Original Article

Remote ischemic preconditioning and cognitive dysfunction following coronary artery bypass grafting: A systematic review and meta-analysis of randomized controlled trials

ABSTRACT

Introduction: Postoperative cognitive dysfunction (POCD) is a common neurological issue following cardiopulmonary bypass (CPB)-assisted heart surgery. Remote ischemic preconditioning (RIPC) increases the tolerance of vital organs to ischemia/reperfusion injury, leading to reduced brain injury biomarkers and improved cognitive control. However, the exact mechanisms underlying RIPC's neuroprotective effects remain unclear. This systematic review aimed to explore the hypothesis that RIPC lowers neurocognitive dysfunction in patients undergoing CPB surgery.

Method: All relevant studies were searched in PubMed, ScienceDirect, EBSCOhost, Google Scholar, Semantic Scholar, Scopus, and Cochrane Library database. Assessment of study quality was carried out by two independent reviewers individually using the Cochrane Risk of Bias (RoB-2) tool. Meta-analysis was performed using a fixed-effect model due to low heterogeneity among studies, except for those with substantial heterogeneity.

Results: A total of five studies with 1,843 participants were included in the meta-analysis. RIPC was not associated with reduced incidence of postoperative cognitive dysfunction (five RCTs, odds ratio [OR:] 0.79, 95% confidence interval [CI]: 0.56–1.11) nor its improvement (three RCTs, OR: 0.80, 95% CI: 0.50–1.27). In addition, the analysis of the effect of RIPC on specific cognitive function tests found that pooled SMD for RAVLT 1-3 and RAVLT LT were −0.07 (95% CI: −0.25,012) and −0.04 (95% CI: −0.25–0.12), respectively, and for VFT semantic and phonetic were −0.15 (95% CI: −0.33–0.04) and 0.11 (95% CI: −0.40–0.62), respectively.

Conclusion: The effect of RIPC on cognitive performance in CABG patients remained insignificant. Results from previous studies were unable to justify the use of RIPC as a neuroprotective agent in CABG patients.

Key words: Cardiopulmonary bypass, cognition, coronary artery bypass grafting, ischemia/reperfusion injury, postoperative cognitive dysfunction, remote ischemic preconditioning

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Introduction

Following the cardiopulmonary bypass (CPB)-assisted heart surgery, several neurological and behavioral problems, such as dementia, delirium, and postoperative cognitive dysfunction (POCD) are commonly found. POCD is a common clinical issue that affects a variety of cognitive domains, including attention, memory, executive function, and information processing speed.[1] A recent meta-analysis found that the prevalence of POCD after cardiac surgery was 28% between the 1st and 4th months and 22% between the 6th and 12th months postoperatively.[2] Several mechanisms have been highlighted to cause this disorder, including cerebral autoregulation dysfunction, body response to surgical procedure (stress and inflammatory status), cerebral microembolic formation, cerebral hyperthermia, hemodilution, hypercoagulation, and low mean arterial pressure.[3]

In a variety of clinical conditions, it has been demonstrated that brief transient sublethal episodes of ischemia in non-vital tissue (e.g., skeletal muscles) increase the tolerance of remote vital organs (e.g., heart, brain, and kidneys) to subsequent prolonged ischemia/reperfusion injury, a phenomenon known as remote ischemic preconditioning (RIPC).[4] The benefits are demonstrated by lower levels of brain injury biomarkers (S100-β and neuron-specific enolase [NSE]) and improved cognitive control (conflict resolution), which are strengthened with repeated RIPC administration.[5-7] However, the precise processes by which RIPC reduces ischemic/reperfusion (I/R) injury in the brain remain unknown. According to the currently accepted theory, humoral factors and local autacoids (e.g., nitric oxide, nitrite, and adenosine) are generated as a consequence of brief I/R injury, which activates afferent neuronal and humoral pathways.[8]

The therapeutic value of RIPC in neuroprotection for patients undergoing cardiovascular surgery is contentious. Two investigations[9,10] failed to demonstrate the neuroprotective effects of RIPC in lowering postoperative cognitive impairment in persons undergoing heart surgery, whether on CPB or not. In contrast, Hudetz *et al*.[11] demonstrated in a pilot study that RIPC prevented the short-term deterioration of cognitive function following cardiac surgery. This notion is supported further by previous experimental data indicating that RIPC has advantages in terms of cerebral I/R injury.[12,13] As a result, RIPC could be a simple, non-invasive, and low-cost method for reducing the severity of perioperative ischemia episodes with no reported adverse reactions. As a result, the objective of this systematic review and meta-analysis is to explore the hypothesis that RIPC lowers the incidence and severity of neurocognitive dysfunction in patients having CPB surgery.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines for conducting and reporting our systematic review.[14] We registered our protocol on PROSPERO (registration number: CRD42023430880).

