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Clinical Outcomes of Remote Ischemic Preconditioning Prior to Cardiac Surgery: A Meta-Analysis of Randomized Controlled Trials

Brian Pierce, MD; Indra Bole, MD; Vaiibhav Patel, MD; David L. Brown, MD

Background—Multiple randomized controlled trials of remote ischemic preconditioning (RIPC) prior to cardiac surgery have failed to demonstrate clinical benefit. The aim of this updated meta-analysis was to evaluate the effect of RIPC on outcomes following cardiac surgery.

Methods and Results—Searches of PubMed, Cochrane, EMBASE, and Web of Science databases were performed for 1970 to December 13, 2015. Randomized controlled trials comparing RIPC with a sham procedure prior to cardiac surgery performed with cardiopulmonary bypass were assessed. All-cause mortality, acute kidney injury (AKI), and myocardial infarction were the primary outcomes of interest. We identified 21 trials that randomized 5262 patients to RIPC or a sham procedure **prior to** undergoing cardiac surgery. The majority of patients were men (72.6%) and the mean or median age ranged from 42.3 to 76.3 years. Of the 9 trials that evaluated mortality, 188 deaths occurred out of a total of 4210 randomized patients, with 96 deaths occurring in 2098 patients (4.6%) randomized to RIPC and 92 deaths occurring in 2112 patients (4.4%) randomized to a sham control procedure, demonstrating no significant reduction in all-cause mortality (risk ratio [RR], 0.987; 95% CI, 0.653–1.492, P=0.95). Twelve studies evaluated AKI in 4209 randomized patients. In these studies, AKI was observed in 516 of 2091 patients (24.7%) undergoing RIPC and in 577 of 2118 patients (27.2%) randomized to a sham procedure. RIPC did not result in a significant reduction in AKI (RR, 0.839; 95% CI, 0.703–1.001 [P=0.052]). In 6 studies consisting of 3799 randomized participants, myocardial infarction occurred in 237 of 1891 patients (12.5%) randomized to RIPC and in 282 of 1908 patients (14.8%) randomized to a sham procedure, resulting in no significant reduction in postoperative myocardial infarction (RR, 0.809; 95% CI, 0.615–1.064 [P=0.13]). A subgroup analysis was performed a priori based on previous studies suggesting that propofol may mitigate the protective benefits of RIPC. Three studies randomized patients undergoing cardiac surgery to RIPC or sham procedure in the absence of propofol anesthesia. Most of these patients were men (60.3%) and the mean or median age ranged from 57.0 to 70.6 years. In this propofol-free subgroup of 434 randomized patients, 71 of 217 patients (32.7%) who underwent RIPC developed AKI compared with 103 of 217 patients (47.5%) treated with a sham procedure. In this cohort, RIPC resulted in a significant reduction in AKI (RR, 0.700; 95% CI, 0.527–0.930 [P=0.014]). In studies of patients who received propofol anesthesia, 445 of 1874 (23.7%) patients randomized to RIPC developed AKI compared with 474 of 1901 (24.9%) who underwent a sham procedure. The RR for AKI was 0.928 (95% CI, 0.781–1.102; P=0.39) for RIPC versus sham. There was no significant interaction between the two subgroups (P=0.098).

Conclusions—RIPC does not reduce morbidity or mortality in patients undergoing cardiac surgery with cardiopulmonary bypass. In the subgroup of studies in which propofol was not used, a reduction in AKI was seen, suggesting that propofol may interact with the protective effects of RIPC. Future studies should evaluate RIPC in the absence of propofol anesthesia. (*J Am Heart Assoc*. 2017;6:e004666. DOI: 10.1161/JAHA.116.004666.)

Key Words: cardiac surgery • meta-analysis

Thirty years ago, Murry et al[1] first described ischemic preconditioning (IPC) after observing that anesthetized dogs subjected to prolonged circumflex coronary artery occlusion and reperfusion demonstrated a marked reduction of myocardial infarct size when exposed to 4 brief episodes of ischemia in the circumflex territory separated by 5 minutes of reperfusion prior to the prolonged occlusion. Remote IPC (RIPC) evolved from the same in vivo canine heart model

where ischemia-reperfusion injury could be attenuated in the left anterior descending coronary artery distribution after application of occlusion and reperfusion to the circumflex coronary artery.[2] With this finding, Przyklenk et al[2] concluded that protective mediators induced by ischemia could be transferred to distant, "regional" cardiomyocytes. Subsequent studies demonstrated that protection against ischemia-reperfusion injury in humans could be extended to distant organs, such as the kidney and brain.[3,4] The discovery that protection could be conferred by ischemia-reperfusion cycles in distant skeletal muscle elicited invasively by rapid stimulation of the gastrocnemius in rabbits[5] and noninvasively by a tourniquet in humans[6] spurred widespread clinical interest.

Given that cardiac surgery has the potential for ischemia and reperfusion injury to the heart, kidney and brain,[7–9] RIPC has long been viewed as an attractive approach to mitigate the deleterious clinical consequences of these events. Prior studies have shown that RIPC before cardiac surgery results in reductions in biomarkers of renal and cardiac injury.[10,11] However, randomized controlled trials (RCTs) of RIPC evaluating clinical cardiovascular and renal outcomes as well as overall mortality have not shown benefit.[12,13] Many of these trials utilized propofol anesthesia, which has been shown to negatively impact the benefits of RIPC.[14] With the recent publication of the two largest trials of RIPC to date,[15,16] we performed an updated meta-analysis of RCTs to better evaluate the clinical merit of this intervention.

Methods

Study Selection

A systematic search of published studies in any language in the PubMed, Cochrane, EMBASE, and Web of Science databases from 1970 to December 13, 2015, was performed independently by two authors (V.P. and I.B.). Search terms included *remote ischemic preconditioning, cardiac surgery, kidney injury,* and *renal failure,* as well as combinations of these terms. A filter for RCTs was used. Bibliographies of retrieved articles and prior reviews on the subject were searched for other relevant studies.

