

Effects of on-pump versus off-pump coronary artery bypass grafting on myocardial metabolism

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Abstract

Background: On-pump coronary artery bypass grafting (ON-PCABG) and off-pump coronary artery bypass grafting (OF-PCABG) greatly affect myocardial metabolism (MCMB). However, no study has systematically explored and compared the impacts of ON-PCABG and OF-PCABG on MCMB. This study will aim to explore and to compare the effects of ON-PCABG and OF-PCABG on MCMB systematically.

Methods: We will conduct the comprehensive literature search from the following electronic databases from inception to the present: Cochrane Library, EMBASE, MEDLINE, CINAHL, AMED and 4 Chinese databases without language restrictions. This systematic review will only concern randomized controlled trials (RCTs) and case-control studies of ON-PCABG and OF-PCABG on MCMB. The methodological quality of each entered study will be assessed by using Cochrane risk of bias tool.

Results: Primary outcomes include myocardial cellular markers, myocardial lactate, oxygen utilization, pyruvate, and intramyocardial concentrations of glucose, urea and lactate. Secondary outcome comprises of glutathione, superoxide dismutase, myeloperoxidase, and oxidative stress and any other complications post surgery.

Conclusion: This study will provide a high-quality synthesis and will assess and compare the effects of ON-PCABG and OF-PCABG on MCMB based on the current relevant literature evidence.

Dissemination and ethics: The results will be submitted to peer-reviewed journals for publication. This study does not require ethic approval, because it only analyzes the data from published literature.

Systematic review registration: PROSPERO CRD42019125381.

Abbreviations: AMED = Allied and Complementary Medicine Database, CABG = coronary artery bypass grafting, CINAHL = Cumulative Index to Nursing and Allied Health Literature, MCMB = myocardial metabolism, RCTs = randomized controlled trials.

Keywords: coronary artery bypass grafting, effects, myocardial metabolism, safety, systematic review

1. Introduction

Postoperative myocardial damage has been reported in several studies in patients receiving coronary artery bypass grafting (CABG) surgery.^[1-4] Its rate, degree and recovery mainly depend on the preoperative cardiac status, types of surgery, myocardial protection, and also the types of CABG, including on-pump coronary artery bypass grafting (ON-PCABG) and off-pump coronary artery bypass grafting (OF-PCABG).^[5-8] Previous

studies have reported that the portion of morbidity associated with cardiopulmonary bypass mainly contributed to the inflammatory, immune responses, and intraoperative myocardial damage.^[9-11]

Actually, multiple mediator factors may result in tissue damage through myocardial metabolism (MCMB).^[12-16] Although a variety of studies have reported the effects of ON-PCABG and OF-PCABG on myocardial metabolism (MCMB),^[17-22] no study has systematically assessed and compared the effects of ON-PCABG with OF-PCABG on MCMB. Therefore, in this systematic review, we will assess and compare the effects of ON-PCABG and OF-PCABG CABG on MCMB.

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2. Methods and design

2.1. Objective

This aims of this systematic review is to investigate and compare the effects of ON-PCABG and OF-PCABG CABG on MCMB.

2.2. Study registration

This systematic review protocol has been registered on PROSPERO with number of CRD42019125381. The report this study has based on the guideline of Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting

