β-Blockers and Volatile Anesthetics May Attenuate Cardioprotection by Remote Preconditioning in Adult Cardiac Surgery: A Meta-analysis of 15 Randomized Trials

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Objective: **Clinical trials on cardioprotection by remote ischemic preconditioning (RIPC) for adult patients undergoing cardiac surgery revealed mixed results. Previous meta-analyses have been conducted and found marked heterogeneity among studies. The aim of this meta-analysis was to evaluate the factors affecting cardioprotection by remote preconditioning in adult cardiac surgery.**

Design: **A meta-analysis of randomized controlled trials.**

Setting: **University hospitals.**

Participants: **Adult subjects undergoing cardiac surgery.**

Interventions: **RIPC.**

Measurements and Main Results: **Fifteen trials with a total of 1,155 study patients reporting postoperative myocardial biomarker (CK-MB or troponin) levels were identified from PubMed, Embase, and the Cochrane Library (up to July 2012). Compared with controls, RIPC significantly reduced postoperative biomarkers of myocardial injury (standardized mean difference = −0.31, $p = 0.041$; heterogeneity test: $I^2 = 83.5\%$). This effect seemed more significant in valve surgery (standardized mean difference = −0.74, $p = 0.002$) than in coronary artery surgery (standardized mean difference = −0.23; $p = 0.17$). Univariate meta-regression analyses suggested that the major sources of significant heterogeneity were β-blockers (%) (coefficient = 0.0161, $p = 0.022$, adjusted $R^2 = 0.37$) and volatile anesthetics (coefficient = 0.6617, $p = 0.065$, adjusted $R^2 = 0.22$). These results were further confirmed in multivariate regression and subgroup analyses.**

Conclusions: **Available data from this meta-analysis further confirmed the cardioprotection conferred by RIPC in adult cardiac surgery. Moreover, the cardioprotective effect may be attenuated when combined with β-blockers or volatile anesthetics.**

KEY WORDS: remote ischemic preconditioning, cardioprotection, adult, cardiac surgery

ACUTE MYOCARDIAL INJURY is associated with increased mortality and morbidity after adult cardiac surgery.[1] Despite cardioplegic arrest, the incidence of perioperative myocardial infarction remains high (≈9.8%).[2] Hence, additional strategies should be considered for better protection, especially in those with high-risk status (ie, advanced age, diabetes mellitus, and prolonged cross-clamp time), to increase myocardial tolerance to sustained ischemia.[3]

Remote ischemic preconditioning (RIPC) was first introduced by Przyklenk et al[4] in 1993. By applying several cycles of transient ischemic stimulus to a remote organ (mostly a limb), RIPC has been proven to provide protection from reperfusion injury of the heart, kidney, and brain in various animal models since the early 1990s.[5] As a novel endogenous noninvasive approach, RIPC has been drawing the attention of cardiovascular clinicians. Randomized clinical trials of RIPC in cardiovascular surgery have revealed promising results concerning its effect on postoperative cardiac biomarkers.[6-8] Previous meta-analyses on this topic have been conducted and found that there was marked heterogeneity, especially in adult cardiac surgery.[9,10] However, few of these studies have investigated further the potential sources of heterogeneity.

Recently, randomized controlled trials (RCTs) regarding cardioprotection by RIPC for adult patients undergoing cardiac surgery revealed mixed results.[11-18] Therefore, the present authors conducted a systematic review and meta-analysis to re-evaluate the cardioprotective effect of RIPC and the affecting factors in adult cardiac surgery.

METHODS

Search Strategy and Study Criteria

The authors searched PubMed, Embase, and the Cochrane Library up to July 2012 using the following key words: "remote ischemic preconditioning," "limb ischemic preconditioning," "cardiac surgery," "heart surgery," "myocardial injury," and "cardioprotection." The inclusion criteria were as follows: prospective RCTs published in English, studies involving adult patients undergoing cardiac surgery, and studies that reported postoperative CK-MB or troponin levels. The exclusion criteria were studies only reporting nonmyocardial biomarkers, studies using RIPC in combination with another concomitant intervention, and studies in which RIPC was implemented before the surgical day.

Study Selection, Quality Assessment, and Data Extraction

Two investigators (YL and YY) independently reviewed all abstracts and included the full text in duplicate according to the described search strategy and criteria. A third reviewer (SZ) assessed the eligible studies for consensus in case of disagreement. A quality assessment was completed in accordance with the Jadad score, which includes randomization, blinding, and withdrawals and dropouts (with a possible score between 0 and 5). Trials with a score of more than 3 were considered to be high-quality studies.[19] Data extraction of the study characteristics included the trial design (ie, year, country, surgery, conditioning protocol, and anesthesia) and demographic data (ie, age, male, diabetes mellitus, cross-clamp duration, preoperative myocardial infarction, hypertension, statins, β-blockers, and cardioplegia).