For inclusion, studies were required to be prospective randomized trials of preoperative RIPC or a sham procedure in patients undergoing cardiac surgery performed on cardiopulmonary bypass. In addition, studies had to report at least one clinical end point of interest as an outcome and enroll more than 50 patients. Patient characteristics, study design, and outcomes were systematically reviewed and recorded independently by 3 authors (B.P., I.B., and V.P.). Disagreements were resolved by consensus.

The methodological quality of each trial was evaluated using standard criteria: method of randomization; allocation concealment; patient, investigator, and outcome assessor blinding; selective outcome reporting; incomplete outcome ascertainment; and other potential sources of bias as recommended by the Cochrane Collaboration.[17] The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach for evaluating RCTs was applied.[18]

The following clinical end points were analyzed: all-cause mortality, acute kidney injury (AKI), myocardial infarction (MI), cerebrovascular accident (CVA), hospital length of stay (LOS), and intensive care unit (ICU) LOS. Discrete working definitions of AKI were reclassified as stage I, II, or III based on previous definitions described by the Acute Kidney Injury Advisory Group.[19] Other end point definitions were those used in the individual trials and are summarized in Table 1.[20–33]

Statistical Analysis

Because patient-level data from each trial were not available, a meta-analysis of summary statistics from individual trials was performed. Data from each trial were analyzed on an intention-to-treat basis according to the recommendations of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[34] Trial results for each end point were summarized with risk ratios (RRs) and standardized mean differences as the measures of effect. RRs were employed because accurate time-to-event data were not available in all trials. Summary RRs or standardized mean differences and 95% CIs were calculated using a random-effects model for combining results across studies, which incorporates between- and within-study variance and provides a more conservative summary. A random-effects model was preferred because heterogeneity across patient characteristics and clinical trial design would be unlikely to result in a consistent treatment effect across trials.[35] When no events were observed within a treatment group, a 0.5 correction factor was added to all values of that end point for calculation of the RR and its variance.[36,37] To determine whether there was heterogeneity between individual trials, we assessed the Q statistic (a weighted index of effect estimate differences across studies assuming a χ^2 distribution) and I^2 statistic ($[Q-df]/Q\times100$). Because the I^2 value quantifies heterogeneity on a scale of 0% to 100% and represents the extent of inconsistency among trial results rather than a sampling error independent of the number of studies, an I^2 of ≥75% was considered representative of high heterogeneity.[38] To assess for publication bias, funnel plots were evaluated by visual inspection and confirmed by Egger's test.[39] If analysis yielded plot asymmetry, Duval and Tweedie's trim and fill method, a quantitative assessment of publication bias, was performed.[40]

Heterogeneity was explored in subgroup analyses by study quality (high versus low), intraoperative propofol use, additive

Table 1. End Point Definitions

Trial	All-Cause Mortality	AKI	MI	Stroke	ICU LOS	Hospital LOS
Rahman et al, 2010[20]	N/A	>0.5 mg/dL^{-1} creatinine rise on day 4 post-operatively	N/A	N/A	Postoperative ICU stay in days	Postoperative hospital stay in days
Venugopal et al, 2010[21]	Death from any cause within 30 d	AKIN criteria in first 72 h post-operatively	N/A	N/A	N/A	Postoperative hospital stay in days
Li et al, 2010[22]	N/A	N/A	N/A	N/A	Postoperative ICU stay in hours*	Postoperative hospital stay in days
Karuppasamy et al, 2011[23]	N/A	N/A	N/A	N/A	Postoperative ICU stay in hours*	Postoperative hospital stay in days
Wu et al, 2011[24]	N/A	N/A	N/A	N/A	Postoperative ICU stay in hours*	Postoperative hospital stay in days
Choi et al, 2011[25]	N/A	AKIN criteria in first 48 h post-operatively	N/A	N/A	Postoperative ICU stay in days	Postoperative hospital stay in days
Zimmerman et al, 2011[3]	Death from any cause within the index stay	AKIN criteria in first 48 h post-operatively	N/A	N/A	N/A	Postoperative hospital stay in days
Lucchinetti et al, 2012[26]	Death from any cause within the follow-up period (6 mo)	N/A	Perioperative increase in cTnI to 5× the 99th percentile reference range with new pathological Q waves, LBBB, or new angiographic occlusion. Postoperative increase in cTnI to 2× reference range with evidence of ischemia	N/A	N/A	N/A
Xie et al, 2012[27]	Death from any cause within the follow-up period (3-39 mo)	N/A	N/A	N/A	N/A	N/A
Young et al, 2012[13]	N/A	RIFLE criteria for index stay	N/A	N/A	N/A	N/A
Lomivorotov et al, 2012[41]	Death from any cause within the follow-up period (30 d)	N/A	N/A	N/A	Postoperative ICU stay in days	N/A
Meybohm et al, 2013[28]	N/A	AKIN criteria in first 48 h post-operatively	N/A	N/A	Postoperative ICU stay in hours*	Postoperative hospital stay in days

