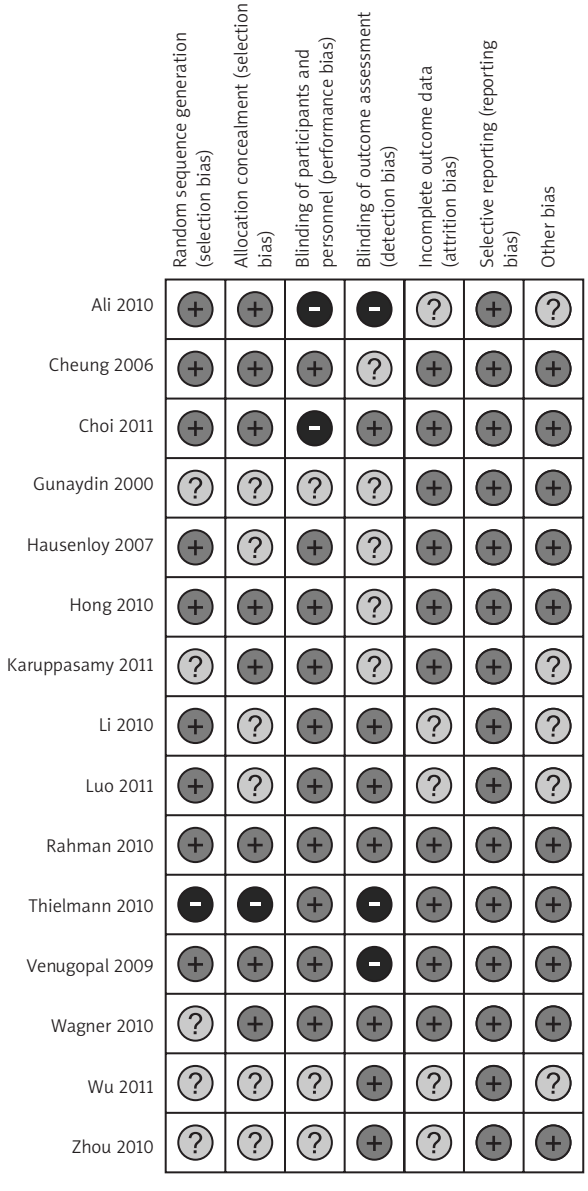


**Fig. 7.** Risk of bias assessment. Individual domain-based analysis

non-diabetic patients were enrolled. For diabetic patients there was a significant, though modest, reduction of myocardial necrosis markers, whereas for non-diabetic patients this effect was large and significant (diabetic: SMD –0.42; 95% CI: –0.66 to –0.19; $p$ = 0.0005 and $I^2$ = 40%; non-diabetic: SMD –1.06; 95% CI: –1.66 to –0.45; $p$ = 0.0006 and $I^2$ = 89%) [9, 21-24, 30].

## Discussion

The results of the analysis appear to suggest that remote ischemic preconditioning is indeed associated with the reduction of the postoperative biomarkers of myocardial injury (Fig. 2). The included evidence is recent and well-designed, yet the number of participants in all the studies and their proof-of-concept character might limit their usability as final evidence. Our analysis suggests several clear-cut points. The impact of rIPC on ischemia-reperfusion injury is detectable clinically, and in some studies its magnitude is very high [9]. Not only is direct myocardial necrosis limited, but so is myocardial stunning, as can be assessed by the lower requirement of inotropic support in patients submitted to the intervention. Sensitivity analysis provided new insights which cannot be gained in the big picture. The more pronounced effect of rIPC in pediatric cardiac surgery might be associated with the lack of coronary disease, young age, or specific features of congenital lesions. We could not venture any conclusions concerning the insignificant effect of rIPC in valve surgery, as the heterogeneity was abnormally high and could not be corrected. After a recent study by Wu *et al*., we hypothesized that technical nuances, such as the anatomic region in which the rIPC protocol is being executed, might play a role in shaping the magnitude of the final effect [28]. To our surprise, when applied in the leg, rIPC was associated with an almost three times greater effect in terms of reducing myocardial injury. Last, but not least, we noted a severe reduction in the cardioprotective benefit of rIPC in the population of patients suffering from diabetes mellitus.

