Local Ischemic Postconditioning during Primary Percutaneous Coronary Intervention: A Meta-Analysis

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Key Words

Acute myocardial infarction • Ischemic postconditioning • Percutaneous coronary intervention

Abstract

Objectives: To investigate current evidence linking ischemic postconditioning (IPC) to cardioprotection in patients receiving primary percutaneous coronary intervention (PCI).

Methods: We performed searches of PubMed, Embase, MEDLINE and Cochrane databases from January 1998 to May 2011 for identifying relevant studies comparing IPC with usual care in patients undergoing primary PCI. A meta-analysis of eligible studies was assessed by Review Manager 5.0.

Results: Thirteen studies were eligible. Compared to the control, observed outcomes such as peak creatine kinase [weighted mean difference (WMD) –537.48, 95% confidence interval (CI) –779.32 to –295.65 IU/l], peak creatine kinase-myocardial band (WMD –61.11, 95% CI –76.56 to –45.66 U/l), complete ST-segment resolution (risk ratio 1.38, 95% CI 1.07 to 1.77), blush grade during reflow (WMD 0.64, 95% CI 0.49 to 0.78), corrected TIMI frame count, single-photon emission computed tomography determining infarct size, long-term left ventricular ejection fraction and short-term and long-term wall motion score indexes were improved in IPC group,

with less occurrence of heart failure during the 3-month to 3.4-year follow-up. **Conclusions:** Though current evidence indicates that IPC provides potential cardioprotection to patients receiving primary PCI, larger adequately powered studies should be undertaken to confirm its advantages.

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Introduction

Ischemic postconditioning (IPC) refers to several cycles of ischemia/reperfusion in the reperfusion treatment, followed by full restoration of coronary perfusion. Zhao et al. [1] first described the concept of IPC in 2003 and indicated it could reduce myocardial injury dramatically. Subsequent nonhuman investigations in vivo and in vitro confirmed such cardioprotective effects of IPC, i.e. significantly reducing infarct size, preventing reperfusion arrhythmias and improving cardiac function [2, 3]. During the emergency coronary intervention, IPC could be achieved by inflating and deflating the balloon alternately. Two years after the first animal experiment on IPC, 2 clinical trials were reported by Staat et al. [4] and Laskey [5]. These pilot studies demonstrated that IPC effectively reduced myocardial injury and improved

prognosis in patients with acute myocardial infarction (AMI) receiving percutaneous coronary intervention (PCI). Clinical studies on IPC have gradually increased in recent years, but have been small, single center studies with inconsistent results. They have been proof-of-principle studies using surrogate end points to define a potential biological effect of IPC using (1) enzyme assessment of myocardial injury, (2) angiographic and invasive measures of coronary flow, (3) measures of left-ventricular function, (4) measures of infarct size and (5) adverse cardiac events during follow-up. We elected to perform a meta-analysis of these published data to ascertain whether IPC limits myocardial injury and improves prognosis in patients with AMI receiving PCI.

Methods

Search Strategy

Literature searches were performed to identify all relevant and published randomized, controlled, prospective studies comparing IPC and usual care in patients with AMI undergoing PCI. We searched electronic databases (PubMed, Embase, MEDLINE and Cochrane) from January 1998 to May 2011, using terms like 'post-conditioning', 'acute myocardial infarction' and 'coronary intervention'. Our search was not restricted to articles in English. Hand research was also performed and the reference lists of all the retrieved articles were screened.

Eligibility Criteria

Criteria for inclusion were as follows: (1) a validated diagnosis of AMI, (2) a routine intervention in control group and IPC treatment during intervention in IPC group, without any differences in other treatments between the two, (3) a similar baseline between IPC and the control group, with a good match of age, gender, ischemic time and risk factors, (4) a randomized, controlled and prospective study, (5) the inclusion of one or more observed outcomes such as peak creatine kinase (CK), peak creatine kinase-myocardial band (CK-MB), complete ST-segment resolution (cSTR), perfusion defect index on single-photon emission computed tomography (PDI-SPECT), blush grade of perfusion, corrected TIMI frame count (CTFC), left ventricular ejection fraction (LVEF), wall motion score index (WMSI) and adverse cardiac events in the follow-up. Continuous variables were expressed as mean and standard deviation. Studies without any of the above-observed outcomes, a dissimilar baseline between the IPC and control groups or with confounding factors were excluded. Only the latest study was included in the meta-analysis for identical or largely similar articles.