Table 1. Continued

Trial	All-Cause Mortality	AKI	MI	Stroke	ICU LOS	Hospital LOS
Thielmann et al, 2013[29]	Death from any cause within the follow-up period (4+ y)	N/A	Perioperative increase in cTnI to 5× the 99th percentile reference range with new pathological Q waves, LBBB, or new angiographic occlusion. Postoperative increase in cTnI to 2× reference range with evidence of ischemia	Any embolic event after immediate postoperative period; a neurological event resulting in a new deficit; any neurological event lasting >24 h unless a cerebral lesion was visualized on imaging	Postoperative ICU stay in days	Postoperative hospital stay in days
Gallagher et al, 2015[30]	Death from any cause within 30 d	AKIN criteria in first 48 h postoperatively	N/A	N/A	Postoperative ICU stay in hours*	Postoperative hospital stay in days
Ahmad et al, 2014[12]	Death from any cause within the index hospital stay	N/A	N/A	N/A	N/A	N/A
Slagsvold et al, 2014[31]	Death from any cause within 30 d	N/A	N/A	N/A	N/A	N/A
Candilio et al, 2015[32]	Death from any cause within 6 wk	RIFLE criteria in first 72 h postoperatively	Myocardial infarction (not defined) by 6 wk	Stroke (not defined) by 6 wk	Postoperative ICU stay in days	Postoperative hospital stay in days
Zarbock et al, 2015[11]	Death from any cause within 30 d	KDIGO criteria in first 72 h postoperatively	Perioperative increase in cTnI to 5× the 99th percentile of reference range with new pathological Q waves, LBBB, or new angiographic occlusion. Postoperative increase in cTnI to 2× reference range with evidence of ischemia	Any embolic event after immediate postoperative period; a neurological event resulting in a new deficit; any neurological event lasting >24 h unless a cerebral lesion was visualized on imaging	Postoperative ICU stay in days	Postoperative hospital stay in days
Pinaud et al, 2016[33]	N/A	AKIN criteria in first 72 h postoperatively	N/A	N/A	Postoperative ICU stay in hours*	N/A
Meybohm et al, 2015[16]	Death from any cause within index hospital stay (maximum 14 d)	Increase in serum creatinine by a factor of ≥2 from baseline	Biomarker values over 5× the 99th percentile of reference range with pathological Q waves or new LBBB in first 72 h. Standard clinical criteria for MI from 72 h onward. Ischemia by echocardiography or angiography. MI diagnosed at autopsy	New, temporary, or permanent focal or global neurological deficit. Evidence of stroke at autopsy	N/A	N/A

Table 1. Continued

Trial	All-Cause Mortality	AKI	MI	Stroke	ICU LOS	Hospital LOS
Hausenloy et al, 2015[15]	Death from any cause within 12 mo	KDIGO criteria in first 72 h post-operatively	Biomarker values >10× the 99th percentile of reference range when associated with new pathological Q waves, new LBBB, or angiographically documented occlusion in the first 72 h postoperatively or biomarker value >100× the 99th percentile in the first 72 h postoperatively	Focal neurological deficit of cerebrovascular cause persisting beyond 24 h or interrupted by death within 24 h	Postoperative ICU stay in days	Postoperative hospital stay in days

AKIN indicates acute kidney injury network; cTnI, cardiac troponin I; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes; LBBB, left bundle branch block; LOS, length of stay; MI, myocardial infarction; N/A, not applicable; RIFLE, risk, injury, failure, loss, end-stage.
*Hours were divided by 24 for unit of measurement uniformity.

European System for Cardiac Operative Risk Evaluation (EuroSCORE), and preoperative potassium-ATP (K-ATP) antagonist use. Unless an anesthetic regimen without propofol was detailed, it was assumed that propofol was administered. In the event of protocol ambiguity, primary authors were contacted for clarification. In trials that did not exclude diabetic patients, it was assumed that K-ATP antagonists were used unless specifically prohibited preoperatively. Sensitivity analyses were performed for each outcome to determine whether any single study disproportionately influenced the pooled estimate by excluding individual trials one at a time and recalculating the combined RR or standardized mean difference for the remaining studies. $P<0.05$ was considered statistically significant and all tests were 2-sided. Statistical analyses were performed with Comprehensive Meta-Analysis (version 2) software (Biostat, Englewood, NJ).

Results

Literature Search

The electronic search yielded 833 citations that were screened by reviewing the title or abstract with subsequent removal of duplicates. Of these, 45 articles were reviewed in full and 21 studies were included for analysis (Figure 1). Characteristics of the studies are listed in Table 2. Eight studies tested RIPC in patients undergoing isolated coronary artery bypass grafting (CABG),[12,20,21,23,26,29,31,41] four studies in patients undergoing isolated valve surgery,[22,24,27,33] and the remaining 9 in patients undergoing any cardiac surgery.* One study included additional perconditioning, the application of short periods of ischemia and reperfusion at a distant site delivered during target organ ischemia; only data from the preconditioning intervention and the sham procedure were included.[22]

Of the 5262 patients included in the analysis, 2624 were randomized to RIPC and 2638 were randomized to a sham procedure. Baseline characteristics of the study populations showed that most patients were men (72.6%). The mean or median ages of patients ranged from 42.3 to 76.3 years. The majority of studies were double-blinded, randomized, and had adequate descriptions of patient attrition. Study quality is summarized in Table 3.

Quantitative Outcomes

Of the 188 deaths in the 4210 randomized patients undergoing cardiac surgery, 96 deaths occurred in the 2098 patients (4.6%) randomized to RIPC, whereas 92 deaths

