Hormozgan Med J. 2019 June; 23(2):e91252. doi: 10.5812/hmj.91252.

Published online 2019 June 3. **Research Article**

Is Cardiac Remote Ischemic Preconditioning (RIPC) More Beneficial in Patients with Diabetes to Reduce Cardiac Troponin I After Elective Percutaneous Coronary Intervention (PCI)?

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Received 2019 March 05; **Accepted** 2019 May 11.

Abstract

Background: Intervention of choice for reperfusion is percutaneous coronary intervention (PCI) in patients with coronary artery disease (CAD), but it may have side effects; one of which is myocardial injury. Cardiac remote ischemic preconditioning (RIPC) can potentially reduce these adverse effects, especially in patients with cardiovascular risk factors.

Methods: This study received ethics approval on November 29, 2017 (ethics code: HUMS.REC.1396.93; IRCT code: IRCT20180306038978N1). It was performed on 240 patients (120 cases in the RIPC group and 120 cases in the control group). The patients undergoing PCI were randomly assigned to the RIPC group (blood pressure cuff was inflated up to 200 mmHg for 30 minutes on the non-dominant arm, and then deflated for 5 minutes (reperfusion); it was repeated 2 more times (3 times in general) or the control group (an uninflated cuff around the non-dominant arm). Cardiac troponin I (cTnI) was compared between the healthy controls and diabetic patients before and after PCI.

Results: No significant difference was observed with regard to positive cTnI ($P = 0.136$). Positive cTnI was insignificantly higher in the control group compared to the intervention group. However, the frequency of positive cTnI was significantly lower in diabetic patients in the RIPC group compared to the controls ($P < 0.001$).

Conclusions: This study demonstrated that RIPC is beneficial in diabetic patients and reduces the release of cTnI after elective PCI in these patients.

Keywords: Remote Ischemic Preconditioning, Cardiac Troponin I, Percutaneous Coronary Intervention, Diabetes

1. Background

Both types of diabetes (type 1 and type 2) are risk factors for ischemic heart disease and many studies, including clinical trials and epidemiological studies, have shown that myocardial infarction and post-infarct complications are more probable in diabetic patients (1, 2). On the other hand, in these patients, especially type 2 diabetes, atherosclerotic cardiovascular diseases occur much earlier in life (3). Not only the risk of cardiovascular events is two- to three folds higher in diabetics but also cardiovascular diseases account for 80% of mortality in type 2 diabetes (4).

For most patients with coronary artery disease (CAD) or ischemic heart disease (IHD), the treatment of choice is reperfusion via percutaneous coronary intervention (PCI), which can relieve coronary stenosis. Diabetic patients are more vulnerable to CAD and will more probably require PCI. However, PCI can lead to serious side effects such as myocardial injury and increase in myocardial biomarkers (biomarkers are increased by more than 3 times the normal reference value after intervention) (5). Therefore, it is particularly important to find appropriate interventions to prevent adverse outcomes and decrease myocardial injury after PCI (6).

Recently, studies have reported that if a remote tissue or organ undergoes brief cycles of ischemia followed by reperfusion, this can prevent fatal injury due to ischemia-reperfusion to the heart (7-9). Some recent meta-analyses (10, 11) reported that remote ischemic preconditioning (RIPC) significantly reduces the release of cardiac biomarkers after cardiac interventions in adults. Furthermore, Thielmann et al. found improving outcomes and a reduction in mortality in patients receiving RIPC (12). On the other hand, Hausenloy et al. showed that in patients

who had undergone elective coronary-artery bypass graft (CABG) with or without valve surgery, clinical outcomes were not improved by RIPC (13).

2. Objectives

Thus, studies should be designed to evaluate the effects of RIPC on the release of cardiac troponin I (cTnI) after elective PCI (12). As was mentioned earlier, diabetic patients are more susceptible to IHD and more frequently require PCI; therefore, the aim of our research was to investigate the effect of RIPC on patients with diabetes.

3. Methods

3.1. Participants

This single-blinded randomized clinical trial was conducted from May 2017 to April 2018 in the Cardiology Department of Bandar Abbas Shahid Mohammadi Hospital. Indication for elective PCI was confirmed by a cardiologist. Inclusion criteria consisted of indication for PCI based on clinical manifestations of patients, according to the Canadian Cardiovascular Society (CCS) with angina pectoris grade II - IV; elective PCI for stenosis of at least one coronary artery (> 75% occlusion in diameter); the location of the stenosis according to the definition of ACC/AHA of A or B lesions; age > 18 years; and informed consent to take part in the study.