Study Selection and Quality Assessment

Two investigators (Y.W. and L.R.) performed the literature search, study selection and data evaluation independently of one another. Disagreements were resolved by discussion or referred to a third investigator (C.Z.). Complete consensus among the authors on the final results was achieved. Studies included in the meta-analysis had to fulfill the eligibility criteria mentioned

above. The main data information was extracted, including year of publication, article title, name of first author, published journal title, study characteristics (random methods, grouping, baseline comparison and follow-up event) and observed outcomes. We adopted the criteria for study quality outlined by the Cochrane Reviewer's Handbook 4.2 for quality assessment of included randomized controlled trials. These criteria were as follows: (1) correct random methods, (2) concealment randomization, (3) blindness assessment, (4) the completeness of the follow-up and using ITT (intention to treat) analysis to deal with the dropouts. Based on the above criteria, studies were divided into 3 categories (A, B and C grades). We assigned the grade A, suggesting minimal possible bias, if all 4 Cochrane criteria were met. We assigned the grade B, considered to have a moderate probability of bias, if 1 or more were partially met; and if 1 or more were not met, it indicated a high probability of bias, so we assigned the grade C.

Statistics

We used the χ^2 test to verify data heterogeneity between studies, with $p > 0.05$ indicating data homogeneity. In order to test the overall effects, a fixed-effects model was used unless there was significant heterogeneity in the studies, which required a random-effects model [6]. For continuous variables, we used the weighted mean difference (WMD) as the study effect estimate. For discrete variables, we calculated the risk ratio (RR) with 95% confidence interval (CI) comparing the IPC group with the control group. A 2-tailed p value of <0.05 was considered significant. All statistical analysis was performed in statistical software (Review Manager 5.0).

Results

Study Selection

We identified 18 potentially relevant articles on IPC associated with PCI by scanning the titles and the abstracts. Five studies were excluded in the full text evaluation for the following reasons: 1 was possibly a duplicate [7], 1 was a retrospective chart review [8], 1 lacked any of our requisite outcomes [9], 1 was an ongoing study [10] and all the data of the 5th study were presented as medians and 25th and 75th percentiles [11]. Finally, by screening the whole article, we selected 13 studies for meta-analysis. These eligible studies contained a total of 673 patients, with 352 in the IPC group and 321 in the control group. Two articles reported the same trial with the observation of different outcomes. The characteristics of the 13 studies included in the meta-analysis are summarized in table 1. Table 2 notes the outcomes reported in each study.

Study Quality

The analysis of study quality in the 13 eligible studies is presented in table 3. Baselines between the IPC group and the control group in all the studies were comparable.

Table 1. Characteristics of studies included in the meta-analysis

Study (first author)	Total IPC/Con	Age, years IPC/Con	Ischemia time, min IPC/Con	Post-con- ditioning protocol	Culprit artery (IPC/Con)			TIMI grade (0/1/2) before PCI (IPC/ Con)
					LAD	LCX	RCA	
Staat 2005 [4]	16 (12)/14 (13)	58/56	331/318	60 s × 4	6/6	–	10/8	(16/0/0)/(14/0/0)
Laskey 2005 [5]	10 (5)/7 (5)	58/58	341/286	90 s × 2	5/4	1/1	4/2	–
Ma 2006 [7]	47 (31)/47 (33)	64/64	–	30 s × 3	23/25	11/8	13/14	(30/12/5)/(33/10/4)
Ma 2007 [12]	32 (21)/29 (20)	64/64	396/426	30 s × 3	17/15	7/5	8/9	(21/8/3)/(20/6/3)
Yang 2007 [13]	23 (20)/18 (11)	59/63	312/264	30 s × 3	15/11	2/1	6/6	(23/0/0)/(18/0/0)
Thibault 2008 [14]	17 (13)/21 (16)	56/56	283/297	60 s × 4	9/11	–	8/10	(17/0/0)/(21/0/0)
Laskey 2008 [15]	12 (7)/12 (7)	60/58	228/222	90 s × 2	12/12	–	–	(9/3/0)/(8/4/0)
Lønborg 2010 ¹ [16, 17]	59 (45)/59 (47)	61/62	241/255	30 s × 4	26/23	5/11	28/25	(59/0/0)/(59/0/0)
Xue 2010 [18]	23 (22)/20 (19)	54/62	246/324	60 s × 4	10/12	–	13/8	(23/0/0)/(20/0/0)
Lin 2010 ² [19]	25 (21), 24 (17)/26 (17)	59, 58/63	–	30 s × 3, 60 s × 3	16, 13/16	2, 2/2	7, 9/8	(25/0/0), (24/0/0)/(26/0/0)
Garcia 2011 [20]	22 (19)/21 (16)	61/55	–	30 s × 4	8/5	5/2	9/14	(22/0/0)/(21/0/0)
Liu 2011 [21]	30 (22)/34 (23)	59/59	310/324	30 s × 3	16/20	3/4	11/10	(30/0/0)/(34/0/0)

Con = Control; LAD = left anterior descending artery; LCX = left circumflex; RCA = right coronary artery.