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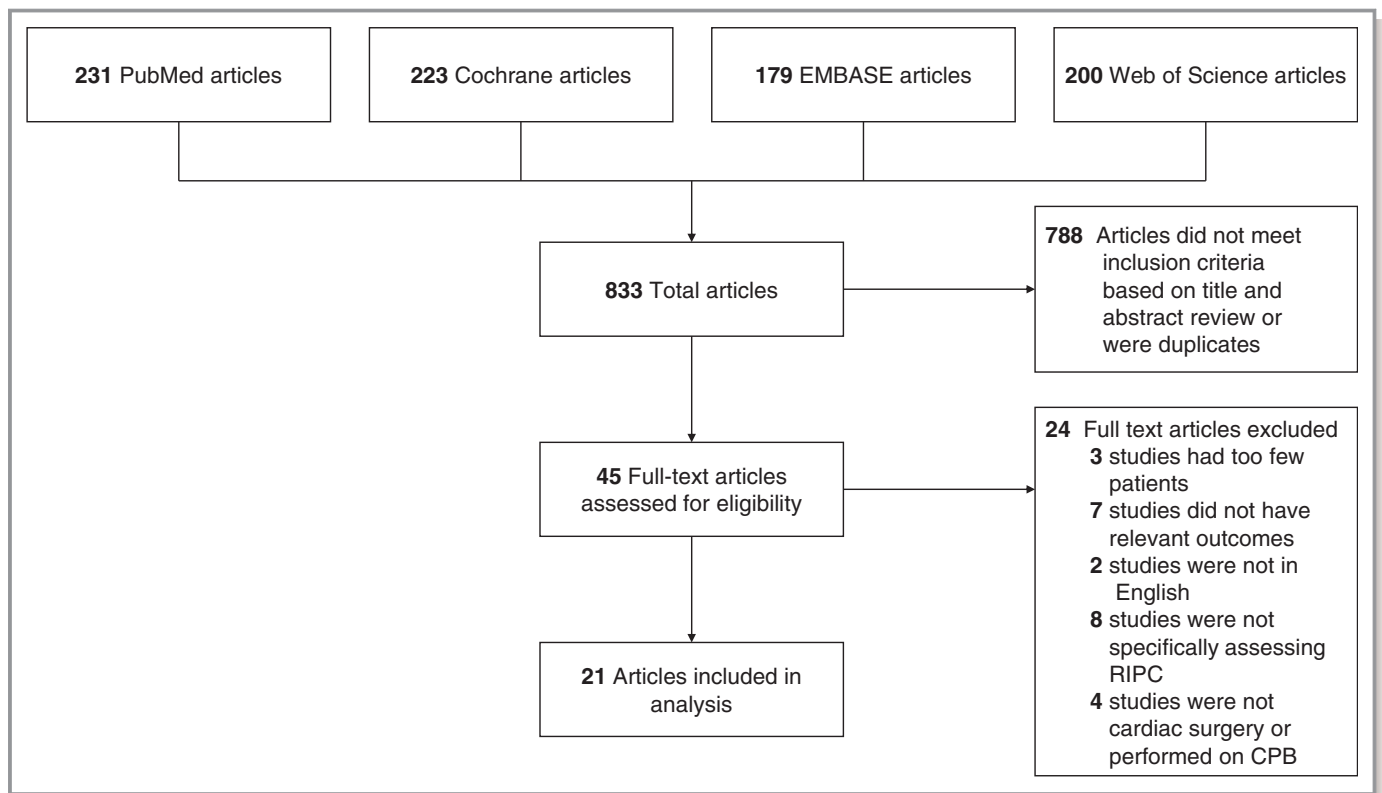*References 3, 11, 13, 15, 16, 25, 28, 30, 32.

Figure 1. Study selection. Flow diagram depicts study selection for inclusion in the meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[34] RIPC indicates remote ischemic preconditioning.

occurred in the 2112 patients (4.4%) randomized to a sham control procedure. The RR for mortality for RIPC versus sham was 0.987 (95% CI, 0.653–1.492; P=0.95 [I^2=16%]) (Figure 2A). AKI occurred in 516 of 2091 patients (24.7%) undergoing RIPC and in 577 of 2118 patients (27.2%) who underwent a sham procedure. The RR for AKI for RIPC versus sham procedure was 0.839 (95% CI, 0.703–1.001; P=0.052 [I^2=41%]) (Figure 2B). Postoperative MI occurred in 237 of 1891 patients (12.5%) randomized to RIPC and in 282 of 1908 patients (14.8%) randomized to a sham procedure. The RR for MI for RIPC versus sham was 0.809 (95% CI, 0.615–1.064; P=0.13 [I^2=27%]) (Figure 2C). Postoperative CVA was diagnosed in 34 of 1864 patients (1.82%) who underwent RIPC and in 37 of 1880 patients (1.97%) who underwent a sham procedure. The RR for CVA for RIPC versus sham was 0.939 (95% CI, 0.592–1.489; P=0.79 [I^2=0%]) (Figure 2D). The standardized difference in mean ICU LOS was 0.010 days (95% CI, −0.116 to 0.137; P=0.87 [I^2=41%]) between the 1381 patients in the RIPC group and the 1396 patients in the sham control group (Figure 2E). Similarly, the standardized difference in mean hospital LOS was 0.026 days (95% CI, −0.091 to 0.143; P=0.67 [I^2=0%]) for the 559 patients undergoing RIPC versus 567 patients having a sham procedure (Figure 2F). Summarized quantitative data for the entire sample can be seen in Table 3.

Subgroup Analyses, Sensitivity Analyses, and Publication Bias

Subgroup analysis showed no differences in outcomes when compared by the use of K-ATP antagonists (results not shown). In the subgroup of studies of patients who did not receive propofol, we observed that most of these patients were men (60.3%) and the mean or median age ranged from 57.0 to 70.6 years. In this propofol-free subgroup, 71 of 217 patients (32.7%) who underwent RIPC developed AKI compared with 103 of 217 patients (47.5%) treated with a sham procedure. The RR for AKI was 0.700 (95% CI, 0.527–0.930; P=0.014) for RIPC versus sham. In studies of patients who received propofol, 445 of 1874 (23.7%) who received RIPC developed AKI compared with 474 of 1901 (24.9%) who underwent a sham procedure. The RR for AKI was 0.928 (95% CI, 0.781–1.102; P=0.39) for RIPC versus sham (Figure 3). Summarized quantitative data for these subgroups can be seen in Table 4. There was no significant interaction between the two subgroups (P=0.098). Additionally, there were no differences in the effect of RIPC on development of stage I, II, or III AKI, and there was no difference in the effect of RIPC on the development of severe AKI, defined as stage II or III AKI (results not shown).

