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Clinical effect of postconditioning in ST-elevation myocardial infarction patients treated with primary percutaneous coronary intervention: a meta-analysis of randomized controlled trials*

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Abstract: Objective: To evaluate the clinical effect of postconditioning on patients with ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI). Methods: Randomized controlled trials were identified by searching relevant databases published up to April 2nd, 2014. A meta-analysis of eligible studies was performed by Stata 12.0 and Review Manager 5.2 with a fixed-effect model. Results: Ten studies providing adverse cardiac events in a total of 1346 STEMI patients treated with primary PCI were identified. The occurrence of heart failure was significantly reduced in patients treated with postconditioning compared with usual care (risk ratio (RR) 0.533; 95% confidence intervals (CI) 0.368–0.770), whereas non-fatal reinfarction slightly increased in the postconditioning group (RR 2.746; 95% CI 1.007–7.488). No significant difference in total major adverse cardiac events (MACEs) was observed between the two groups (RR 0.876; 95% CI 0.671–1.144). Conclusions: Postconditioning in STEMI patients undergoing primary PCI significantly reduces the risk of heart failure, but fails to decrease the incidence of total MACEs and the risk of non-fatal reinfarction.

Key words: Myocardial infarction, Postconditioning, Coronary intervention
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1 Introduction

Although the acute treatment and follow-up strategy of patients with acute ST-segment elevation myocardial infarction (STEMI) has improved, the incidence of death or heart failure after STEMI is still high. Reperfusion of the infarct-related artery (IRA), preferably by primary percutaneous coronary intervention (PCI), is the most effective method to limit infarct size, preserve the left ventricular (LV) function, and prevent the development of heart failure (Steg *et al*., 2012) . However, effective restoration of blood flow in the IRA may paradoxically result in further damage to the heart muscle (i.e. reperfusion injury). This phenomenon, occurring within the first minute following reperfusion and responsible for 50% of the final infarct volume as indicated by animal studies (Yellon and Hausenloy, 2007), can exert an adverse effect on the efficacy of primary PCI. Therefore, it is necessary to explore a clinically feasible, applicable, and effective therapeutic strategy to decrease the reperfusion injury and increase the benefit of primary PCI.

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Ischemic preconditioning, referring to repetitive cycles of occlusion-reperfusion conducted just before the longer coronary artery occlusion, was first introduced as an effective method to mitigate reperfusion injury (Murry *et al*., 1986). However, its clinical application has been limited as the occlusion is often established at the admission of a patient for acute myocardial infarction (AMI). Zhao *et al*. (2003) first described postconditioning in which a sequence of repetitive interruption of the coronary blood flow applied immediately after reopening of the occluded vessel remarkably decreased myocardial infarct size in a canine model. Unlike preconditioning, postconditioning can be directly translated into clinical practice, especially in patients undergoing primary PCI. Staat *et al*. (2005) first identified reduction of infarct size measured by creatine kinase using a postconditioning procedure in the human heart. Subsequently, postconditioning has been extensively investigated, and some beneficial effect has been reported, such as improvement of distal myocardial perfusion (Laskey, 2005), enhancement of coronary endothelial function and cardiomyocyte salvage (Ma *et al*., 2006), reduction in myocardial infarct size determined by single-photon emission computed tomography (Yang *et al*., 2007; Thibault *et al*., 2008) or cardiac magnetic resonance (Lønborg *et al*., 2010a), and amelioration of the left ventricular ejection fraction (LVEF) (Thibault *et al*., 2008). Patients treated with postconditioning were suggested to have improved on the New York Heart Association classification (Lønborg *et al*., 2010b). However, recent studies suggested that postconditioning could neither decrease infarct size (Sörensson *et al*., 2010; Freixa *et al*., 2012; Elżbieciak *et al*., 2013) nor increase LVEF in short- or long-term follow-up (Freixa *et al*., 2012; Elżbieciak *et al*., 2013). A multicenter, prospective, and randomized trial observed no improvement of myocardial reperfusion or short-term clinical outcomes in the postconditioning arm (Hahn *et al*., 2013). To date, the clinical role of postconditioning still remains elusive because of such factors as small-sample size, using surrogate end points such as infarct size, coronary flow, or LV function rather than clinical events to evaluate the effect of postconditioning. Therefore, we undertook a meta-analysis focusing on adverse cardiac events to assess postconditioning's clinical effect in STEMI patients treated with primary PCI.

2 Materials and methods

2.1 Literature search

Literature searches were performed to identify all relevant and published randomized, controlled, prospective studies comparing postconditioning with usual care in patients with STEMI through the PubMed, EMBASE, Cochrane Central Register of Controlled Trials database, and the ClinicalTrials.gov database up to April 2nd, 2014. References of all the retrieved articles were also screened and reviewed. No language limitation constraint was applied. The following search terms were used: myocardial infarction, postconditioning, and coronary intervention. We contacted authors of original studies for detailed data if needed.

Criteria for inclusion were as follows: (1) completed randomized, controlled, and prospective trial comparing postconditioning with usual care in STEMI patients treated with primary PCI; (2) study published in peer-reviewed journals with full text available; (3) study reporting one or more kinds of adverse cardiac events including deaths, heart failure, target vessel revascularization (TVR), stent thrombosis, non-fatal reinfarction, and angina. All the three criteria had to be satisfied for inclusion.

