Stenting technique, gender, and age are associated with cardioprotection by ischaemic postconditioning in primary coronary intervention: a systematic review of 10 randomized trials

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Aims We sought to perform a systematic review and meta-analysis to evaluate the potential factors affecting ischaemic postconditioning (IPoC) for patients with ST-segment elevation acute myocardial infarction (STEMI) in primary percutaneous coronary intervention (PCI).

Methods and results Ten randomized controlled trials (RCTs) on IPoC reporting myocardial enzyme levels or left ventricular ejection fraction (LVEF) in a total of 560 STEMI patients were identified in PubMed, EMBase, and Cochrane Library (up to February 2012). Compared with controls, IPoC significantly reduced elevated cardiac enzyme levels [standardized mean difference = \(-0.84\); 95% confidential interval (CI): \(-1.26\) to \(-0.43\); \(P < 0.00001\); heterogeneity test, \(I^2 = 81.0\%\)] and improved LVEF [weighted mean difference (WMD) = 3.98%; 95% CI: 1.27–6.70%; \(P = 0.004\); heterogeneity test, \(I^2 = 87.1\%\)]. The effect on LVEF remained significant after 1 year (WMD = 5.04%; 95% CI: 4.20–5.88%; \(P < 0.00001\); heterogeneity test, \(I^2 = 0.0\%\)). Univariate meta-regression analysis suggested that the major sources of significant heterogeneity (\(P < 0.1\)) were the use of direct-stenting technique (%) (coefficient = \(-0.886\); \(P = 0.069\); adjusted \(R^2 = 0.34\)) and male proportion (%) (coefficient = \(-0.022\); \(P = 0.098\); adjusted \(R^2 = 0.28\)) for myocardial enzyme levels, and age (coefficient = \(-1.34\); \(P = 0.025\); adjusted \(R^2 = 0.55\)) for LVEF (%). Subsequent multivariate regression and subgroup analysis confirmed these results.

Conclusion Available evidence from this systematic review and meta-analysis of 10 RCTs suggests that IPoC may confer cardioprotection in terms of myocardial enzyme levels and LVEF for STEMI during primary PCI. These effects are more pronounced among young and male patients, and those in whom direct-stenting techniques were used. Future studies should focus on the mortality in high-quality, large-scale clinical trials with long-term follow-up.

Keywords Ischaemic postconditioning • Acute myocardial infarction • Percutaneous coronary intervention • Cardioprotection

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Introduction

Timely restoration of coronary perfusion following ST-segment elevation acute myocardial infarction (STEMI) remains the most effective strategy to reduce infarct size (IS) and improve outcomes. Reperfusion to the ischaemic myocardium, however, may itself be associated with myocardial ischaemia/reperfusion (IR) injury. This unexpected phenomenon may negate the clinical benefits of thrombolysis or percutaneous coronary intervention (PCI).1 A considerable efforts have been directed at this problem, but results are mixed. Several isolated reports suggested that peri-operative administration of cariporide, adenosine, magnesium, nicorandil, and therapeutic hypothermia may increase myocardial salvage but lack of precise effectiveness.2,3 Hence, alternative strategies need to be identified in the clinical setting.4

Ischaemic postconditioning (IPoC) was first introduced by Zhao et al.5 in 2003. By applying three cycles of 30 s ischaemia/30 s reperfusion following a 60 min coronary artery occlusion in dogs, IS was found to be reduced by 44%. Since then, such use of IPoC has been proved in numerous animal studies as outlined in a comprehensive review.6 In humans, IPoC has also been shown to prevent reperfusion-induced endothelial dysfunction7,8 and offers a novel promising approach for the unpredictable coronary artery occlusion in clinical practice.8 In 2005, Laskey et al.9 reported a significant decreased ST-segment elevation and better distal myocardial perfusion in postconditioned patients with STEMI. Staat et al.10 and Yang et al.11 then observed decreased cardiac enzyme levels and improved left ventricular ejection fraction (LVEF) by using IPoC in PCI. Recently, several randomized control trials (RCTs) with controversial results have been published12–15. Hence, we conducted a systematic review and meta-analysis to evaluate the potential factors affecting IPoC (compared with controls) on cardiac enzyme levels and LVEF in STEMI patients undergoing primary coronary intervention.