Table 2. Characteristics of Trials

Study	Country, Enrollment Years	No. of Patients Enrolled (RIPC/Sham)	Mean or Median Age (RIPC/Sham)	Male (RIPC/Sham), %	Inclusion Criteria	Primary End Point	CABG, Valve Surgery, or Mixed	Propofol Use	K-ATP Antagonist Use	Preconditioning Site and Duration (Cycles×min)
Rahman et al, 2010[20]	UK, 2007–2009	162 (80/82)	63/65	89.0/88.0	Isolated first-time multivessel CABG	Troponin AUC at 48 h	CABG	Yes	No	UL, 3×5
Venugopal et al, 2010[21]	UK, 2006–2008	78 (38/40)	64.0/66.0	79.0/85.0	Elective CABG	Perioperative AKI in first 72 h	CABG	Unknown	No	UL, 3×5
Li et al, 2010[22]	China, 2009	53 (26/27)	45.8/42.3	30.0/50.0	Age 18 to 65 y, rheumatic heart valve disease	Troponin release at 30 min and 4, 12, and 72 h after declamping	Valve replacement	Yes	No	LL, 4×4
Karuppasamy et al, 2011[23]	UK, 2008–2009	54 (27/27)	66.9/67.3	81.0/85.0	Elective CABG	Troponin release at 6, 12, 24, and 48 h postoperatively	CABG	Yes	No	UL, 3×5
Wu et al, 2011[24]	Japan, 2009–2010	75 (50/25)	46.2/43.6	40.0/28.0	Age 18 to 60 y, mitral valve replacement	Postoperative inotrope requirement, ICU LOS, hospital LOS	Valve replacement	Unknown	No	UL, 3×5
Choi et al, 2011[25]	South Korea, 2008–2009	76 (38/38)	57.0/60.0	39.5/39.5	Elective, complex valvular heart surgery	Postoperative biomarkers of renal injury and incidence of AKI	Mixed	No	No	LL, 3×10
Zimmerman et al, 2011[3]	US, 2008–2009	118 (59/59)	62.0/65.0	69.0/68.0	Elective cardiac surgery on CPB	Postoperative AKI	Mixed	No	Yes	LL, 3×5
Lucchinetti et al, 2012[26]	Canada, 2008–2010	55 (27/28)	59.0/62.0	96.0/86.0	Elective CABG, age 50 to 85 y	Postoperative high-sensitivity troponin release	CABG	Yes	No	LL, 4×5
Xie et al, 2012[27]	China, 2007–2011	73 (38/35)	51.1/50.4	50.0/47.1	Elective valve surgery	Troponin I level at 6, 12, 24, 48 and 72 h	Valve	Yes	Yes	UL, 3×5
Young et al, 2012[13]	New Zealand, 2010–2011	96 (48/48)	65.5/64.4	60.4/64.6	Double-valve or triple-valve surgery, mitral valve surgery, CABG	Postoperative high-sensitivity troponin T at 6 and 12 h and AKI	Mixed	Yes	Yes	UL, 3×5
Lomivorotov et al, 2012[41]	Russia 2010–2011	80 (40/40)	56.6/58.1	90.0/92.5	Adults undergoing CABG on CPB	Postoperative hemodynamic markers and troponin I and CK-MB at 6, 24, and 48 h	CABG	Yes	No	UL, 3×5
Meybohm et al, 2013[28]	Germany 2009–2010	180 (90/90)	70.0/68.0	76.7/85.6	Age >18 y undergoing cardiac surgery on CPB	Postoperative neurocognitive dysfunction at days 5 to 7	Mixed	Yes	No	UL, 4×5

Table 2. Continued

Study	Country, Enrollment Years	No. of Patients Enrolled (RIPC/Sham)	Mean or Median Age (RIPC/Sham)	Male (RIPC/Sham), %	Inclusion Criteria	Primary End Point	CABG, Valve Surgery, or Mixed	Propofol Use	K-ATP Antagonist Use	Preconditioning Site and Duration (Cycles×min)
Thielmann et al, 2013[29]	Germany 2008–2012	329 (162/167)	68.2/69.1	83.0/80.0	Adults with triple-vessel disease undergoing primary, isolated, elective CABG on CPB	Perioperative myocardial injury reflected by AUC for troponin I	CABG	Yes	Unknown	UL, 3×5
Gallagher et al, 2015[30]	UK, 2011–2012	86 (43/43)	68.7/72.8	76.7/83.7	Patients with chronic kidney disease undergoing CABG	Postoperative AKI within 48 h	Mixed	Unknown	Yes	UL, 3×5
Ahmad et al, 2014[12]	Pakistan, 2012–2013	67 (35/32)	54.5/55.2	77.1/78.1	Patients with class III angina and triple-vessel disease	Postoperative CK-MB levels at 1, 6, 12, and 24 h	CABG	Yes	Unknown	UL, 3×5
Slagsvold et al, 2014[31]	Norway, 2011	60 (30/30)	64.0/68.0	90.0/76.7	Urgent or elective first-time CABG surgery	Mitochondrial respiration in situ as assessed by left ventricular biopsy	CABG	Yes	Yes	UL, 3×5
Candilio et al, 2015[32]	UK, 2010–2012	178 (89/89)	65.0/66.0	81.0/75.0	Adult patients undergoing CABG and/or valve surgery	Perioperative myocardial infarction, measured by 72-h AUC hsTnT	Mixed	Yes	No	UL, 3×5
Zarbock et al, 2015[11]	Germany, 2013–2014	240 (120/120)	70.1/70.6	63.3/62.5	Adults at high risk for acute kidney injury undergoing cardiac surgery with CPB	Postoperative acute kidney injury at 72 h	Mixed	No	No	UL, 3×5
Pinaud et al, 2016[33]	France, 2011–2012	99 (50/49)	75.8/72.9	54.0/48.9	Age >18 y undergoing elective aortic valve replacement	Postoperative AUC troponin I at 72 h	Valve	Yes	No	UL, 3×5
Meybohm et al, 2015[16]	Germany, 2011–2014	1385 (692/693)	65.8/66.0	73.4/75.0	Age >18 y undergoing elective cardiac surgery requiring CPB	Composite of death, MI, stroke or acute renal failure	Mixed	Yes	No	UL, 4×5
Hausenloy et al, 2015[15]	UK, 2010–2015	1612 (801/811)	76.1/76.3	70.4/72.7	Age >18 y; additive EuroSCORE ≥5 undergoing on-pump CABG (with or without valve surgery)	Composite of death from cardiovascular causes, nonfatal MI, coronary revascularization, or stroke	Mixed	Yes	No	UL, 4×5