2.2 Data extraction and quality assessment

Two investigators (Biao TANG and Jian CHENG) independently performed the literature search, study selection, and data evaluation. Disagreements were resolved by discussion or referred to a third investigator (Shen-wen FU) if necessary. The main information was extracted, including name of the first author, year of publication, article title, study characteristics, and clinical events such as death, heart failure, TVR, stent thrombosis, non-fatal reinfarction, and angina. Major adverse cardiac event (MACE) was defined as a composite of death, heart failure, TVR, stent thrombosis, and non-fatal reinfarction. The bias of each study was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1 (Higgins and Green, 2011).

2.3 Statistical analysis

For discrete variables (events of death, heart failure, TVR, stent thrombosis, reinfarction, angina,

and MACE), we calculated the risk ratio (RR) with 95% confidence interval (CI) comparing the postconditioning group with the control group. The Cochrane Chi-square test was used to examine heterogeneity across studies. The I^2 statistic was calculated as an estimation of the proportion of variation in treatment effect that was due to between-study heterogeneity. A value of 0% meant no heterogeneity, and values of 25%, 50%, and 75% indicated low, moderate, and high, respectively. A fixed-effect model was used to test the overall effect unless there was marked heterogeneity (when the Cochrane Chi-square $P<0.1$ or $I^2>50\%$) in the studies, which required a random-effect model (Kahn and Sempos, 2000). Meta-regression analyses were implemented to investigate potential effect modification by study characteristics (e.g. procedures, risk factors). Subgroup analyses should be conducted if a significant association of study characteristics with effect was identified in meta-regression analyses. Publication bias was assessed by examining the asymmetry of a funnel plot and weighted by the Egger regression test (Egger *et al.*, 1997). In order to assess the study quality, sensitivity analysis was performed by omitting each study at one time and calculating the remaining pooled effect. A two-tailed $P<0.05$ was considered statistically significant. Statistical analysis was conducted by using Stata 12.0 (Stata Corporation, College Station, TX, USA) and Review Manager 5.2 (the Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark).

3 Results

3.1 Study characteristics

After screening a total of 341 eligible publications, we identified 25 potentially relevant articles based on titles and abstracts. Fifteen studies were excluded from the full text assessment for not observing clinical events. Finally, 10 studies were selected for meta-analysis (Fig. 1).

These eligible studies contained 1346 patients, with 674 in the postconditioning group and 672 in the control group. The risk of the bias is presented as percentages across all included studies (Fig. 2). The characteristics of studies included in the meta-analysis are summarized in Tables 1 and 2. The thrombectomy technique and glycoprotein (GP) IIb/IIIa inhibitor were used in five and seven studies, respectively (Table 2). Death and heart failure events were observed in all studies, and non-fatal reinfarction, TVR, stent thrombosis, and angina events were analyzed in six, five, four, and four trials, respectively (Table 3). The detailed information about outcomes of four trials was acquired by sending e-mails to the first author (Lønborg *et al*., 2010a; 2010b; Elżbieciak *et al*., 2013; Sörensson *et al*., 2013).

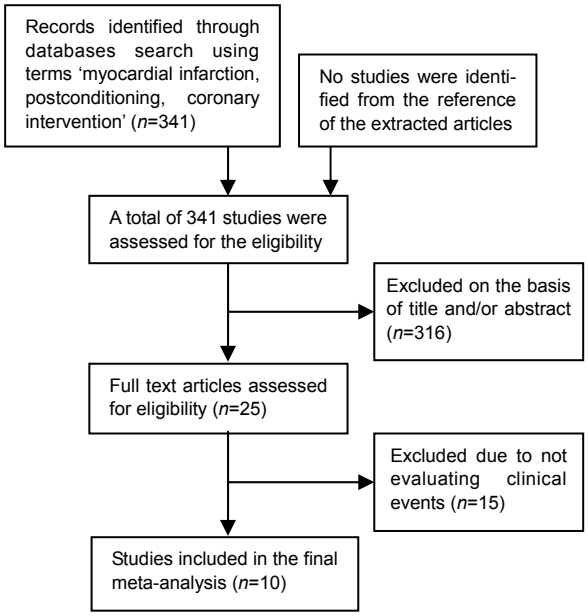

Fig. 1 Flow diagram for assessment and selection of articles

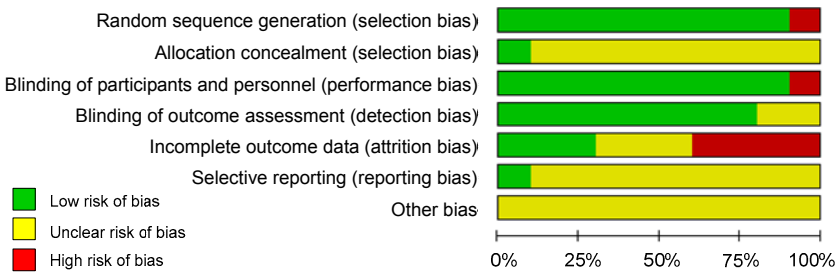

Fig. 2 Risk of bias graph

Review authors' judgments about each risk of bias item presented as percentages across all included studies