Methods

Search strategy and study criteria

We searched PubMed, EMBase, and Cochrane Library (up to February 2012) using keywords terms ‘ischemic postconditioning’, ‘postconditioning’, ‘myocardial infarction’, ‘percutaneous coronary intervention’, ‘cardioprotection’, and ‘myocardial injury’. Inclusion criteria were: (i) prospective RCTs published in English; (ii) the primary PCI as the intervention; (iii) studies clearly reporting cardiac enzyme levels, LVEF, or CK-MB in PCI. Patients and demographic data,9 irretrievable or unclear data,20 and only 77.2% of primary PCI involved.21 We also excluded one of the two comparisons in Zhao’s trial22 for abnormal twice more reduction in the effect size of cTnI in the 60 s group than that in 30 s one (SMD: −4.69 vs. −1.56). Ten trials10–15,22–26 ultimately met our criteria with a total of 560 patients (Figure 1). The ischaemic protocol (cycles × IR) was 3–4 × 30 s/30 s in five11,12,15,23 studies, 4 × 60 s/60 s in four,10,13,14,25 and 2 × 90 s/180 s in one.24 For myocardial biomarkers, troponin I or T was used in four,14,15,22,25 studies, CK-MB in two,12,13 and CK in four.10,11,23,24 Three12,22,25 trials reported long-term LVEF data. The direct-stenting technique was used exclusively in three trials, partly (2.63%) used in one,14 and not used in six.11–13,15,23,24 Eight of 10 studies had a Jadad score of 2,10–14,22,24,25 and the remaining 3.15,23. The study characteristics and demographic data were summarized in Tables 1 and 2.

Cardiac biomarkers and left ventricular ejection fraction

Myocardial enzyme levels and LVEF were the primary endpoints of interest. Area under the curve (AUC) of the total serum troponin level was preferable for its potential superiority. If AUC data were not available, peak troponin or creatine kinase isoenzyme MB (CK-MB) or CK level was extracted in turn. The follow-up was divided into three time periods: ‘short term (in hospital)’, ‘medium term (≤6 months)’, and ‘long term (≥1 year)’.

Data synthesis and analysis

For continuous results (reported with mean and standard deviation or median and inter-quartile range), we calculated weighted mean differences (WMD) for LVEF and standardized mean differences (SMD) for myocardial enzyme levels to obtain the pooled estimates with 95% confidence intervals (CIs). Heterogeneity was explored by using I². A random-effect model was used for analysis in the case of significant heterogeneity among trials (I² ≥ 50%, P < 0.1).17 Meta-regression and subgroup analysis were conducted to explore the potential sources of significant heterogeneity and a P-value of < 0.1 was accepted. To reduce the possibility of overfitting in the regression model, at least five studies or substudies were set for the identification of every one influential factor.18,19 Sensitivity analyses were used to assess the robustness of our results by removing each included study at one time to obtain and evaluate the remaining overall estimates of myocardial enzyme levels. Publication bias was assessed using Begg’s and Egger’s test. A value of P < 0.05 (two-sided) was considered to be statistically significant. All statistical analysis was performed in Stata software (version 9.0; Stata Corporation, College Station, TX, USA).

Results

Study characteristics

After 211 abstracts were excluded from restricted search due to irrelevant content, duplicate publications, or ongoing trials, 13 potential studies were selected for detailed evaluation. Three studies were further excluded because of inadequate study patients and demographic data,9 irretrievable or unclear data,20 and only 77.2% of primary PCI involved.21 We also excluded one of the two comparisons in Zhao’s trial22 for abnormal twice more reduction in the effect size of cTnI in the 60 s group than that in 30 s one (SMD: −4.69 vs. −1.56). Ten trials10–15,22–26 ultimately met our criteria with a total of 560 patients (Figure 1). The ischaemic protocol (cycles × IR) was 3–4 × 30 s/30 s in five11,12,15,23 studies, 4 × 60 s/60 s in four,10,13,14,25 and 2 × 90 s/180 s in one.24 For myocardial biomarkers, troponin I or T was used in four,14,15,22,25 studies, CK-MB in two,12,13 and CK in four.10,11,23,24 Three12,22,25 trials reported long-term LVEF data. The direct-stenting technique was used exclusively in three trials, partly (2.63%) used in one,14 and not used in six.11–13,15,23,24 Eight of 10 studies had a Jadad score of 2,10–14,22,24,25 and the remaining 3.15,23. The study characteristics and demographic data were summarized in Tables 1 and 2.
Effect of postconditioning on cardiac biomarkers and left ventricular ejection fraction

Post-operative elevated myocardial enzyme levels were significantly reduced by IPoC (SMD = 0.84; 95% CI: -1.26 to -0.43; P < 0.00001) with significant heterogeneity ($I^2 = 81.0\%$) (Figure 2). No evidence of significant publication bias was observed ($P = 0.089$, Begg’s test; $P = 0.088$, Egger’s test).

Two studies were divided into different comparisons for the LVEF data with different follow-ups, respectively [expressed as Garcia I and Garcia II; Zhao(30) I and Zhao(30) II]. Thus, there were a total of 10 comparisons. Compared with the control group, IPoC significantly improved LVEF by 3.98% with significant heterogeneity ($I^2 = 87.1\%$; 95% CI: 1.27–6.70%; $P = 0.004$). The subgroup result for long-term studies was also of statistical significance ($I^2 = 0.0\%$; WMD = 5.04%; 95% CI: 4.20–5.88%; $P < 0.00001$) (Figure 3).