AKI indicates acute kidney injury; AUC, area under the curve; CABG, coronary artery bypass grafting; CK-MB, creatinine kinase, myocardial B fraction; CPB, cardiopulmonary bypass; EuroSCORE, European System for Cardiac Operative Risk Evaluation; hsTnT, high-sensitivity troponin T; ICU, intensive care unit; K-ATP, potassium-ATP; LL, lower limb; LOS, length of stay; MI, myocardial infarction; RIPC, remote ischemic preconditioning; UK, United Kingdom; UL, upper limb; US, United States.

Table 3. Study Quality and Risk of Bias Using the GRADE Criteria[18]

Quality Assessment							No. of Patients		Effect		Quality	Importance
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Remote Ischemic Preconditioning	Sham Preconditioning	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
12	Randomized trials	Serious*,†	Serious‡,§	Not serious	Not serious	None	96/2098 (4.6%)	92/2112 (4.4%)	RR 0.98 (0.63–1.53)	1 fewer per 1000 (from 16 fewer to 23 more)	⊕⊕◯◯ Low	CRITICAL
Acute kidney injury												
12	Randomized trials	Serious*,†	Not serious	Serious‖	Not serious	None	516/2091 (24.7%)	577/2118 (27.2%)	RR 0.85 (0.69–1.03)	41 fewer per 1000 (from 8 more to 84 fewer)	⊕⊕◯◯ Low	CRITICAL
Myocardial infarction												
6	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	237/1891 (12.5%)	282/1908 (14.8%)	RR 0.80 (0.61–1.04)	30 fewer per 1000 (from 6 more to 58 fewer)	⊕⊕⊕⊕ High	IMPORTANT
Stroke												
6	Randomized trials	Not serious	Serious‡	Not serious	Not serious	None	34/1864 (1.8%)	37/1880 (2.0%)	RR 0.94 (0.59–1.49)	1 fewer per 1000 (from 8 fewer to 10 more)	⊕⊕⊕◯ Moderate	IMPORTANT
ICU length of stay												
12	Randomized trials	Very serious*,†,¶	Very serious‡,§,#	Not serious	Not serious	None	1381	1396	—	SMD 0.004 SD more (0.11 fewer to 0.12 more)	⊕◯◯◯ very low	IMPORTANT
Hospital LOS												
13	Randomized trials	Very serious*,†,¶	Very serious‡,§,#	Not serious	Not serious	None	559	567	—	SMD 0.005 SD fewer (0.12 fewer to 0.11 more)	⊕◯◯◯ very low	IMPORTANT

GRADE indicates Grades of Recommendation, Assessment, Development, and Evaluation; ICU, intensive care unit; LOS, length of stay; RR, risk ratio; SMD, standardized mean difference. GRADE score quality is reflected by: high quality (at least 4 ⊕ overall), moderate quality (3 ⊕), low quality (2 ⊕), and very low quality (one or less)

*Randomization methods not consistently described.
†Multiple trials were not double-blinded.
‡Direction of effect not consistent.
§Point estimates varied widely.
‖Definition of outcome varied.
¶Patient attrition not described.
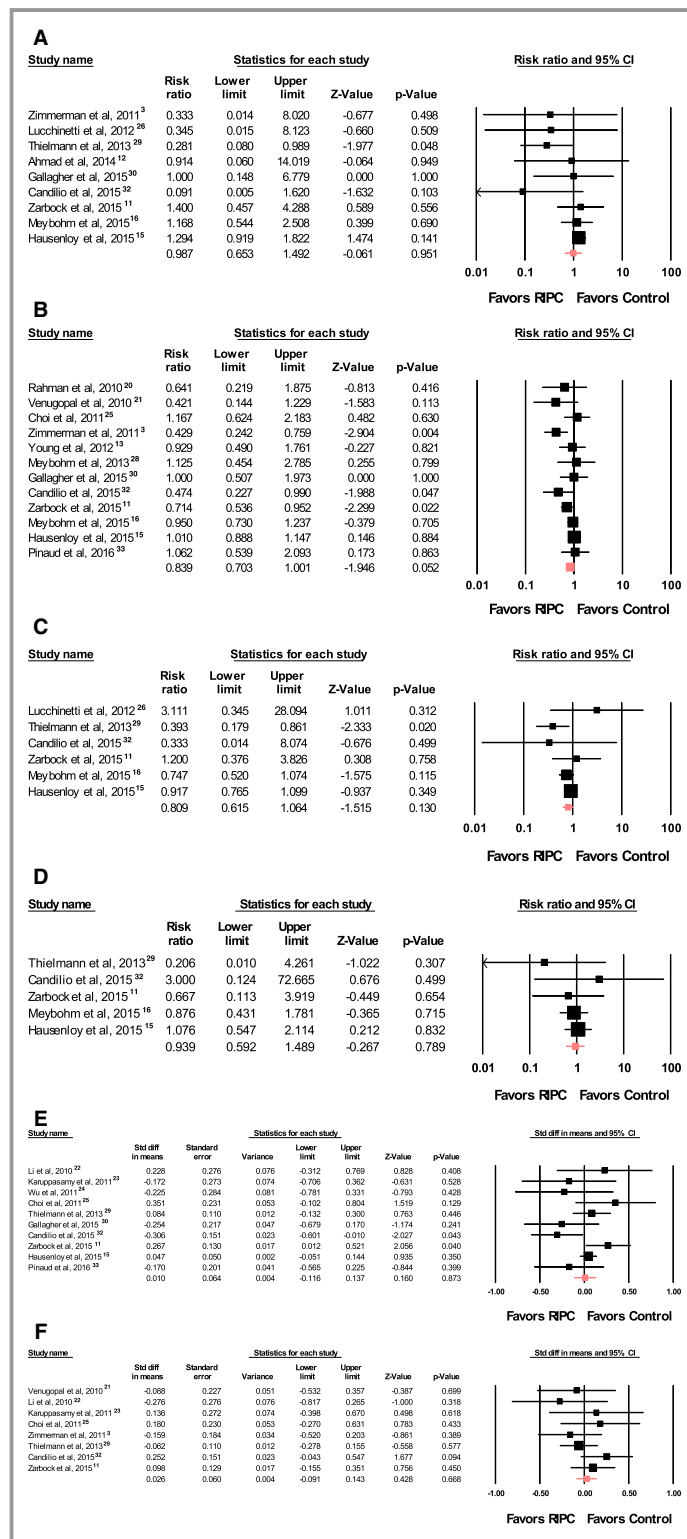#Significant statistical heterogeneity.