Table 1 Characteristics of studies included in the meta-analysis

Study	Country	Number of P/C	Ischemic time of P/C (min)	Postconditioning Protocol*	Number of P/C at TIMI grade 0–1 before PCI
Yang *et al*., 2007	China	23/18	312/264	30 s×3	23/18
Lønborg *et al*., 2010a#	Denmark	59/59	241/255	30 s×4	59/59
Lønborg *et al*., 2010b#	Denmark	59/59	241/255	30 s×4	59/59
Garcia *et al*., 2011	USA	22/21	270/264	30 s×4	22/21
Freixa *et al*., 2012	Spain	39/40	326/330	60 s×4	39/37
Tarantini *et al*., 2012	Italy	39/39	212/194	60 s×4	39/39
Hahn *et al*., 2013	Korea	350/350	196/195	60 s×4	336/331
Elżbieciak *et al*., 2013	Poland	18/21	318/226	60 s×4	18/21
Sörensson *et al*., 2013	Sweden	33/35	180/165	60 s×4	33/35
Dong *et al*., 2013	China	32/30	300/294	30 s×3	32/30

P: postconditioning; C: control; TIMI: thrombolysis in myocardial infarction; PCI: percutaneous coronary intervention. * Data are expressed as duration of balloon inflation×number of inflations. # Lønborg *et al*. (2010a; 2010b) published two articles on the same trial, followed up at 3 and 15 months, respectively

Table 2 Demographic and clinical characteristics of studies included in the meta-analysis

Study	Age (year)	Number of P/C					GP IIb/IIIa inhibitor	Thrombectomy
		Male	Diabetes	Hypertension	Dyslipidaemia	TIMI grade 3 after PCI		
Yang *et al*., 2007	58.6/63.3	20/11	6/5	16/11	14/10	21/16	No	No
Lønborg *et al*., 2010a	61/62	45/47	4/4	22/19	27/24	56/52	Yes	Yes
Lønborg *et al*., 2010b	61/62	45/47	4/4	22/19	27/24	56/52	Yes	Yes
Garcia *et al*., 2011	61/55	19/16	1/4	14/10	16/15	NR	No	No
Freixa *et al*., 2012	59/60	33/29	9/7	19/20	17/14	35/36	Yes	Yes
Tarantini *et al*., 2012	59.6/59.5	33/33	7/1*	23/19	20/19	38/38	Yes	No
Hahn *et al*., 2013	60/60	276/261	84/87	161/159	139/159	321/306	Yes	Yes
Elżbieciak *et al*., 2013	60.1/58.4	12/18	4/5	14/19	11/18	18/21	Yes	No
Sörensson *et al*., 2013	63/62	28/31	9/10	5/11	NR	31/30	Yes	No
Dong *et al*., 2013	70/68.4	20/22	11/11	23/19	NR	26/17	No	Yes

P: postconditioning; C: control; TIMI: thrombolysis in myocardial infarction; GP: glycoprotein; NR: not reported. * P=0.0056, but major adverse events seem to be more frequent in postconditioning group irrespective of diabetic status (P=0.053 for all patients; P=0.080 for patients without diabetes)

Table 3 Summary of outcomes reported in studies included in the meta-analysis

Study	Death	Reinfarction	Heart failure	TVR	Stent thrombosis	Angina	Stroke	Follow-up
Yang *et al*., 2007	√	√	√	√				In hospital
Lønborg *et al*., 2010a	√	√	√	√	√	√		3 months
Lønborg *et al*., 2010b	√	√	√	√	√	√	√	15 months
Garcia *et al*., 2011	√		√					3.4 years
Freixa *et al*., 2012	√		√		√			6 months
Tarantini *et al*., 2012	√		√	√			√	6 months
Hahn *et al*., 2013	√	√	√	√	√			1 month
Elżbieciak *et al*., 2013	√	√	√					24 months
Sörensson *et al*., 2013	√	√	√			√		12 months
Dong *et al*., 2013	√		√			√		1 month

TVR: target vessel revascularization

3.2 Events of heart failure during follow-up

The occurrence of heart failure in patients treated with postconditioning was significantly lower than that in the control group as calculated using the fixed-effect model (RR 0.533, 95% CI 0.368–0.770, P=0.001; Fig. 3). I^2 of 0% indicated high homogeneity. The funnel plot had a symmetrical appearance (Fig. 4), consistent with Egger's test that there was no publication bias (95% CI 1.242–0.838, P=0.659). Sensitivity analysis implemented by sequentially removing each included study and reanalyzing the remaining RR and 95% CI revealed the robustness of overall heart failure results (Fig. 5). Meta-regression analyses were performed to explore the possible effect of study characteristics on heart failure by using age, gender, percentage of hypertension or diabetes mellitus, use of thrombectomy or GP IIb/IIIa inhibitor, follow-up time, and postconditioning protocol. No significant relationship was found between the mentioned variables and heart failure events.