Table 1**Search strategy utilized in Cochrane Library database.**

Number	Search terms
1	Mesh descriptor: (coronary artery bypass) explode all trees
2	Mesh descriptor: (coronary artery bypass, off-pump) explode all trees
3	((coronary [*]) or (artery bypass [*]) or (off-pump [*]) or (on-pump [*]) or (heart attack [*]) or (heart diseases [*])):ti, ab, kw
4	Or 1–3
5	MeSH descriptor: (myocardium) explode all trees
6	MeSH descriptor: (metabolism) explode all trees
7	((myocardium [*]) or (myocardial [*]) or (metabolism [*]) or (metabolic [*]) or (networks [*]) or (metabolic networks and pathways [*]) or (metabolic networks and pathways [*])):ti, ab, kw
8	Or 5–7
9	(advanced nursing care) explode all trees
10	((care [*]) or (psychological care [*]) or (nursing care [*]) or (nursing [*]) or (advanced care [*]) or (health care [*])):ti, ab, kw
11	Or 9-10
12	MeSH descriptor: (randomized controlled trial) explode all trees
13	MeSH descriptor: (case-control studies) explode all trees
14	((controlled trial [*]) or (clinical trial [*]) or (placebo [*]) or (sham [*]) or (randomly [*]) or (randomized [*]) or (trial [*]) or (study [*]) or (case-control [*]) or (case [*]) or (control [*]) or (case control study [*])):ti, ab, kw
15	Or 12-14
16	4 and 8 and 11 and 15

Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) statement guidelines.^[2,3]

2.3. Inclusion criteria for study selection

2.3.1. Type of studies. This systematic review protocol will include randomized controlled trials (RCTs) and case-control studies of ON-PCABG and OF-PCABG CABG on MCMB. The other types of studies will be excluded, including non-clinical studies, case reports, and case series.

2.3.2. Type of participants. Patients with coronary heart disease of any age underwent ON-PCABG or OF-PCABG, regardless males or females will be all considered for inclusion. However, patients with severe chronic obstructive lung disease will be excluded.

2.3.3. Type of interventions. Intervention of ON-PCABG will be included in the experimental group. However, the combination of ON-PCABG with other treatments will be excluded. Control intervention can include OF-PCABG CABG alone.

2.3.4. Type of outcome measurements. Primary outcomes include myocardial cellular markers, myocardial lactate, oxygen utilization, pyruvate, and intramyocardial concentrations of glucose, urea, and lactate.

Secondary outcome comprises of glutathione, superoxide dismutase, myeloperoxidase, and oxidative stress. In addition, complications post surgery will also be assessed.

2.4. Search methods for the identification of studies

2.4.1. Electronic searches. We will search the comprehensive relevant studies from the following databases from the inception to the present: Cochrane Library, EMBASE, MEDLINE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED), Chinese Biomedical Literature Database, China National Knowledge Infrastructure, VIP Information, and Wanfang Data. Any randomized controlled trials (RCTs) and case-control studies concerning the effects of ON-PCABG and OF-PCABG CABG will be fully considered for inclusion. The

sample size of search strategy for Cochrane Library is presented in Table 1. Identical search strategies for other electronic databases will be built and applied.

2.4.2. Search for other resources. Aside from the above 9 electronic databases, the sources of clinical registry and reference list of relevant studies will also be checked to avoid missing any potential eligible studies.

2.5. Data collection and analysis

2.5.1. Study selection. Two review authors will independently conduct the study selection by scanning the titles and abstract summary, as well as reading the full-texts if it is necessary according to the predefined eligibility criteria. The whole procedure of the study selection is abided by the PRISMA flow chart, and it is presented in Figure 1. A third review author will be invited to solve the disagreements between the 2 review authors.

2.5.2. Data extraction and management. Two review authors will independently carry out the data extraction based on the predefined data extraction sheet. It includes the following information, such as title, first author, published year, location, disease diagnosis, inclusion and exclusion criteria, sample size, age, randomization, allocation, blinding, treatment details, and outcome measurements. A third review author will be consulted if any divergences regarding the data extraction will occur between 2 review authors.

2.5.3. Dealing with missing data. If any data are missing, incorrect, insufficient, or unclear, the primary authors will be contact by email to inquire those data. If we will not receive any reply, then the available data will be analyzed, and its impact will be discussed in the manuscript.

2.5.4. Risk of bias assessment. We will utilize the Cochrane Handbook for Systematic Reviews of Interventions tool to assess the risk of bias for each included RCT. This tool comprises of seven domains, and we will assess each domain as high risk of bias, or unclear risk bias, or low risk of bias. Two review authors will independently assess the risk of bias for each domain in each included RCT. A third review author will resolve the disagreements by discussion if they exist between 2 review authors.