Search strategy

We searched PubMed, Semantic, Google Scholar, Scopus, Cochrane, EBSCOhost, and ScienceDirect databases until June 2023 to retrieve relevant studies. A combination of keywords related to RIPC, CABG, and cognitive dysfunction was used [Table 1 shows the full-search strategy]. Only clinical studies were considered in this systematic review.

Study selection

Several inclusion criteria were employed to select publications for this systematic review. These include English-language articles, primary data source studies (randomized controlled trials/RCTs, non-RCTs, and observational studies), and adult patients who underwent coronary artery bypass grafting (CABG) received the RIPC procedure and had their cognitive function assessed. Studies were omitted if they

Table 1: Full search terms strategy

Keywords	Database
"remote ischemic preconditioning," "CABG," "coronary artery bypass grafting," "cognitive"	Semantic Scholar
"remote ischemic preconditioning" AND "coronary artery bypass grafting" AND "cognitive"	Google Scholar
"remote ischemic preconditioning" AND "coronary artery bypass grafting" AND "cognitive"	EBSCOhost
RIPC OR "remote ischemic preconditioning" OR "remote preconditioning") AND (CABG OR "coronary artery bypass grafting" OR "coronary bypass") AND ("cognitive dysfunction" OR "cognitive" OR "cognition")	Cochrane Library
(RIPC OR "remote ischemic preconditioning" OR "remote ischemic conditioning" OR "remote preconditioning" OR "remote conditioning") AND (CABG OR "coronary artery bypass grafting" OR "coronary artery bypass surgery" OR "coronary revascularization" OR "coronary bypass" OR "cardiac surgery") AND ("cognitive dysfunction" OR "cognitive" OR "cognition" OR "neurocognitive" OR "neuropsychological" OR "brain function")	PubMed
(RIPC OR "remote ischemic preconditioning" OR "remote preconditioning") AND (CABG OR "coronary artery bypass grafting" OR "coronary bypass") AND ("cognitive dysfunction" OR "cognitive" OR "cognition")	Science Direct
(RIPC OR "remote ischemic preconditioning" OR "remote ischemic conditioning" OR "remote preconditioning" OR "remote conditioning") AND (CABG OR "coronary artery bypass grafting" OR "coronary artery bypass surgery" OR "coronary revascularization" OR "coronary bypass" OR "cardiac surgery") AND ("cognitive dysfunction" OR "cognitive" OR "cognition" OR "neurocognitive" OR "neuropsychological" OR "brain function")	Scopus

were a systematic review, review article, opinion-based article, studies involving children, or if the complete text of the study was not obtainable.

Data extraction and quality assessment

Two reviewers (RF and OA) screened titles and abstract records according to eligibility criteria for inclusion using Rayyan QCRI. All were blinded in this process. When there was no consensus, a senior reviewer (TPU), blinded to the other reviewers' suggestions, made the final decision. After the studies were collected, the following information was extracted: authorship, years, country, study populations, use of CPB and also timing, duration, and location of RIPC, and neuropsychological testing. The data were recorded using an Excel spreadsheet. We assessed the quality and risk of bias of the included studies using the Cochrane Risk of Bias (RoB-2) tool. We rated each study as having low, high, or unclear risk of bias for each of the following domains: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data addressed, selective reporting, and other potential bias.

Statistical analysis

POCD incidence and improvement were assessed and reported as odds ratios (ORs) and 95% confidence intervals (CIs). For the analysis of specific cognitive function tests supplied as numerical data, we calculated standardized mean differences (SMD). Heterogeneity was discovered using the I^2 statistic, with >50% indicating significant heterogeneity. Pooled analysis was performed using a fixed-effect model due to low heterogeneity among studies, except for those with substantial heterogeneity, which utilized a random-effect model. *P* values of 0.05 were used to evaluate statistical significance. The statistical analysis was carried out using RevMan 5.4.1 (Cochrane Collaboration).