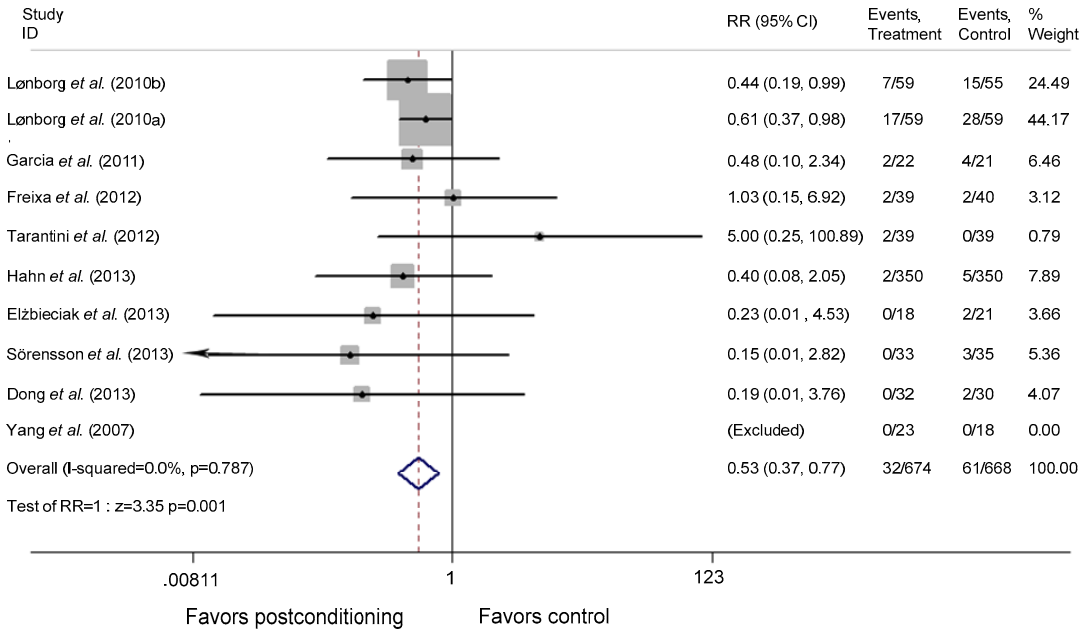

Fig. 3 RR (95% CI) of the effect of postconditioning on heart failure

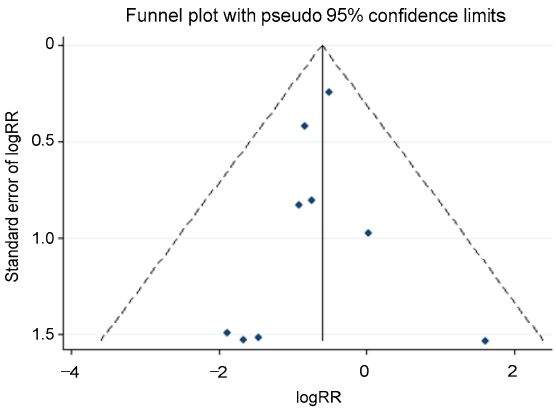

Fig. 4 Funnel plot for the analysis of heart failure

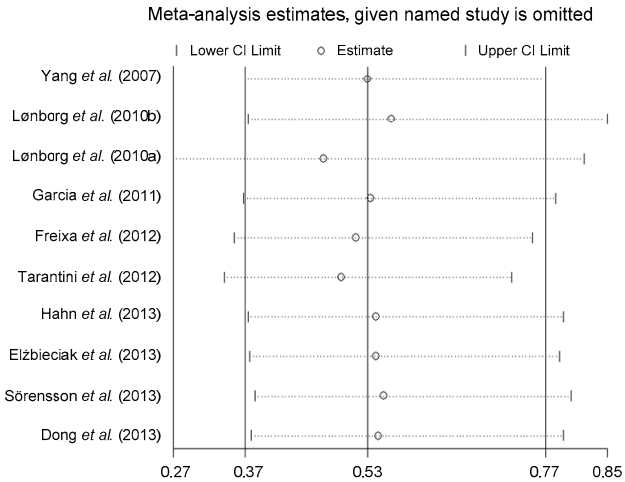

Fig. 5 Sensitivity analysis conducted by omitting each study one at a time

The remaining RR and 95% CI are presented

3.3 MACE during follow-up

Data on the outcomes of MACE in a follow-up from the hospitalization period to 3.4 years are presented in Fig. 6. No significant difference in MACE was observed between the postconditioning and control groups (RR 0.876, 95% CI 0.671–1.144, *P*=0.330).

3.4 Events of non-fatal reinfarction during follow-up

Six studies reported reinfarction events involving a total of 1084 patients, with 542 in each group in a follow-up of hospitalization period to 24 months. There was a marginal significant increase in non-fatal reinfarction events in the postconditioning group compared with the control group (RR 2.746, 95% CI 1.007–7.488, *P*=0.048; Fig. 7). Meta-regression was not performed because only six studies were included (Higgins and Green, 2011).

3.5 Other clinical events during follow-up

Table 4 shows data on the outcomes of death, TVR, stent thrombosis, and angina in a follow-up of in hospital to 3.4 years and no significant difference was observed between the postconditioning and control arm.