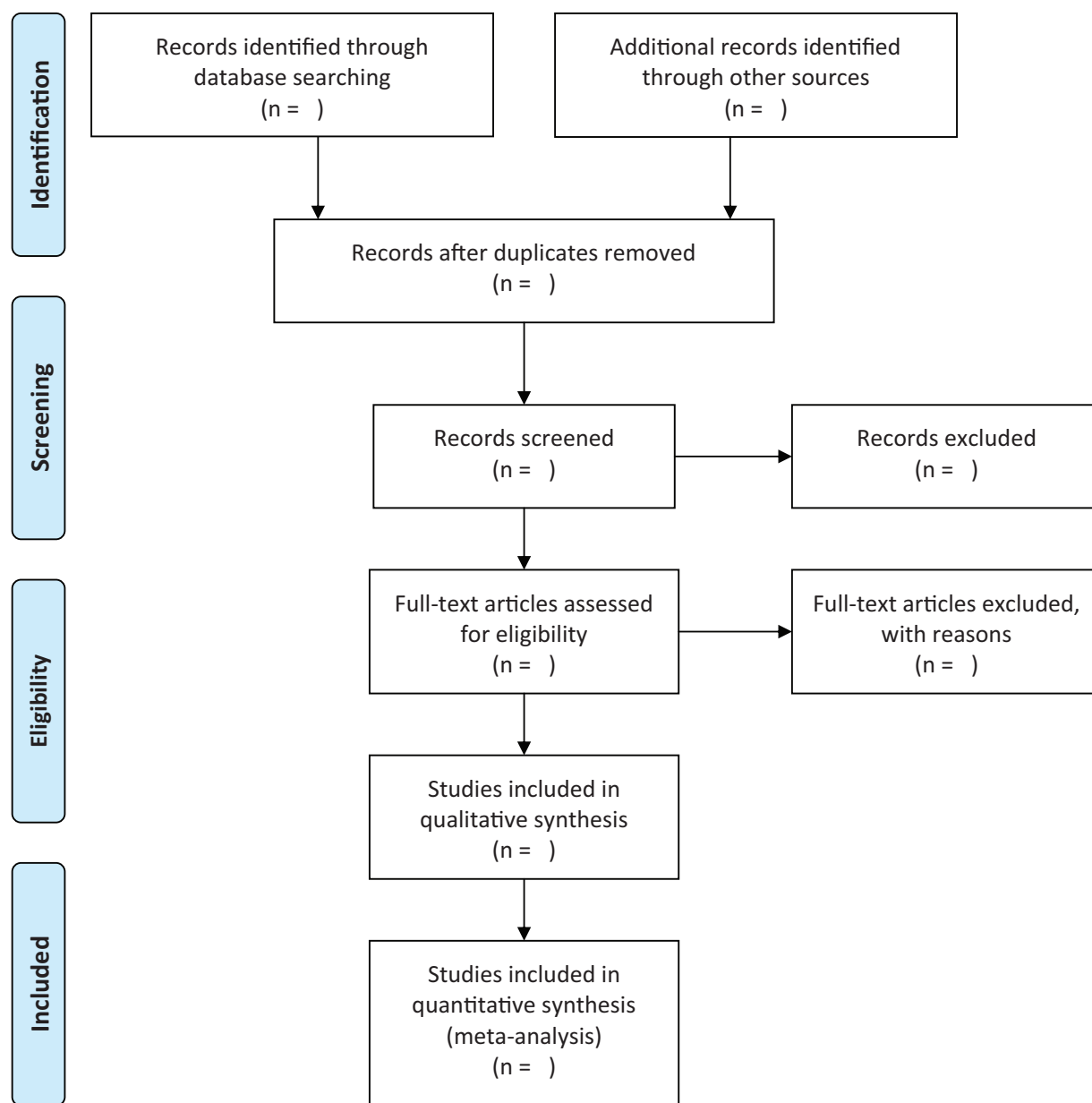


Figure 1. Flow diagram of study selection process.