Results

The process of database search and study identification is shown in Figure 1. Our literature search yielded 572 records after removing duplicates. We screened the titles and abstracts of these records and excluded 459 records that did not meet our inclusion criteria. We obtained the full texts of the remaining 113 articles and assessed them for eligibility. We excluded 108 articles for various reasons [Figure 1]. We included five studies[7,9,10,15,16] in our systematic review, involving a total of 1,843 patients.

Study characteristics

Table 2 summarizes the characteristics and results of the included studies in this systematic review. The study design was a randomized controlled trial. One study included patients with off-pump surgeries,[9] whereas the remaining with on-pump heart surgeries.[7,10,15,16] Four studies applied remote ischemic preconditioning (RIPC) after anesthetic induction,[7,10,15,16] whereas one study reported RIPC application before coronary anastomosis.[9] RIPC protocol comprised three to four cycles of upper limb ischemia that involved inflating the blood pressure cuff for 5 min to a pressure of 200 mmHg or at least a pressure that was 40 mmHg higher than the systolic arterial pressure, followed by 5–10 min reperfusion (with the cuff deflated).

Cognitive function was measured by different neuropsychological tests that covered various cognitive domains. The most common tests were the trail making test (TMT),[9,10,15,16] digit span test,[9,10,16] Mini-Mental

Table 2: Study characteristics

No.	Authors	Country	Number of patients	Study design	Surgery type	Duration and location of RIPC	Neuropsychological testing
1.	Gasparovic *et al*. 2019[15]	Croatia	70	RCT	On-pump CABG	Upper limb, 3 × 5 min, after anesthetic induction	MOCA, TMT-A, and TMT-B
2.	Joung *et al*. 2013[9]	South Korea	70	RCT	Off-pump CABG	Upper limb, 4 × 5 min, before coronary artery anastomosis	SVLT, digit span (forward and backward) test, TMT-A, TMT-B, and DSST
3.	Meybohm *et al*. 2013[10]	Germany	180	RCT	On-pump CABG	Upper limb, 4 × 5 min, after anesthetic induction	MMSE, RAVLT: RAVLT 1-3, RAVLT LT, Purdue Pegboard Test, STROOP I, STROOP II, STROOP III, TMT, digit span (forward and backward) test, DSST, executive function, and VFT (semantic and phonetic)
4.	Meybohm *et al*. 2018[16]	Germany	1,403	RCT	On-pump CABG	Upper limb, 4 × 5 min, after anesthetic induction	MMSE, RAVLT: RAVLT 1-3, RAVLT, Purdue Pegboard Test, STROOP I, STROOP II, STROOP III, TMT, digit span (forward and backward) test, DSST, executive function, and VFT (semantic and phonetic)
5.	Zhu *et al*. 2022[7]	China	120	RCT	On-pump CABG	Upper limb, 3 × 5 min, after anesthetic induction	NSE, MMSE, and MOCA

DSST=Digit Symbol Substitution Test, MMSE=Mini–Mental State Examination, MOCA=Montreal Cognitive Assessment, NSE=Neuron-specific enolase (NSE), RAVLT=Rey's Auditory Verbal Learning Test, RAVLT LT=Rey's auditorial verbal learning test long-term memory, RCT=Randomized Controlled Trial, STROOP=Stroop Color Word Interference Test, SVLT=Seoul Verbal Learning Test, TMT=Trail Making Test, VFT=Verbal Fluency Test