¹ Lønborg et al. published 2 articles on the same trial, observing different outcomes.

² Lin et al. compared 60-second postconditioning with 30-second postconditioning and no postconditioning (routine) in this study.

Table 2. Summary of outcomes in the 13 prospective studies included in the meta-analysis

Study (first author)	Peak CK	Peak CK-MB	STR	PDI- SPECT	Blush grade	CTFC	LVEF	WMSI	Follow-up events
Staat 2005 [4]	*				*				
Laskey 2005 [5]	*								
Ma 2006 [7]	*	*				*		*	
Ma 2007 [12]	*	*				*		*	
Yang 2007 [13]	*		*	*	*		*		
Thibault 2008 [14]				*			*	*	
Laskey 2008 [15]	*						*		
Lønborg 2010 [16]			*						15 month*
Lønborg 2010 [17]							*		3 month*
Xue 2010 [18]		*	*	*			*	*	
Lin 2010 [19]							*	*	
Garcia 2011 [20]	*	*					*	*	3.4 year*
Liu 2011 [21]	*	*			*	*	*	*	

STR = ST-segment resolution.

* Indicated outcomes described in relative studies. Lønborg et al. wrote 2 articles reporting the same trial but observing different outcomes.

Measurement data was compared by Student's *t* test and count data was compared by χ^2 test between the 2 groups. If details pertaining to randomization, blinding, drop-outs and withdraws were not specified in the original articles, the chief investigator (Y.W.) was responsible for

getting clarification from the primary author by e-mail or telephone. In terms of quality, each of these studies would be graded level B according to the Cochrane Reviewer's Handbook 4.2 for quality assessment of included randomized controlled trials.

Fig. 1. A meta-analysis of 8 eligible studies on peak CK.

Table 3. Quality assessments of studies included in the meta-analysis

Study (first author)	Technique of randomization	Concealed randomization	Blinded assessment	Dropout rate	Similar baseline
Staat 2005 [4]	Yes	Yes	Yes	Unclear	Yes
Laskey 2005 [5]	Yes	Yes	Unclear	Unclear	Yes
Ma 2006 [7]	Yes	Unclear	Unclear	Unclear	Yes
Ma 2007 [12]	Yes	Yes	Unclear	Unclear	Yes
Yang 2007 [13]	Yes	Yes	Unclear	Unclear	Yes
Thibault 2008 [14]	Yes	Yes	Yes	0	Yes
Laskey 2008 [15]	Yes	Yes	Yes	Unclear	Yes
Lønborg 2010 ¹ [16, 17]	Yes	Yes	Yes	0	Yes
Xue 2010 [18]	Yes	Yes	Yes	Unclear	Yes
Lin 2010 ² [19]	Yes	Yes	Unclear	Unclear	Yes
Garcia 2011 [20]	Yes	Unclear	Unclear	0.12	Yes
Liu 2011 [21]	Yes	Yes	Unclear	Unclear	Yes

¹ Lønborg et al. published 2 articles on the same trial but observing different outcomes.

² Lin et al. compared 60-second postconditioning with 30-second postconditioning and no postconditioning (routine) in this study.

Biochemical Markers of Acute Myocardial Infarction

The commonly used biochemical markers of AMI are CK and CK-MB, which are associated with infarct size. Eight studies compared the impact of IPC with the control (i.e. no IPC) on the peak of serum myocardial enzyme concentration after acute infarction. Four of these studies indicated that IPC reduced the peak CK after myocardial infarction, while the others indicated oppos-

ing results. Our meta-analysis of these studies suggested that IPC significantly decreased peak CK after myocardial infarction (WMD -537.48, 95% CI -779.32 to -295.65 IU/liter, $p < 0.0001$) (fig. 1). Similarly, IPC also significantly decreased peak CK-MB (WMD -61.11, 95% CI -76.56 to -45.66 IU/liter, $p < 0.00001$) (fig. 2). Therefore, it was showed that IPC can reduce ischemic necrosis of myocardium after acute infarction.

Fig. 2. A meta-analysis of 5 eligible studies on peak CK-MB.

Fig. 3. A meta-analysis of 3 eligible studies on SPECT determining infarct size.