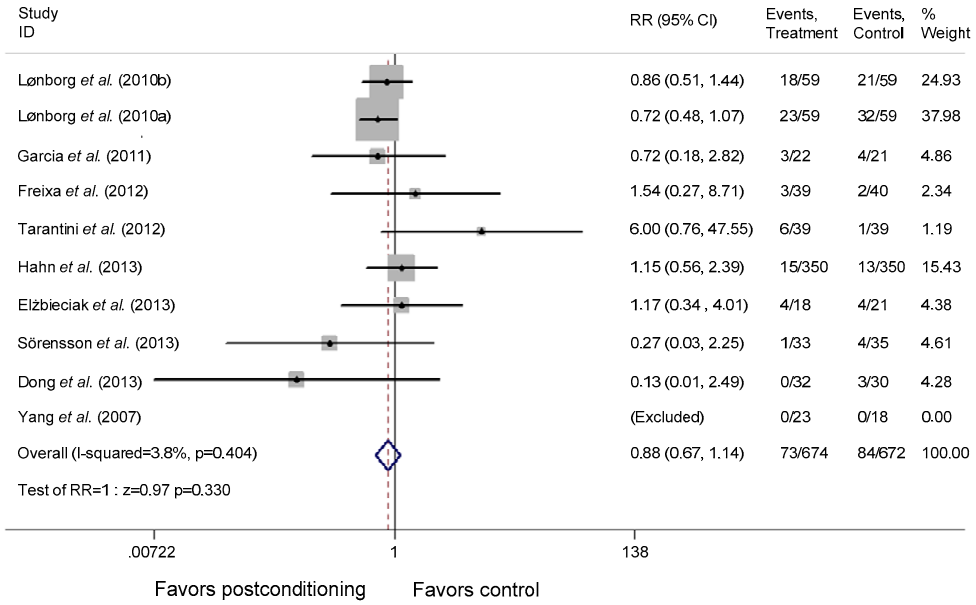

Fig. 6 RR (95% CI) of the effect of postconditioning on MACE

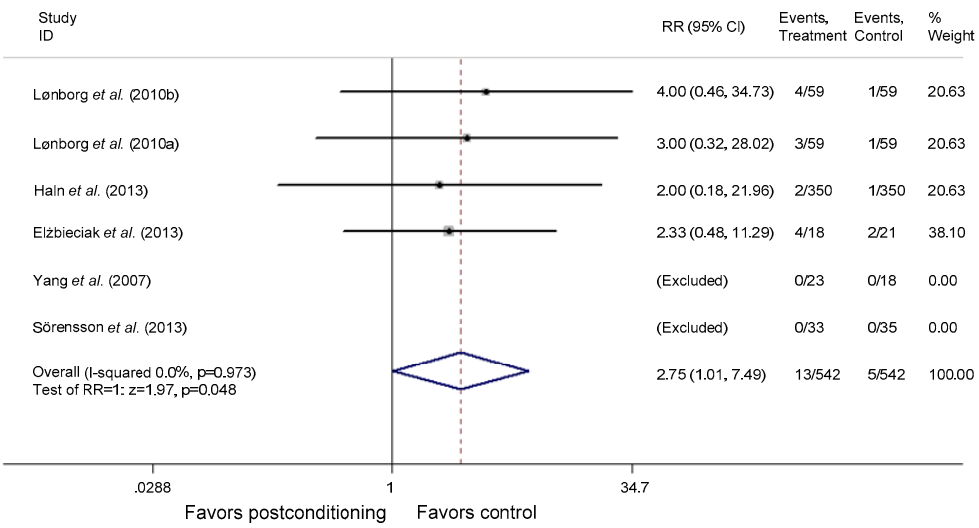

Fig. 7 RR (95% CI) of the effect of postconditioning on non-fatal reinfarction

Table 4 Meta-analysis of other end points of studies included

Events	Sample size of P/C	I^2 (%)	RR	95% CI	*P*-value
Death	674/672	0.0	1.642	0.853–3.159	0.138
TVR	530/525	0.0	1.667	0.611–4.546	0.318
Stent thrombosis	507/508	0.0	1.002	0.421–2.389	0.996
Angina	183/183	0.0	1.239	0.608–2.524	0.554

P: postconditioning; C: control; TVR: target vessel revascularization

4 Discussion

Despite great improvement in the reperfusion treatment of STEMI with the introduction of thrombolysis and primary PCI, prompt opening of the culprit vessel may contribute to additional myocardial damage, such as myocardial stunning, no reflow and ventricular arrhythmia (Kloner and Jennings, 2001; Piper *et al.*, 2003; Hausenloy and Yellon, 2008). Unlike ischemic preconditioning, postconditioning can be easily performed during primary PCI. Although its cardioprotective effect has been well studied in different animal models (Argaud *et al.*, 2005; Tang *et al.*, 2006; Lim *et al.*, 2007; Mykytenko *et al.*, 2007), the clinical effect of postconditioning is still unclear from divergent results from clinical trials and small sample sizes. The current meta-analysis involving 1346 patients from 10 randomized trials reveals that postconditioning is associated with a significant decrease of heart failure and a slight increase of non-fatal reinfarction, as compared with the usual care. No remarkable difference is observed between two groups in terms of MACE and other events including death, TVR, stent thrombosis, and angina.

Primary PCI is the most effective reperfusion therapeutic strategy for STEMI patients if it can be conducted within guideline-recommended time frames. The long-term clinical goal is the prevention of heart failure and improvement of LV contractile function, one of the predictors of long-term prognosis after PCI for AMI (de Silva *et al.*, 2012). A meta-analysis with a small size (n=272) showed that postconditioning significantly reduced heart failure (Wei *et al.*, 2012). Our data confirm the conclusion with a larger sample size. Another meta-analysis revealed that the improvement of LVEF leveled off and became non-significant with the extension of follow-up (Wang *et al.*, 2013). Our meta-regression analysis finds no significant association of follow-up time with heart failure events. Hence, the protective effect of postconditioning on heart failure is sustainable. The inconsistent effect of postconditioning on LVEF and heart failure may be partly attributed to the fact that many patients with symptoms and signs of heart failure have preserved LVEF (Solomon *et al.*, 2005).

The evidence of thrombectomy in STEMI has been well established (Bavry *et al.*, 2008; de Luca *et al.*, 2008; Burzotta *et al.*, 2009). Patients randomized to thrombus aspiration had a significantly increased rate of complete ST-segment resolution and improved myocardial blush grade. Although not powerful enough to evaluate the clinical outcome, cardiac mortality at one year was reduced (Vlaar *et al.*, 2008). However, thrombectomy was performed in relatively few patients in studies concerning postconditioning because the importance of thrombectomy during primary PCI in STEMI patients was acknowledged only after the trial design (Lønborg *et al.*, 2010a; Tarantini *et al.*, 2012), or for fear that use of thrombectomy might interfere with the postconditioning procedure, which should be implemented within 1 min after coronary reperfusion (Freixa *et al.*, 2012). Our meta-regression analysis shows no relationship between heart failure and use of thrombectomy, thus indicating that thrombectomy will not reduce the efficacy of postconditioning with respect to heart failure.