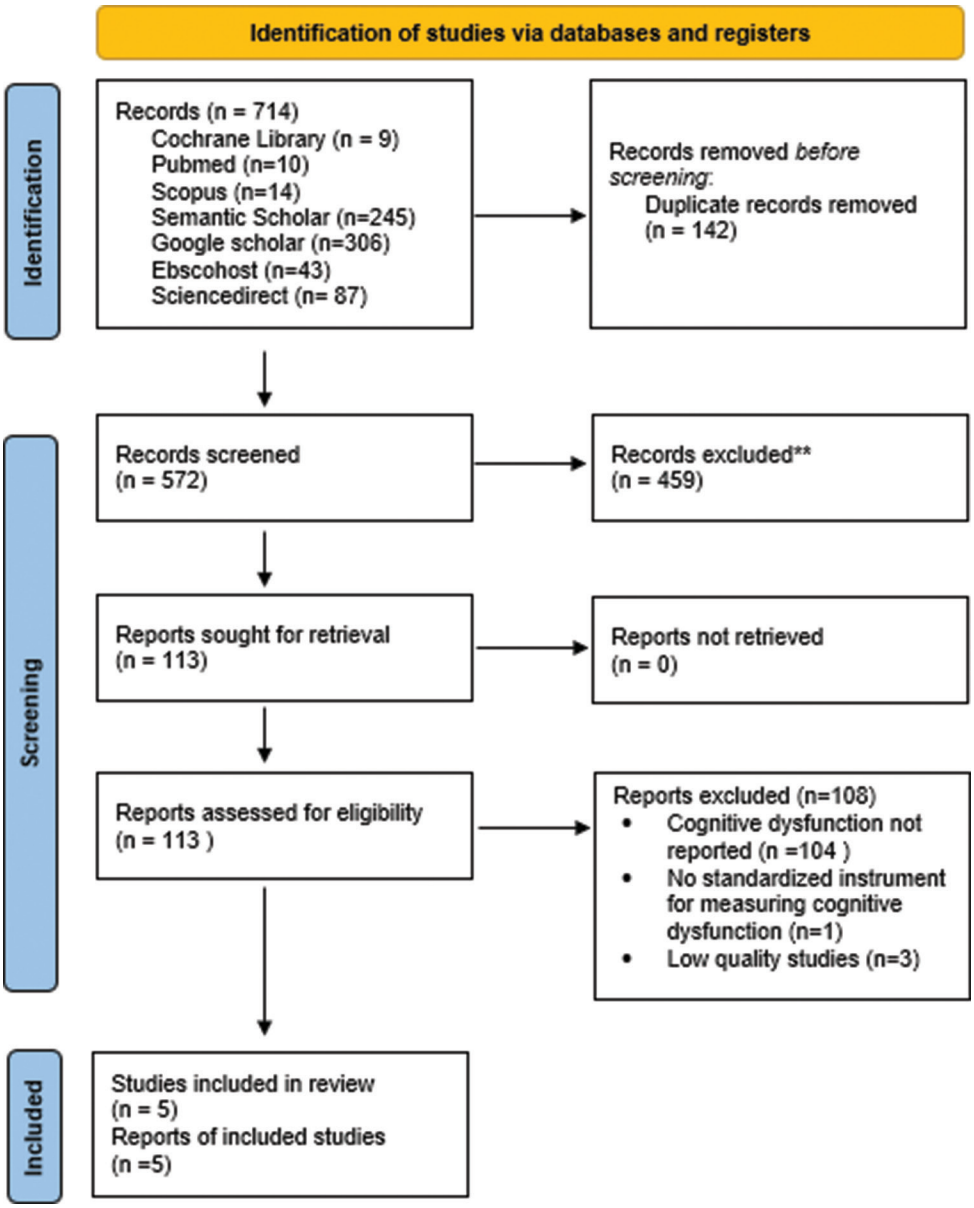

Figure 1: PRISMA flow diagram

State Examination (MMSE),[7,10,16] the Montreal Cognitive Assessment (MOCA),[7,15] Rey's auditorial verbal learning test long-term memory (RAVLT),[10,16] and verbal fluency test (VFT).[10,16] Cognitive decline was defined differently by each study, based on either absolute or relative changes in cognitive function scores or clinical cut-offs. However, the findings of the included studies were inconsistent and inconclusive. Two RCTs[7,15] reported that RIPC might help attenuate cognitive dysfunction, whereas the remaining three RCTs[9,10,16] found no significant difference between RIPC and control groups.

Study quality

Table 3 presents the quality and risk of bias. All studies reported the use of randomization methods and adequate allocation concealment. Additionally, all studies reported adequate blinding of participants and personnel. It is worth noting that all studies received a rating of 7 for the risk of bias, indicating good-quality studies (low risk of bias).

Meta-analysis result

Figure 2 showed forest plot of the collected study. Pooled meta-analysis showed that RIPC did not significantly affect the incidence of POCD (five RCTs, OR = 0.79, 95% CI = 0.56–1.11) with no reported heterogeneity (I^2 = 19%). Forest plots for POCD improvement also showed similar findings, with no impact of RIPC on POCD improvement (three RCTs, OR = 0.80, 95% CI = 0.50–1.27) with no heterogeneity (I^2 = 0%). We used SMD to analyze the influence of RIPC on specific cognitive function tests

Table 3: Risk of bias assessment

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome assessment	Selective reporting	Other bias	Total
Gasparovic *et al*. 2019[15]	Low	Low	Low	Low	Low	Low	Low	Low
Joung *et al*. 2013[9]	Low	Low	Low	Low	Low	Low	Low	Low
Meybohm *et al*. 2013[10]	Low	Low	Low	Low	Low	Low	Low	Low
Meybohm *et al*. 2018[16]	Low	Low	Low	Low	Low	Low	Low	Low
Zhu *et al*. 2022[7]	Low	Low	Low	Low	Low	Low	Low	Low