Myocardial Infarct Size Measured by Imaging

There were 3 studies describing the outcome of SPECT infarct size (fig. 3). The meta-analysis of these studies demonstrated that the perfusion defect index on SPECT, an estimate of infarct size, was significantly reduced in the IPC group versus the control group, with a WMD of -9.09% (95% CI -12.53 to -5.64 , $p < 0.00001$).

Markers of Reperfusion

Reperfusion outcomes following IPC were described by cSTR, blush grade during reflow and CTFC in the eligible studies. Figure 4 shows data on the outcome of cSTR. Three trials were included in the meta-analysis, with 2 suggesting no improvement in cSTR for IPC pre-treatment. The pooled estimate of RR from all 3 trials was

statistically significant (RR 1.38, 95% CI 1.07 to 1.77, $p = 0.01$). The blush grade, a marker of myocardial perfusion, was significantly higher in the hearts of the IPC group than in those of the controls, with a WMD (IPC vs. control) of 0.64 (95% CI 0.49 to 0.78, $p < 0.00001$) (table 4). CTFC was also used to evaluate the velocity of coronary flow after PCI. Patients of the IPC group had faster CTFC than patients of the control group, with a WMD (IPC vs. control) of -4.33 (95% CI -5.61 to -3.05 , $p < 0.00001$) (table 4).

Cardiac Function Measures

Table 5 presents data on the outcomes of LVEF and WMSI in patients with AMI undergoing primary PCI. There are some differences in the methods used to assess

Table 4. A meta-analysis for reperfusion outcomes after primary PCI

Outcomes of reperfusion	Contributing studies (references)	Sample size (IPC/control)	Treatment effect		
			WMD	95% CI	p value
Blush grade	[4, 13, 21]	69/66	0.64	0.49 to 0.78	<0.00001
CTFC	[7, 12, 21]	109/110	-4.33	-5.61 to -3.05	<0.00001

Table 5. Impact of IPC on LVEF and WMSI in the short and long term

Outcomes of LV function	Contributing studies (references)	Sample size (IPC/control)	Treatment effect		
			WMD	95% CI	p value
LVEF, within 7 days	[13, 15, 18-21]	159/157	0.18	-0.75 to 1.10	0.71
LVEF, over 3 months	[14, 17, 19, 20]	131/137	7.79	7.12 to 8.46	<0.00001
WMSI, within 7 days	[18, 20, 21]	102/106	-0.45	-0.48 to -0.42	<0.00001
WMSI, over 3 months	[7, 12, 14, 19]	109/110	-0.33	-0.36 to -0.31	<0.00001

Fig. 4. A meta-analysis of 3 eligible studies on cSTR.

LVEF, with 6 studies using echocardiography [13-15, 18, 19, 21], 1 using MRI [17], and 1 using echocardiography or MRI for each group, respectively [20]. LVEF was comparable between the IPC group and the control group in the short term within 7 days after PCI (WMD 0.18, 95% CI -0.75 to 1.10, $p = 0.71$). But in the long term over 3 months, LVEF was significantly more improved in the IPC group than in the control group (WMD 7.79, 95% CI 7.12 to 8.46, $p < 0.00001$). Patients undergoing IPC had a lower WMSI (a value of 1 is normal segmental motion and higher values indicate poorer contraction) than those who received usual primary PCI in both the short term

within 7 days (WMD -0.45, 95% CI -0.48 to -0.42, $p < 0.00001$) and the long term over 3 months (WMD -0.33, 95% CI -0.36 to -0.31, $p < 0.00001$).

Cardiac Events during Follow-Up

Only 3 studies reported adverse cardiac events occurring during follow-up, including death, reinfarction, heart failure (NYHA 2-4), angina (CCS 1-4) and stent thrombosis. The long-term benefit of IPC was indicated in our meta-analysis. Table 6 presents data on the outcomes of adverse cardiac events in a follow-up of 3 months to 3.4 years. IPC reduced heart failure significantly more

Table 6. Meta-analysis on the long-term follow-up outcomes of the included trials

Outcomes of adverse cardiac events in follow-up	Contributing studies (references)	Sample size IPC/control	RR		
			M-H	95% CI	p value
Heart failure (NYHA 2–4)	[16, 17, 20]	136/136	0.55	0.37 to 0.83	0.004
Death	[16, 17, 20]	136/136	3.49	0.74 to 16.49	0.11
Angina (CCS 1–4)	[16, 17]	114/115	1.41	0.65 to 3.05	0.38
Reinfarction	[16, 17]	114/115	3.53	0.75 to 16.64	0.11
Stent thrombosis	[16, 17]	114/115	0.43	0.06 to 2.89	0.39

than the usual treatment (RR 0.55, 95% CI 0.37 to 0.83, $p = 0.004$), but no significant differences were in death, angina, reinfarction and stent thrombosis were observed (table 6).