Using GP IIb/IIIa inhibitors as a bailout therapy is reasonable in patients undergoing primary PCI in the event of angiographic evidence of a large thrombus, slow or no-reflow, and other thrombotic complications (Steg *et al.*, 2012). Data from a recent meta-analysis (Wang *et al.*, 2013) indicated the biomarker (creatine kinase, creatine kinase-myocardial band, troponin T/troponin I) for myocardial injury reduced significantly in studies not using GP IIb/IIIa inhibitors but not in those using the pharmacological substance. They explained that GP IIb/IIIa inhibitors and postconditioning achieved balance on protection by acting through a similar mechanism. We observe

no significant relationship of heart failure in the use of GP IIb/IIIa inhibitors. A possible explanation of this ambivalence is that the troponin I value assessed at 72 h from the symptom onset rather than creatine kinase-myocardial band is associated with infarct volume (di Chiara *et al.*, 2010), a powerful indicator correlated with prognosis of STEMI (Eitel *et al.*, 2013).

It is not conclusive whether different postconditioning protocols have different cardioprotective effect. Cohen *et al.* (2007) suggested that a 30-s algorithm ensured that the pH did not increase abruptly and presented enough time to secure a proper production of reactive oxygen species. Additionally, Granfeldt *et al.* (2009) proposed that brief cycles of reperfusion/reocclusion were recommended in small animal models, while longer periods (60 s) might be more effective in larger species. In the present meta-regression analysis, the protocols are not correlated with heart failure, suggesting that protocol is not a crucial factor in postconditioning's beneficial effect on heart failure.

Paradoxically, postconditioning appears to be harmful where non-fatal reinfarction is involved, with marginal significance. A higher rate of induced coronary embolization may be an explanation. Also, the cardiac protective role of postconditioning disappears when other adverse events including death, TVR, stent thrombosis, angina, and general MACE are selected as the end point. So we should express caution on the result because heart failure is a relatively subjective index compared to other end points.

Several limitations in this study should be described. First, heterogeneity (such as different inclusion/exclusion criteria, postconditioning protocol, definition of heart failure, use of thrombectomy, and GP IIb/IIIa inhibitors) across studies did exist and might affect the generalization and interpretation of the meta-analysis results. However, we addressed this issue by regression analyses. Second, the hazard ratio (HR) should have been presented rather than RR because the follow-up duration in each trial was different and the time at which events occurred was important. But 7 of the 10 articles did not provide log-rank *P*-value, expected events, variance, survival curve, or time at which a certain event occurred, so HR could not be calculated (Tierney *et al.*, 2007). Third, our analysis was based on a relatively small sample. The small study effect has been well described in our previous work and the beneficial effect suggested by meta-analysis of small studies should be further validated in a meta-trial (Zhang *et al.*, 2013). Fourth, a recent prospective, randomized clinical trial about postconditioning with a sample size of 272 was not included because it published 21 d after the closing date of current meta-analysis (Limalanathan *et al.*, 2014).

5 Conclusions

Our meta-analysis suggests that the use of postconditioning in STEMI patients undergoing primary PCI is associated with a significantly lower risk of heart failure, but the risk of non-fatal reinfarction may increase. The effect of postconditioning on other end points, including death, TVR, stent thrombosis, angina, as well as MACE during follow-up, is neutral. Future multicenter, prospective, randomized trials with the primary end point of clinical events are needed to clarify the prognostic effect of postconditioning.

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Compliance with ethics guidelines

Xian-qing HU, Jian CHENG, Biao TANG, Zhong-heng ZHANG, Ke HUANG, Yi-ping YANG, Yan-yan MAO, Ming ZHONG, and Shen-wen FU declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Argaud, L., Gateau-Roesch, O., Raisky, O., *et al.*, 2005. Postconditioning inhibits mitochondrial permeability transition. *Circulation*, **111**(2):194-197. [doi:10.1161/01.CIR.0000151290.04952.3B]

Bavry, A.A., Kumbhani, D.J., Bhatt, D.L., 2008. Role of adjunctive thrombectomy and embolic protection devices in acute myocardial infarction: a comprehensive meta-analysis of randomized trials. *Eur. Heart J.*, **29**(24):2989-3001. [doi:10.1093/eurheartj/ehn421]

Burzotta, F., de Vita, M., Gu, Y.L., *et al.*, 2009. Clinical impact of thrombectomy in acute ST-elevation myocardial infarction: an individual patient-data pooled analysis of 11 trials. *Eur. Heart J.*, **30**(18):2193-2203. [doi:10.1093/eurheartj/ehp348]