Sensitivity analysis and potential sources of heterogeneity

Sensitivity analysis excluding each included study at one time revealed that each individual study was consisted with the direction
and size of the overall myocardial enzymatic effect (all \( P \leq 0.001 \)) (Figure 4 and Table 3).

Country (Asia or non-Asia), postconditioning time (>60 or \( \geq 60 \) s), age, male (%), diabetes (%), hypertension (%), smoke (%), dyslipidaemia (%), and direct-stenting usage (100% = 1; 2.63 or 0% = 0) were included in the random-effect univariate meta-regression analysis for both myocardial enzyme levels and LVEF (%). As a result, the identified major sources of heterogeneity were direct-stenting usage (coefficient = \( -0.886; \ P = 0.069; \) adjusted \( R^2 = 0.34 \)) and male proportion (%) (coefficient = \( -0.022; \ P = 0.098; \) adjusted \( R^2 = 0.28 \)) for myocardial enzyme levels, and age (coefficient = \( -1.34; \ P = 0.025; \) adjusted \( R^2 = 0.55 \)) for LVEF (%) (Figure 5). Subsequent multivariate analysis was then conducted based on these three identified factors. As only 10 effect sizes were obtained, every two identified factors at a time was included in this multivariate regression model for myocardial enzyme levels and LVEF (%). Consequently, the effect of age on LVEF (%) remained statistically significant (\( P = 0.091 \) regressed with male proportion; \( P = 0.035 \) regressed with direct-stenting usage). There was also a trend in direct-stenting usage for myocardial

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Male (%)</th>
<th>Diabetes (%)</th>
<th>Dyslipidaemia (%)</th>
<th>Baseline LVEF (%)</th>
<th>Direct stent (%)</th>
<th>( \beta )-blockers (%)</th>
<th>Statins (%)</th>
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<td>Staat et al.(^{10})</td>
<td>57</td>
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<td>16.27</td>
<td>64</td>
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<td>68.09</td>
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<td>NA</td>
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<tr>
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<td>75.61</td>
<td>26.83</td>
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<td>0</td>
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<td>NA</td>
</tr>
<tr>
<td>Thibault et al.(^{25})</td>
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<td>10.89</td>
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<td>45.11</td>
<td>100</td>
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<td>41.67</td>
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<td>NA</td>
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<tr>
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<td>NA</td>
<td>100</td>
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<td>0</td>
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</table>

LVEF, left ventricular ejection fraction; NA, not available.

Table 2 Summarized demographic data of included randomized trials

Figure 2 Forest plot for myocardial enzyme levels, expressed as standardized mean difference (SMD). Post-operative troponin, CK-MB or CK levels was significantly reduced by ischemic postconditioning (IPoC) (SMD = \( -0.84; \ P < 0.00001 \)).
**Figure 3** Forest plot for LVEF, expressed as weighted mean difference (WMD). IPoC significantly improved post-PCI LVEF (% (WMD = 3.98%, P = 0.004).

**Figure 4** Sensitivity analysis evaluating the influence of each individual study (left side) on the overall estimate. The remaining results with 95% confidence interval (CI) is presented.
enzyme levels (P = 0.102 regressed with male proportion). When compared with the non-direct-stenting subgroup, the direct-stenting subgroup demonstrated a significant reduction in myocardial enzyme levels [SMD: –1.49 3 (P = 0.001) vs. –0.579 (P = 0.004); P = 0.06 for subgroup difference].

**Discussion**

In this systematic review and meta-analysis of 10 randomized trials involving 560 patients, we confirmed that, as compared with coronary intervention alone, IPoC could confer cardioprotection by reducing elevated myocardial enzyme levels and improving LVEF in STEMI patients after PCI. Furthermore, such protective effects were more significant in younger, female patients, or when the direct-stenting techniques were used.

Up to now, PCI remains a key treatment option for patients with STEMI. Percutaneous coronary intervention, however, is associated with a significant incidence of heart failure (≈25%) and cardiac death (≈10%), partly due to reperfusion injury. In fact, paradoxical injury during reperfusion may cause irreversible cardiomyocyte damage and myocardial stunning, resulting in elevated cardiac enzyme levels and aggravated LVEF. High level of cardiac enzymes is an important predictor of long-term mortality in STEMI patients after PCI. Post-PCI LVEF is a simple and powerful predictor of long-term cardiovascular outcomes and all-cause mortality in patients with heart failure. Therefore, strategies to reduce myocardial enzyme levels and improve LVEF after PCI are very important and may ameliorate long-term outcomes. In our current analysis, positive cardioprotective effects were shown in seven studies. Controversial or negative studies, however, also exist with regard to the effect of IPoC. Our analysis combining all these positive and negative studies showed results similar to that by Hansen et al., in which a reduction in peak creatine kinase levels and improvement in LVEF after primary PCI were associated with IPoC. Moreover, 3 of the 10 included trials reported the long-term effect of IPoC on LVEF and subgroup analysis revealed that this benefit could last for more than 1 year.