According to our review, four studies included in the analysis reported no benefit from rIPC in the setting of cardiac surgery [20, 21, 24, 29]. In all studies but one, the upper extremity was used for the provision of the remote ischemic stimulus. Two of the four studies used pulse oximeters to ascertain that no collateral flow was present during the execution of the protocol. Hong *et al*. and Karuppasamy *et al*. enrolled diabetic patients. Additionally, Rahaman *et al*. executed the rIPC protocol with the longest time period from rIPC to ischemic insult, 74 (±16) minutes, while Hong *et al*. managed to provide the whole protocol in just 19 (±11) minutes prior to the insult; neither of them managed to find rIPC of cardioprotective value. Hong *et al*. hypothesized that in off-pump CABG, with intracoronary shunt deployment, there is too little damage to the myocardium due to ischemia and reperfusion; therefore, even if statistically insignificant, the reduction of 26% of cTnI AUC over 72 hours was indeed clinically relevant in this individual case. It still remains unknown whether these factors played any role in the negative results in the aforementioned studies.

The effect of rIPC was found to be the most pronounced among pediatric patients operated on due to congenital cardiac anomalies (mainly VSDs). Nevertheless, the effect seemed proportionally small. This can be explained by the generally low-risk population included in proof-of-concept trials. Only Rahman *et al*. enrolled emergency CABG patients, who are, by definition, not the most suitable subjects for studying the effect of any intervention. As observed by Peters, the studies comparing the effects of rIPC in fact include very complex populations, bearing a myriad of confounding morbidities [34]. Therefore, we would like to propose a standardization of subjects that might bear more resemblance to the 'real-life' population and in whom the benefit of rIPC would be the most visible. We postulate that the most suitable population for future research would be a high-risk population of patients submitted to non-emergency on-pump CABG with the use of intermittent cold blood cardioplegia, aged fifty years and older, especially if the patients are burdened with one or more of the following risk factors: female gender, history of previous myocardial infarction (more than seven days but less than two years before surgery), LVEF lower than 30%, previous ischemic stroke, transient ischemic attack, or diabetes mellitus. In such a population, relevant end-points of all-cause mortality, perioperative cerebrovascular accident (CVA), PMI, or the need for mechanical support would be easy to assess, and the question whether rIPC is genuinely efficacious in heart protection could be answered. Additionally, we do not recommend using volatile anesthetics, as these might reduce the overall benefit of rIPC by mechanisms that are not entirely recognized [34]. We encourage the use of the lower extremities for the provision of the rIPC stimulus, as this has shown a greater magnitude of protective effect in several of the aforementioned studies [21].

### *Comparison of our study with other meta-analyses*

Takagi *et al*. authored the first meta-analysis rendering comparable results, yet he only assessed myocardial necrosis markers and combined outcomes from cardiac and vascular surgery, with a modest number of patients submitted to rIPC [12, 13, 35]. We believe that the sensitivity analysis and nearly one thousand patients included in our analysis, along with an additional risk of bias assessment, makes this document the primary source of evidence for the usefulness of rIPC in cardiac surgery.

### *Study strengths and limitations*

There is a tendency among small studies to render a large treatment effect associated with the studied intervention; we could not overcome this problem, because large clinical studies have not come into existence so far. Moreover, we understand the limitation of meta-analytical approaches in combining only published data, which, inevitably, introduces bias in contemporary reviews. High heterogeneity and the mixed population enrolled were overcome by using a random effect model, subgroup analysis, and scrutiny of symmetry in the analysis of the funnel plot. We could not provide more clinically relevant outcomes, such as perioperative myocardial infarction, in-hospital mortality, and long-term mortality, as these are still unavailable. Instead, we used surrogate outcomes, such as myocardial necrosis markers release in lieu of perioperative myocardial necrosis and inotropic support requirement in lieu of low-output syndrome due to myocardial stunning, as these outcomes are associated with long-term prognosis for patients submitted to cardiac surgery [36].

### *Future research*

Multicenter studies enrolling 'real-life' populations in a prospective, randomized manner are currently taking place. These studies will assess clinically relevant endpoints such as PMIs and in-hospital mortality. The long-term effects of rIPC in cardiac surgery should be studied thereafter.

## Conclusions

This meta-analysis provides evidence that rIPC should be considered as a tool for providing myocardial protection in cardiac surgery patients, with all limitations characteristic of proof-of-concept trials, upon which the evidence was built.

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