Discussion

AMI is a major cause of death and heart failure in both high- and low-income countries [22]. Recent studies have confirmed that rapid reperfusion is critical to rescue the ischemic myocardium. However, reperfusion has the potential to cause secondary injury to the myocardium, including myocardial stunning, no reflow and ventricular arrhythmias [23–25]. Ischemic preconditioning was first introduced as a powerful strategy to attenuate reperfusion injury [26], but it obviously had limited utility in clinical practice as it required an intervention before a patient experienced symptomatic cardiac ischemia or infarction. However, unlike ischemic preconditioning, IPC performed during angioplasty is technically simple and safe, for cycles of ‘ischemia/reperfusion’ can be easily achieved by repeatedly deflating and inflating the balloon in the culprit artery. The underlying mechanism of cardioprotection was initially attributed to the reduction of oxidative stress, decreasing intracellular calcium overload, improving endothelial function and depressing inflammation like ischemic preconditioning [4]. Further observations underlying the cardioprotective effects of IPC have been well studied in different animal models [27–31] and reviewed in multiple reviews [32–34].

The clinical applicability and simple technique of IPC permitted it to be readily assimilated into angioplasty interventions for acute ischemia. In 2005, Staat et al. [4] demonstrated that IPC by angioplasty could reduce infarct size by 36%, assessed by early CK release in the human heart. This study indicated the feasibility and

cardioprotection of IPC in the human heart for the first time. Multiple subsequent clinical trials have confirmed positive outcomes associated with IPC [7, 13, 18–21], but small sample size and less positive outcomes in other studies called for a meta-analytic approach. Our meta-analysis indicated that IPC caused a reduction of about 500 IU in peak CK after AMI, showing that IPC can reduce ischemic necrosis of myocardium after acute infarction. Other beneficial effects of IPC in the human heart were also observed, such as reducing SPECT-determined myocardial infarct size, and improving reperfusion outcomes, cardiac function and prognosis. Moreover, IPC did not improve LVEF within 7 days, but did improve it significantly over 3 months. Thibault et al. [14] demonstrated that myocardial stunning might mask any beneficial effect of contractile function within days to weeks after AMI, but no longer interfered with the effects of IPC in improving the recovery of regional contractile function after several months. The meta-analysis by Hansen et al. [35] did not analyze the long-term benefit of IPC because the studies observing follow-up outcomes to determine IPC’s long-term benefit were performed after their meta-analysis. We presented data on outcomes of adverse cardiac events in a follow-up of 3 months to 3.4 years, which showed that IPC significantly reduced heart failure, but no significant differences were observed in death, angina, reinfarction and stent thrombosis. These revealed that IPC could improve cardiac function by reducing reperfusion-induced myocardial injury and infarct size. Clearly, here there are statistical differences to support use of this technique in routine practice.

The ongoing trial POSTEMI (Postconditioning in ST-Elevation Myocardial Infarction) is a prospective, randomized control study, which selected 260 patients. The purpose was to evaluate the impact of IPC on the final myocardial infarct size in patients with ST-segment elevation myocardial infarction [10]. We look forward to

seeing whether our meta-analytic findings are confirmed by POSTEMI, and, regardless of these findings, clearly a number of technical questions about IPC have still to be clarified. Though a lot of studies on IPC in animal models or humans have been well performed, we still feel puzzled by many questions. For example, 'What is the most efficient, simplest and safest postconditioning procedure for human hearts?' The postconditioning protocols in recent studies included $30\text{ s} \times 3$, $30\text{ s} \times 4$, $60\text{ s} \times 3$, $60\text{ s} \times 4$, and $90\text{ s} \times 3$ and the most popular protocol was $30\text{ s} \times 3$ (table 1). One may question whether different protocols have different cardioprotective effects. However, only 1 study tested the hypothesis that postconditioning of $60\text{ s} \times 3$ was more efficient than postconditioning of $30\text{ s} \times 3$ [19]. Therefore, additional trials of a large scale are needed to address the time window for triggering postconditioning in patients undergoing PCI.

Conclusion

IPC has a potent protective effect on the ischemic heart. These virtues (ease of use and benefit) make it worthy of consideration in a selected group of patients with ST-elevation myocardial infarction.

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