In 7 of 10 included trials, the direct-stenting technique was not used. This technique has been shown to offer more superior results by minimizing coronary microembolisms in PCI. So far, the potential role of the stenting technique in cardioprotection with IPoC has not been studied yet. Heusch et al. and Heusch had suggested that the negating effects of coronary microembolizations on IPoC-induced cardioprotection might be eliminated if direct stenting was used. Our results from meta-regression and subgroup analysis confirmed this presumption. However, whether this cardioprotective potential is affected by the stenting technique needs further larger randomized trials in the future.

There has always been a concern whether cardioprotective effects of IPoC established in young and healthy animals could be translated into the clinical population with various co-morbidities and cofounders (such as gender and age) in clinical practice. Studies on ISs have shown different results that are often species- and gender-specific. Results from our investigation showed a wide-ranging male proportion (32.5–94.5%) and further pooled analysis suggested an increased effect size in cardiac enzymes by 0.22 per 10% increase in male proportion. Another potential modifier is age. Previous laboratory studies on the cardioprotective effects of ageing on IPoC have shown inconsistent results. In our analysis, the mean age of STEMI patients ranged from 55 to 63 years, and the overall estimate seemed not influenced. However, regression analysis showed that age was negatively correlated with LVEF, reducing by 1.34% per 1 year increase. These two intriguing findings may provide some suggestions for the clinical usage of IPoC.

The possible mechanisms underlying the cardioprotective phenotype of IPoC for patients with STEMI are not fully understood. In previous laboratory studies, both reperfusion injury salvage kinase (RISK) including AKT and ERK1/2, and Survivor Activating Factor Enhancement (SAFE) involving JAK-STAT signal pathway have been proposed while elucidating the IS-sparing effect of IPoC. Moreover, mitochondrial permeability transition pore (mPTP) has been recognized as the end effector of both the RISK and the SAFE pathway during ischaemic conditioning. Ischaemic postconditioning has been proved to reduce the susceptibility to mPTP open in cardiac mitochondria isolated from reperfused rabbit heart. In addition, mimicking mPTP open by atractyloside during reperfusion could abolish the effect of IPoC on cell apoptosis of rat hearts. On the other hand, reperfusion with cyclosporin A (CsA), an inhibitor of mPTP, was shown to provide significant protection in the human endothelium and isolated atrial trabeculae. More importantly, the proof-of-concept clinical study has confirmed that administration of CsA during PCI could afford 20% IS reduction measured by magnetic resonance imaging. Additionally, IPoC has been shown to protect against endothelial injury of IR in healthy volunteers and in STEMI patients undergoing PCI. Taken together, these evidence from animal and clinical studies may partly explain the effect of IPoC in PCI.

There are several limitations to our analysis. First, we were unable to access the individual patient data. The results of
meta-regression analysis were mainly based on the published aggregate patient data, such as mean age and male proportion. Therefore, the potential influences of other co-morbidities (diabetes, dyslipidaemia, and smoking) and cardiovascular medications (such as β-blocker, statins, and adenosine) may be underestimated. Secondly, the difference in LVEF between groups, rather than the change from the baseline, was used in the pooled analysis with inadequate demographic data. Thirdly, the sample size in each studies is relatively small. Fourthly, the random-effect model used in our pool analysis was mainly based on the value of $I^2$ (≥50%). However, one important assumption is that the distribution of these effect sizes is normality, which is difficult to establish the validity. We cannot rule out the exact potential influence of this common unresolved issue on this study. Fifthly, the quality of trials included in our analysis are relatively low (Jadad < 3 in 8 of 10 studies), which is not surprising as double blinding is difficult in the setting of PCI. Lastly, early and late mortality remains inconclusive because of insufficient data.

Conclusions

Available evidence from the present systematic review and meta-analysis suggests that IPoC may confer cardioprotection for STEMI during primary PCI. Cardioprotective effects of IPoC are

Figure 5 Meta-regression plots on myocardial enzyme levels (A) and LVEF(%) (B). (A) Male proportion (%) (coefficient = −0.022; $P = 0.098$); (B) Age (coefficient = −1.34; $P = 0.025$).
more pronounced among young and male patients, and those in whom direct-stenting techniques were used. Future studies should focus on the mortality in high-quality, large-scale clinical trials with long-term follow-up.

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