2.5.5. Measurement of treatment effect. Enumeration data will be expressed as risk ratio and 95% confidence intervals, while continuous data will be described as mean difference and 95% confidence intervals. If the same outcome measured by different tools, then the data will be converted to the standardized mean difference and 95% confidence intervals.

2.5.6. Assessment of heterogeneity. The heterogeneity will be checked by I^2 test. If the value of I^2 is less than 50%, the heterogeneity is regarded as acceptable, and a fixed-effect model will be used to pool the data. If the value of I^2 is more than 50%, significant heterogeneity will be considered, and a random-effect will be applied to pool the data.

2.5.7. Data synthesis. If the heterogeneity is acceptable, the data will be pooled by using a fixed-effect model, and a meta-

analysis will be carried out by using RevMan 5.3 software. Otherwise, if the heterogeneity is substantial, the data will be pooled by using a random-effect model, and a subgroup analysis will be conducted. If the heterogeneity is acceptable (normally $I^2 \leq 50\%$) after the subgroup analysis, a meta-analysis will be performed. Otherwise, the data will not be pooled and a meta-analysis will not be carried out anymore. Instead, a narrative summary will be described.

2.5.8. Subgroup analysis. Subgroup analysis will be performed in accordance with the different interventions, controls, and outcome measurements.

2.5.9. Sensitivity analysis. Where appropriate, sensitivity analysis will be conducted to check the robust of the pooled data by eliminating the impact of low-quality studies.

2.5.10. Publication biases. Funnel plot will be carried out if sufficient studies are included (normally more than 10 studies).^[24] In addition, we will also conduct Egg regression for quantitative analysis.^[25]

3. Discussion

This study will be performed to evaluate and compare the effects of ON-PCABG and OF-PCABG on MCMB based on the current relevant clinical literature evidence. To our best knowledge, it is the first systematic study to assess and compare the effects of ON-PCABG and OF-PCABG on MCMB. Its results will summarize latest evidence on the effects of ON-PCABG and OF-PCABG on MCMB. This evidence may be very helpful for the future researchers and clinical practice.

Author contributions

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Writing – review & editing: Hong-Tao Xie, Shun Zhang, Yong-Cang Tian, De-Jun Liu, Ben-Jian Bai.