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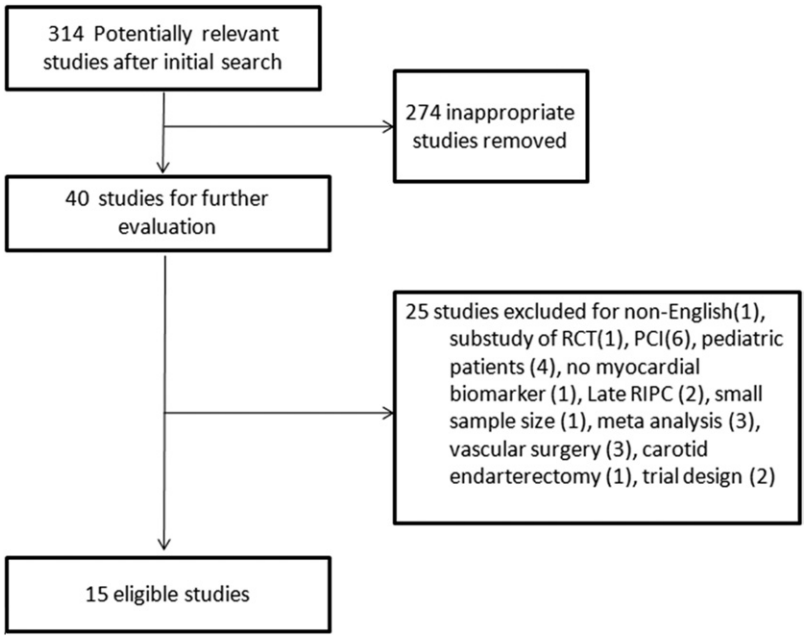

Fig 1. The search process for eligible studies of RIPC in adult cardiac surgery. RCT, randomized controlled trial; PCI, percutaneous coronary intervention.

Postoperative Measurements

The primary endpoint was postoperative CK-MB or troponin levels. The area under the curve (AUC) of the total serum troponin levels was preferable in the analysis for its potential superiority. If AUC data were not available, CK-MB or troponin levels were used. The secondary endpoints were mortality, mechanical ventilation duration, intensive care unit stay, and hospital length of stay.

Data Synthesis and Analysis

Standardized mean differences (SMDs), which are obtained by dividing the mean difference by the standard deviation of measurements, with 95% confidence intervals (CIs) were calculated for postoperative CK-MB or troponin levels with different scales in the primary analysis. For the secondary analysis, heterogeneity was explored by using I^2. A random-effects model was used for the analysis in case of significant heterogeneity among trials ($I^2 \geq 50\%$). Publication bias was assessed using the Begg's and Egger's tests. Further exploration for the potential sources of significant heterogeneity was conducted by meta-regression (a p value of <0.1 was accepted) and subgroup analyses. A p value <0.05 (2-sided) was considered statistically significant in the hypothesis test. All statistical analyses were performed by REVMAN (version 5.0; Cochrane Collaboration, Oxford, UK) and Stata (version 11.0; StataCorp, College Station, TX).

RESULTS

Study Characteristics

After 274 abstracts were excluded from the initial search because of irrelevant content, duplicate publications, or a nonclinical design, 40 potential studies were selected for detailed evaluation. Among the articles retrieved in a complete form, 6 were excluded for percutaneous coronary intervention, 4 for vascular surgery, 4 for pediatric cardiac surgery, 3 for a meta-analysis design, 2 for an ongoing trial, and 6 for other reasons. The search process is displayed in Figure 1. The authors excluded 1 of the 2 comparisons in Wu et al's trial[13] in which the cardiac biomarker levels abnormally decreased more than 6 times to reduce the potential bias (SMD = −3.341 v −0.577). One of the 2 comparisons from Li et al's trial[20] was not included because remote ischemic conditioning was conducted during cardiac arrest. The authors divided Kottenberg et al's study into 2 comparisons because of the totally different substudy designs (expressed as Kottenberg et al I and Kottenberg et al II). Finally, the search included 15 RCTs with 16 comparisons and enrolled 1,155 adult patients from 9 countries.[6,11-18,20-25] Four were conducted in the United Kingdom[6,11,12,21]; 3 in China[13,14,20]; and the others in Korea,[22,25] Germany,[17,23] Canada,[15] New Zealand,[18] Pakistan,[24] and Russia.[16] Ten[6,11,12,15-17,21-24] studies focused on coronary artery bypass graft (CABG) surgery, four[13,14,20,25] on valve surgery, and one[18] on combined surgery. Eight studies had a Jadad score of more than 3 points.[6,11,12,14,15,18,20,22,24,25] For myocardial biomarkers, troponin I or T was used in 13 studies (11 reported AUC within 48 hours[11,12,16] or 72 hours[6,14,15,17,20-23]) and CK-MB in only 2.[24,25] Twelve comparisons in 12 studies[11,12,15-18,20-25] were balanced with volatile agents (ie, sevoflurane, isoflurane, enflurane, or halothane). Ten studies[11-14,18,20,21,24-26] used blood cardioplegia, and 3[16,17,23] used only crystalloid solution for cardiac arrest. The study characteristics are summarized in Tables 1 and 2.

Postoperative Measurements

The overall pooled analysis revealed a significant decrease in postoperative myocardial enzyme levels by RIPC, with a