Figure 2. Comparison of outcomes between remote ischemic preconditioning (RIPC) and sham procedure. A, All-cause mortality. B, Acute kidney injury. C, Myocardial infarction. D, Stroke. E, Intensive care unit length of stay. F, Hospital length of stay. The sizes of the squares representing the point estimates for each study are proportional to the weight of the study. Diamonds indicate the overall risk ratio (RR) or standardized mean difference and 95% CIs for the outcome of interest.
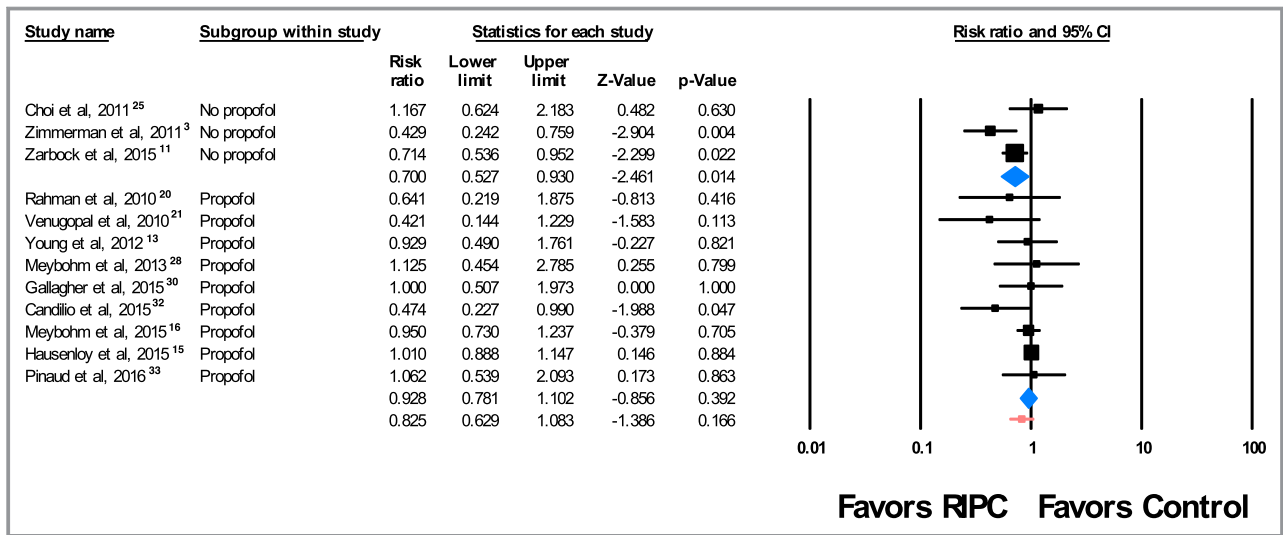
Figure 3. Subgroup analysis of cardiac surgeries performed with and without propofol anesthesia. The sizes of the squares representing the point estimates for each study are proportional to the weight of the study. Diamonds indicate the overall risk ratio (RR) and 95% CIs. RIPC indicates remote ischemic preconditioning.

Sensitivity analyses showed no significant differences in outcomes when results were compared by study quality (high versus low), type of surgery performed (CABG, valve, or mixed), severity of illness (based on additive Euro-SCORE), or duration or site of RIPC (results not shown). Visual inspection of the funnel plots suggested possible publication bias (Figure 4). This was further analyzed using the trim and fill method. The RR of AKI of 0.839 (95% CI, 0.702–1.001) was unchanged by the trim and fill method, suggesting no publication bias. This was confirmed by the Egger's test, which indicated lack of publication bias (P=0.055).

In addition, sensitivity analyses to assess potential effects of qualitative differences on study design and patient selection showed that exclusion of any one trial from analysis of mortality, AKI, MI, CVA, ICU LOS, and hospital LOS did not change the overall findings (data not shown).

Discussion

In this meta-analysis of 5262 patients undergoing RIPC for cardiac surgery with cardiopulmonary bypass, we found that RIPC conferred no clinical benefit. The intervention failed to reduce the incidence of all-cause mortality, MI, CVA, and ICU or hospital LOS. There was a strong trend towards reduction of AKI in patients who underwent RIPC.

Previous meta-analyses have also failed to demonstrate clinical benefit of RIPC.[42,43] However, two aspects of this meta-analysis differentiate it from prior studies. First, this analysis includes two recent, large, high-quality RCTs of RIPC in patients undergoing cardiac surgery not included in previous meta-analyses.[15,16] The inclusion of these trials increased the study population 2-fold. Second, as far as we are aware, this is the first meta-analysis to evaluate outcomes as a function of propofol and K-ATP antagonist use.