References

- [1] van Boxtel AG, Bramer S, Soliman Hamad MA, et al. Perioperative serum aspartate aminotransferase level as a predictor of survival after coronary artery bypass grafting. *Ann Thorac Surg* 2012;94:1492–8.
- [2] Berg K, Langaas M, Ericsson M, et al. Acetylsalicylic acid treatment until surgery reduces oxidative stress and inflammation in patients undergoing coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2013;43:1154–63.
- [3] Antonitsis P, Anastasiadis K, Koliakos G, et al. Intramyocardial implantation of autologous bone marrow-derived stem cells combined with coronary artery bypass grafting in patients with ischemic cardiomyopathy: a pilot study. *Hippokratia* 2012;16:366–70.
- [4] Castaño M, González-Santos JM, López J, et al. Effect of preoperative oral pravastatin reload in systemic inflammatory response and myocardial damage after coronary artery bypass grafting. A pilot double-blind placebo-controlled study. *J Cardiovasc Surg (Torino)* 2015;56:617–29.
- [5] Yakut N, Tulukoğlu E, Emrecan B, et al. Which is first: left anterior descending artery anastomosis or right coronary artery anastomosis in off-pump coronary artery bypass grafting? *Heart Surg Forum* 2009;12:E256–60.
- [6] Balciunas M, Bagdonaite L, Samalavicius R, et al. Pre-operative high sensitive C-reactive protein predicts cardiovascular events after coronary artery bypass grafting surgery: a prospective observational study. *Ann Card Anaesth* 2009;12:127–32.
- [7] Tempe DK, Dutta D, Garg M, et al. Myocardial protection with isoflurane during off-pump coronary artery bypass grafting: a randomized trial. *J Cardiothorac Vasc Anesth* 2011;25:59–65.
- [8] Haneya A, Philipp A, Diez C, et al. Myocardial protection in patients undergoing coronary artery bypass grafting surgery using minimized extracorporeal circulation in combination with volatile anesthetic. *ASAIO J* 2010;56:532–7.
- [9] Bull DA, Neumayer LA, Stringham JC, et al. Coronary artery bypass grafting with cardiopulmonary bypass versus off-pump cardiopulmonary bypass grafting: does eliminating the pump reduce morbidity and cost? *Ann Thorac Surg* 2001;71:170–5.
- [10] Ben-Abraham R, Weinbroum AA, Lotan D, et al. Interleukin-8 secretion following cardiopulmonary bypass in children as a marker of early postoperative morbidity. *Paediatr Anaesth* 2002;12:156–61.
- [11] Salis S, Mazzanti VV, Merli G, et al. Cardiopulmonary bypass duration is an independent predictor of morbidity and mortality after cardiac surgery. *J Cardiothorac Vasc Anesth* 2008;22:814–22.
- [12] Hong X, Fan H, Lu R, et al. Merit of anisodamine combined with opioid (-receptor activation in the protection against myocardial injury during cardiopulmonary bypass. *Biomed Res Int* 2013;2013:212801.
- [13] Zitta K, Meybohm P, Bein B, et al. Activities of cardiac tissue matrix metalloproteinases 2 and 9 are reduced by remote ischemic preconditioning in cardiosurgical patients with cardiopulmonary bypass. *J Transl Med* 2014;12:94.
- [14] Nguyen BA, Suleiman MS, Anderson JR, et al. Metabolic derangement and cardiac injury early after reperfusion following intermittent cross-clamp fibrillation in patients undergoing coronary artery bypass graft surgery using conventional or miniaturized cardiopulmonary bypass. *Mol Cell Biochem* 2014;395:167–75.
- [15] Zakkar M, Guida G, Suleiman MS, et al. Cardiopulmonary bypass and oxidative stress. *Oxid Med Cell Longev* 2015;2015:189863.
- [16] De Hert S, Moerman A. Myocardial injury and protection related to cardiopulmonary bypass. *Best Pract Res Clin Anaesthesiol* 2015;29:137–49.
- [17] Mantovani V, Kennergren C, Bugge M, et al. Myocardial metabolism assessed by microdialysis: a prospective randomized study in on- and off-pump coronary bypass surgery. *Int J Cardiol* 2010;143:302–8.
- [18] Drenger B, Gilon D, Chevion M, et al. Myocardial metabolism altered by ischemic preconditioning and enflurane in off-pump coronary artery surgery. *J Cardiothorac Vasc Anesth* 2008;22:369–76.
- [19] Sahlman A, Ahonen J, Nemlander A, et al. Myocardial metabolism on off-pump surgery; a randomized study of 50 cases. *Scand Cardiovasc J* 2003;37:211–5.
- [20] Wang JY. Clinical analysis of 143 patients with coronary heart disease who underwent extracorporeal circulation and coronary artery bypass grafting. 2010; Shandong University, (Doctorial Dissertation).
- [21] Chen YY, Ren S, Fu Q, et al. Changes of cardiotrophin-1 and brain natriuretic peptide after off-pump coronary artery bypass grafting. *Tianjin Med J* 2009;37:823–5.
- [22] Wang X. Changes of myocardial injury markers after in on- and off-pump coronary artery bypass grafting. *Qingdao Med J* 2008;30:90–2.
- [23] Shamseer L, Moher D, Clarke M, et al. PRISMA-P Group Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
- [24] Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at: <http://www.cochrane-handbook.org>. Accessed December 10, 2018.
- [25] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.