Cohen, M.V., Yang, X.M., Downey, J.M., 2007. The pH hypothesis of postconditioning: staccato reperfusion reintroduces oxygen and perpetuates myocardial acidosis. *Circulation*, **115**(14):1895-1903. [doi:10.1161/CIRCULATIONAHA.106.675710]

de Luca, G., Dudek, D., Sardella, G., *et al*., 2008. Adjunctive manual thrombectomy improves myocardial perfusion and mortality in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction: a meta-analysis of randomized trials. *Eur. Heart J*., **29**(24):3002-3010. [doi:10.1093/eurheartj/ehn389]

de Silva, K., Webb, I., Sicard, P., *et al.*, 2012. Does left ventricular function continue to influence mortality following contemporary percutaneous coronary intervention? *Coron. Artery Dis*., **23**(3):155-161. [doi:10.1097/MCA.0b013e328351162d]

di Chiara, A., Dall'armellina, E., Badano, L.P., *et al.*, 2010. Predictive value of cardiac troponin-I compared to creatine kinase-myocardial band for the assessment of infarct size as measured by cardiac magnetic resonance. *J. Cardiovasc. Med.*, **11**(8):587-592. [doi:10.2459/JCM.0b013e3283383153]

Dong, M., Mu, N., Guo, F., *et al*., 2014. The beneficial effects of postconditioning on no-reflow phenomenon after percutaneous coronary intervention in patients with ST-elevation acute myocardial infarction. *J. Thromb. Thrombolysis*, **38**(2):208-214. [doi:10.1007/s11239-013-1010-0]

Egger, M., Smith, G.D., Schneider, M., *et al.*, 1997. Bias in meta-analysis detected by a simple, graphical test. *BMJ*, **315**(7109):629-634. [doi:10.1136/bmj.315.7109.629]

Eitel, I., Wohrle, J., Suenkel, H., *et al.*, 2013. Intracoronary compared with intravenous bolus abciximab application during primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: cardiac magnetic resonance substudy of the AIDA STEMI trial. *J. Am. Coll. Cardiol*., **61**(13):1447-1454. [doi:10.1016/j.jacc.2013.01.048]

Elżbieciak, M., Wita, K., Grabka, M., *et al.*, 2013. Effect of postconditioning on infarction size, adverse left ventricular remodeling, and improvement in left ventricular systolic function in patients with first anterior ST-segment elevation myocardial infarction. *Pol. Arch. Med. Wewn*., **123**(6):268-276.

Freixa, X., Bellera, N., Ortiz-Perez, J.T., *et al.*, 2012. Ischaemic postconditioning revisited: lack of effects on infarct size following primary percutaneous coronary intervention. *Eur. Heart J*., **33**(1):103-112. [doi:10.1093/eurheartj/ehr297]

Garcia, S., Henry, T.D., Wang, Y.L., *et al*., 2011. Long-term follow-up of patients undergoing postconditioning during ST-elevation myocardial infarction. *J. Cardiovasc. Transl. Res*., **4**(1):92-98. [doi:10.1007/s12265-010-9252-0]

Granfeldt, A., Lefer, D.J., Vinten-Johansen, J., 2009. Protective ischaemia in patients: preconditioning and postconditioning. *Cardiovasc. Res*., **83**(2):234-246. [doi:10.1093/cvr/cvp129]

Hahn, J.Y., Song, Y.B., Kim, E.K., *et al.*, 2013. Ischemic postconditioning during primary percutaneous coronary intervention: the effects of postconditioning on myocardial reperfusion in patients with ST-segment elevation myocardial infarction (POST) randomized trial. *Circulation*, **128**(17):1889-1896. [doi:10.1161/CIRCULATIONAHA.113.001690]

Hausenloy, D.J., Yellon, D.M., 2008. Preconditioning and postconditioning: new strategies for cardioprotection. *Diabetes Obes. Metab*., **10**(6):451-459. [doi:10.1111/j.1463-1326.2007.00762.x]

Higgins, J.P.T., Green, S., 2011. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0. The Cochrane Collaboration. Available from http://www.cochrane-handbook.org [Accessed on Mar. 20, 2011].

Kahn, H.A., Sempos, C.T., 2000. Statistical methods in meta-analysis. *In*: Petitti, D.B. (Ed.), Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis, 2nd Ed. Oxford University Press, New York, p.94-118.

Kloner, R.A., Jennings, R.B., 2001. Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: Part 2. *Circulation*, **104**(25):3158-3167. [doi:10.1161/hc5001.100039]

Laskey, W.K., 2005. Brief repetitive balloon occlusions enhance reperfusion during percutaneous coronary intervention for acute myocardial infarction: a pilot study. *Catheter. Cardiovasc. Interv*., **65**(3):361-367. [doi:10.1002/ccd.20397]

Lim, S.Y., Davidson, S.M., Hausenloy, D.J., *et al.*, 2007. Preconditioning and postconditioning: the essential role of the mitochondrial permeability transition pore. *Cardiovasc. Res*., **75**(3):530-535. [doi:10.1016/j.cardiores.2007.04.022]

Limalanathan, S., Andersen, G.O., Klow, N.E., *et al.*, 2014. Effect of ischemic postconditioning on infarct size in patients with ST-elevation myocardial infarction treated with primary PCI results of the POSTEMI (POstconditioning in ST-Elevation Myocardial Infarction) randomized trial. *J. Am. Heart Assoc*., **3**(2):e000679. [doi:10.1161/JAHA.113.000679]

Lønborg, J., Kelbaek, H., Vejlstrup, N., *et al.*, 2010a. Cardioprotective effects of ischemic postconditioning in patients treated with primary percutaneous coronary intervention, evaluated by magnetic resonance. *Circ. Cardiovasc. Interv*., **3**(1):34-41. [doi:10.1161/CIRCINTERVENTIONS.109.905521]

Lønborg, J., Holmvang, L., Kelbaek, H., *et al.*, 2010b. ST-segment resolution and clinical outcome with ischemic postconditioning and comparison to magnetic

resonance. *Am. Heart J*., **160**(6):1085-1091. [doi:10.1016/j.ahj.2010.09.026]