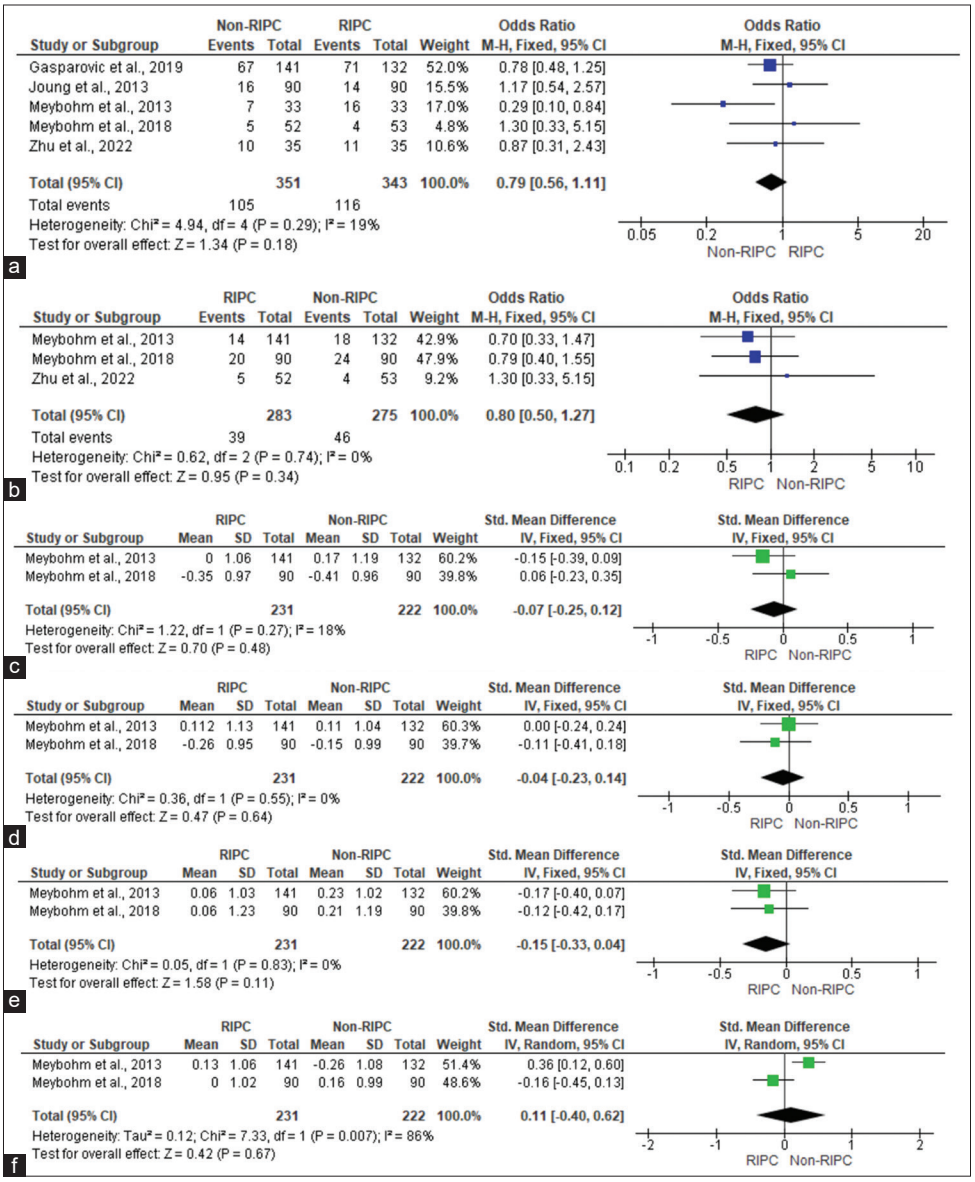

Figure 2: Meta-analysis result. Note: (a). Postoperative cognitive dysfunction (POCD), (b). POCD improvement, (c). Rey's auditory verbal learning test/ RAVLT 1-3, (d). RAVLT long-term memory, (e). verbal fluency test/VFT Semantic, (f). VFT phonetic

such as Rey's auditorial verbal learning test long-term memory (RAVLT LT) and verbal fluency test for semantic and phonetic (VFT). The pooled SMD for RAVLT 1-3 and RAVLT LT were −0.07 (95% CI = −0.25, 0.12) and −0.04 (95% CI = −0.25, 0.12), respectively. Meanwhile, VFT semantic and phonetic were −0.15 (95% CI = −0.33, 0.04) and 0.11 (95% CI = −0.40, 0.62), respectively. These results indicated that RIPC was not associated with improvement in specific cognitive function test, particularly those that assessed long-term memory. We did not perform sensitivity analysis

and funnel plot analysis due to the low amount of included studies and the low heterogeneity of pooled studies.[17]