Although the mechanisms of RIPC have not been fully elucidated, many believe there are components of both humoral and sensory-neuronal pathways that confer organ protection.[44] The neuronal pathway was first described by Jones et al,[45] who demonstrated that myocardial protection could be produced through activation of sensory C fibers by an abdominal incision in mice. Furthermore, transection of the spinal cord and blockade of sensory C fibers by lidocaine

Table 4. Subgroup Analysis of Perioperative Propofol Use

No. (RIPC)	AKI (RIPC)	No. (Sham)	AKI (Sham)	RR (95% CI)	P Value
Propofol used (N=9 trials)[13,15,16,20,21,28,30,32,33]					
1874	445 (23.7%)	1901	474 (24.9%)	0.928 (0.781–1.102)	0.39
Propofol not used (N=3 trials)[3,11,25]					
217	71 (32.7%)	217	103 (47.5%)	0.700 (0.527–0.930)	0.014

AKI indicates acute kidney injury; RIPC, remote ischemic preconditioning; RR, risk ratio.
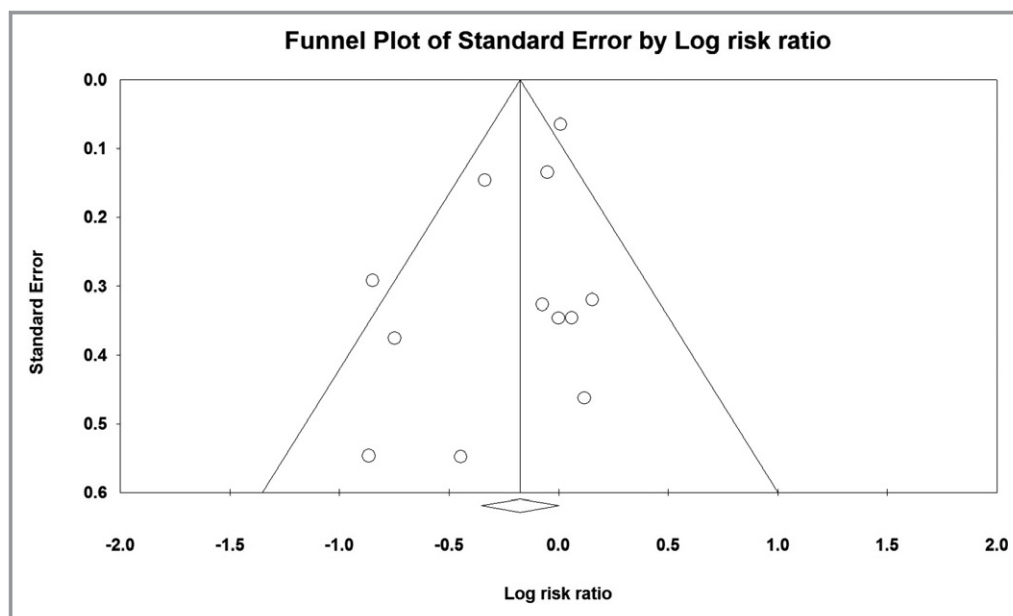
Figure 4. Assessment of publication bias. This funnel plot is a plot of a measure of study size on the vertical axis as a function of effect size on the horizontal axis for acute kidney injury. Large studies appear toward the top of the graph and tend to cluster near the mean effect size. Smaller studies appear toward the bottom of the graph and (since there is more sampling variation in effect size estimates in the smaller studies) will be dispersed across a range of values. In the absence of publication bias, the studies, represented by circles, are distributed symmetrically about the combined effect size. The dashed diamond appearing below the *x* axis represents the summary effect.

abrogated the benefit of preconditioning, suggesting neuronal signal transmission. Similarly, propofol may disrupt mediators of the neuronal pathway and diminish the clinical benefits of RIPC when compared with isoflurane anesthesia.[14,46] Other investigators have suggested propofol itself may be protective and any incremental benefits of RIPC are too small to be detected.[47] Our analysis is congruent with these theories, as we observed a highly significant reduction in AKI in the subgroup of patients who did not receive propofol, despite no benefit in the overall cohort.

In addition to the neuronal pathway, humoral-mediated pathways have also been described. After Huffman et al[48] demonstrated that transfer of serum from preconditioned to recipient rats prior to an induced MI conferred cardiac protection, the mediators of this pathway were explored. Adenosine and bradykinin, among other mediators, have been shown to induce preconditioning of myocytes, thought to be via the activation of the K-ATP channel pathway.[44,49,50] Loukogeorgakis et al[51] implicated the K-ATP pathway in IPC-mediated endothelial protection by demonstrating abolition of the protective effect after administration of glibenclamide, a K-ATP antagonist. In our subgroup analysis, after removal of studies that included patients treated with K-ATP antagonists, clinical benefit of RIPC was still not observed.

Study Limitations

The results of this meta-analysis should be interpreted with consideration of its limitations. First, the majority of trials included in the review were single-center studies with varying inclusion and exclusion criteria. Second, definitions for outcomes and duration of follow-up differed between included trials. Third, because we assumed that all patients in a given trial either did or did not receive propofol, a portion of patients within individual trials may have been miscategorized. Additionally, variability in RIPC protocols may have led to heterogeneity in the analysis. Finally, data were extracted only from RCTs and may not be representative of patients treated in usual practice.

Conclusions

RIPC does not prevent morbidity or mortality in patients undergoing cardiac surgery with cardiopulmonary bypass. In the subgroup of studies in which propofol was not used, a reduction in AKI was seen, suggesting that propofol may interact with the protective effects of RIPC. To evaluate the independent effect of RIPC on outcomes, future studies on RIPC should be performed in the absence of propofol anesthesia.

Disclosures

None.

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Clinical Outcomes of Remote Ischemic Preconditioning Prior to Cardiac Surgery: A Meta–Analysis of Randomized Controlled Trials

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