Ma, X., Zhang, X., Li, C., *et al.*, 2006. Effect of postconditioning on coronary blood flow velocity and endothelial function and LV recovery after myocardial infarction. *J. Interv. Cardiol*., **19**(5):367-375. [doi:10.1111/j.1540-8183.2006.00191.x]

Murry, C.E., Jennings, R.B., Reimer, K.A., 1986. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation*, **74**(5):1124-1136. [doi:10.1161/01.CIR.74.5.1124]

Mykytenko, J., Kerendi, F., Reeves, J.G., *et al.*, 2007. Long-term inhibition of myocardial infarction by postconditioning during reperfusion. *Basic Res. Cardiol*., **102**(1):90-100. [doi:10.1007/s00395-006-0625-0]

Piper, H.M., Meuter, K., Schafer, C., 2003. Cellular mechanisms of ischemia-reperfusion injury. *Ann. Thorac. Surg*., **75**(2):S644-S648. [doi:10.1016/S0003-4975(02)04686-6]

Solomon, S.D., Anavekar, N., Skali, H., *et al.*, 2005. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation*, **112**(24):3738-3744. [doi:10.1161/CIRCULATIONAHA.105.561423]

Sörensson, P., Saleh, N., Bouvier, F., *et al.*, 2010. Effect of postconditioning on infarct size in patients with ST elevation myocardial infarction. *Heart*, **96**(21):1710-1715. [doi:10.1136/hrt.2010.199430]

Sörensson, P., Ryden, L., Saleh, N., *et al.*, 2013. Long-term impact of postconditioning on infarct size and left ventricular ejection fraction in patients with ST-elevation myocardial infarction. *BMC Cardiovasc. Disord*., **13**:22. [doi:10.1186/1471-2261-13-22]

Staat, P., Rioufol, G., Piot, C., *et al.*, 2005. Postconditioning the human heart. *Circulation*, **112**(14):2143-2148. [doi:10.1161/CIRCULATIONAHA.105.558122]

Steg, P.G., James, S.K., Atar, D., *et al.*, 2012. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur. Heart J*., **33**(20):2569-2619. [doi:10.1093/eurheartj/ehs215]

Tang, X.L., Sato, H., Tiwari, S., *et al.*, 2006. Cardioprotection by postconditioning in conscious rats is limited to coronary occlusions <45 min. *Am. J. Physiol. Heart Circ. Physiol*., **291**(5):H2308-H2317. [doi:10.1152/ajpheart.00479.2006]

Tarantini, G., Favaretto, E., Marra, M.P., *et al.*, 2012. Postconditioning during coronary angioplasty in acute myocardial infarction: the POST-AMI trial. *Int. J. Cardiol*., **162**(1):33-38. [doi:10.1016/j.ijcard.2012.03.136]

Thibault, H., Piot, C., Staat, P., *et al.*, 2008. Long-term benefit of postconditioning. *Circulation*, **117**(8):1037-1044. [doi:10.1161/CIRCULATIONAHA.107.729780]

Tierney, J.F., Stewart, L.A., Ghersi, D., *et al.*, 2007. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*, **8**:16. [doi:10.1186/1745-6215-8-16]

Vlaar, P.J., Svilaas, T., van der Horst, I.C., *et al.*, 2008. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. *Lancet*, **371**(9628):1915-1920. [doi:10.1016/S0140-6736(08)60833-8]

Wang, L., Wang, J., Xu, H., *et al.*, 2013. Postconditioning in patients treated with primary percutaneous coronary intervention: an updated meta-analysis. *Catheter. Cardiovasc. Interv*., **82**(5):E662-E671. [doi:10.1002/ccd.25095]

Wei, Y., Ruan, L., Zhou, G., *et al.*, 2012. Local ischemic postconditioning during primary percutaneous coronary intervention: a meta-analysis. *Cardiology*, **123**(4):225-233. [doi:10.1159/000342660]

Yang, X.C., Liu, Y., Wang, L.F., *et al.*, 2007. Reduction in myocardial infarct size by postconditioning in patients after percutaneous coronary intervention. *J. Invasive Cardiol*., **19**(10):424-430.

Yellon, D.M., Hausenloy, D.J., 2007. Myocardial reperfusion injury. *N. Engl. J. Med*., **357**(11):1121-1135. [doi:10.1056/NEJMra071667]

Zhang, Z., Xu, X., Ni, H., 2013. Small studies may overestimate the effect sizes in critical care meta-analyses: a meta-epidemiological study. *Crit. Care*, **17**(1):R2. [doi:10.1186/cc11919]

Zhao, Z.Q., Corvera, J.S., Halkos, M.E., *et al.*, 2003. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am. J. Physiol. Heart Circ. Physiol*., **285**(2):H579-H588. [doi:10.1152/ajpheart.01064.2002]

中文概要

题　目：后适应在接受直接 PCI 治疗的急性 ST 段抬高性心肌梗死患者中的临床疗效：基于随机对照试验的 meta 分析

目　的：探讨后适应对接受直接经皮冠状动脉介入（PCI）治疗的急性 ST 段抬高性心肌梗死（STEMI）患者心血管不良事件的影响。

创新点：进一步明确后适应处理对 STEMI 患者临床预后的影响。

方　法：对符合入选标准的随机对照临床试验进行 meta 分析。

结　论：缺血后适应显著降低 ST 段抬高性心肌梗死患者心衰风险。

关键词：后适应；心肌梗死；冠状动脉介入治疗