Discussion

We screened the study using the PRISMA guidelines and evaluated its quality. All five studies included were evaluated as high-quality (low RoB). Two randomized controlled trials revealed that RIPC enhanced cognitive performance following CABG, whereas three randomized controlled trials found no meaningful difference between the RIPC and control groups. Previously, it had been proposed that RIPC's neuroprotective impact was linked to a variety of processes, including ischemia endurance generated by anti-inflammation, anti-oxidative, anti-apoptosis, anti-excitotoxicity, and mitochondrial protection.[18] However, recent findings found that RIPC was also not associated with enhancement on particular cognitive function tests, notably those that examined long-term memory, such as RAVLT LT and VFT. Several factors, including ischemic/reperfusion injury, hormonal changes, accumulation of inflammatory mediators, and RIPC duration, could influence these findings.[19,20]

Our findings are consistent with previous reviews that suggested that RIPC did not positively impact cognitive function in post-CABG patients. Healy *et al.*,[21] in their study of RIPC effect on clinical endpoints, did not measure cognitive dysfunction directly and found no effect in preventing stroke. Consistent with this finding, a recent meta-analysis found that RIPC was unable to prevent the incidence of POCD and postoperative delirium in adults after cardiac surgery.[22]

POCD development could be caused by several pathways, albeit a definitive reason has yet to be identified. POCD is thought to be linked to systemic inflammatory response syndrome (SIRS) produced by cardiopulmonary bypass or heart surgery. However, a recent investigation discovered that even without a cardiopulmonary bypass, the frequency of POCD remained identical. This could be attributed to the non-specific inflammatory response induced by heart surgery.[23,24] In contrast, research investigating the efficacy of RIPC in stroke patients suggested that it may ameliorate cognitive dysfunction through an assortment of mechanisms. These include anti-inflammatory pathways, increased endogenous fibrinolytic activity, and decreased endogenous coagulation activity and platelet aggregation.[25] By promoting vascular remodeling, specifically arteriogenesis, and angiogenesis, RIPC can prevent or improve cognitive impairment. This increase in cerebral blood flow (CBF) is critical for ensuring adequate cerebral supply after acute or chronic CBF reduction and preventing cognitive deterioration.[26]

Patient-related factors may account for the lack of a substantial effect of RIPC on cognitive impairment. The presence of microemboli in the carotid and cerebral arteries caused by atherosclerosis is recognized to play a substantial role in the pathophysiology of POCD.[27] As a consequence, adjusting for the presence of microemboli may yield more trustworthy results. Other patient-related variables, such as advanced age, dehydration, hypovolemia, and perioperative hemorrhage, may also contribute to the complexity of variables controlling future RCTs. Furthermore, the extent to which RIPC reduces the inflammatory response caused by cardiac bypass is insufficient, resulting in a high incidence of POCD.[28]

There are various limitations to our study. We only considered RCTs published in peer-reviewed publications in English, which could introduce language and publication bias. The number of studies collected was small, restricting further research and raising the possibility of bias. However, we perform a thorough search across many databases using rigorous inclusion and exclusion criteria. In addition, we adopted a rigorous and systematic procedure for screening, obtaining, and analyzing data from the included research. Future studies comparing RIPC to POCD should consider patient-related risk factors such as evidence of microemboli on the carotid artery, perioperative hypovolemia, advanced age, and other confounding factors.

Conclusion

The effect of RIPC on cognitive performance in CABG patients remained insignificant. Due to uneven results across trials, the existing evidence is insufficient to justify the use of RIPC as a neuroprotective or neuroenhancing treatment in CABG patients. More high-quality RCTs with larger numbers of participants, standardized protocols, and extended follow-up periods are required to clarify this issue and provide recommendations for clinical practice.

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Conflicts of interest
There are no conflicts of interest.

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