Exclusion criteria were as follows: emergency PCI, renal dysfunction, high troponin levels before PCI (> 0.09 ng/mL), women of childbearing age, drug history of nicorandil or glibenclamide, intolerance to aspirin or clopidogrel, acute infection, inflammatory muscle diseases, dilated and hypertrophic cardiomyopathy, congenital malformations associated with myocardial ischemia, including congenital coronary stenosis or atresia, abnormal origin of the contralateral coronary sinus, abnormal origin of left coronary artery, coronary artery fistula and myocardial bridge, severe underlying diseases (severe disease, advanced cancers causing low life expectancy, severe liver and kidney dysfunction, and rheumatic diseases), rheumatic heart disease, coronary heart disease and heart failure (NYHA grade III\IV), and rheumatic fever.

3.2. Study Design

The study received Ethics approval on November 29, 2017 (ethics code: HUMS.REC.1396.93; IRCT code: IRCT20180306038978N1). The sample size included 240 patients and was determined based on previous studies with $\alpha = 0.05$ and $\beta = 0.8$. We evaluated two hundred fifty cases who had an indication for elective PCI, confirmed by a cardiologist. Ten patients were excluded regarding the inclusion and exclusion criteria of the study.

Demographic data were recorded in a prepared questionnaire. The participants were randomly allocated to two groups by means of random allocation software. Finally, two hundred forty patients took part in the study; 120 in the intervention group and 120 in the control group.

There are different protocols for RIPC. The protocol used in this study was as follows: an hour before PCI, pressure cuff was wrapped around the upper portion of the non-dominant upper extremity of patients who were randomly assigned to the RIPC group. In this study, RIPC consisted of three 5-min cycles of pressure cuff inflation on the non-dominant arm up to 200 mmHg (ischemia phase). Between every two cycles the cuff was deflated for 5 minutes (reperfusion phase). Each patient in the IRPC group received 3 cycles of ischemia-reperfusion. A deflated cuff was placed on the non-dominant arm of patients in the control group for 30 minutes and no inflation-deflation cycle was performed. At least 6 hours before PCI 300 mg clopidogrel and 300 mg aspirin were administered in all patients. Also, after applying the artery access sheath, heparin bolus (70 to 100 U/kg) was administrated as anti-coagulant to reach blood clotting time of more than 250 seconds. We did not use IIb/IIIa glycoprotein antagonists. All patients received 75 mg aspirin for 4 weeks and 75 mg clopidogrel for one year after receiving the embedded drug-coated stent. Before conducting a remote RIPC, a blood sample was taken (in order to measure the baseline cTnI) and another blood sample was taken 18 hours after PCI for measurement of cTnI. All biochemical measurements were performed without knowing the grouping of individuals. The cTnI was measured using the highly-sensitive enzymatic kit manufactured by VIDAS. A cTnI more than 0.2 μg/L was considered positive, according to Braunwald's Heart Disease textbook.

3.3. Data Analysis

Data were analyzed using the SPSS software version 25. Qualitative variables were compared using chi-square and Fisher's exact tests. To investigate the distribution normality of quantitative variables, the Kolmogorov-Smirnov test was performed; variables without normal distribution were compared using the Mann-Whitney test and those with normal distribution were compared using Student's *t*-test. The significance level of P value was considered 0.05.

4. Results

This study was performed on 240 patients (120 patients in the RIPC group and 120 patients in the control group).

We found that the demographic features and past medical history did not differ between the two groups (P > 0.05) (Table 1). By evaluating laboratory findings, we did not find a significant difference between the two groups in terms of frequency of positive cTnI (P = 0.136); however, the percentage of positive cTnI after PCI was higher in the control group (7.5% vs 2.5%) (Table 2). The frequency of positive cTnI was significantly lower in diabetic patients in the RIPC group compared to the control group (P < 0.001) (Table 3).

Table 1. Anthropometric, Demographic, and Past Medical History Findings

Variables	Groups		
	RIPC (N = 120)	Control (N = 120)	P Value
Age, y	58.38 ± 12.34	57.82 ± 11.50	0.717
Sex (male), No. (%)	75 (62.5)	72 (60)	0.691
Height, cm	171.2 ± 6.32	171.65 ± 5.87	0.601
Weight, kg	70.38 ± 9.72	70.88 ± 9.66	0.79
BMI, kg/m^2	23.94 ± 2.52	24.02 ± 2.77	0.865
Past medical history, No. (%)			
Hypertension	70 (58.3)	80 (66.7)	0.182
Diabetes	50 (41.7)	38 (31.7)	0.108
Hyperlipidemia	48 (40)	44 (36.7)	0.595
Smoking, No. (%)	50 (41.7)	48 (40)	0.793

Abbreviation: BMI, body mass index.

Table 2. Outcome Findings in Both RIPC and Control Patients

Positive cTnI, No. (%)	Groups		
	RIPC (N = 120)	Control (N = 120)	P Value
Before	0	0	-
After	3 (2.5)	9 (7.5)	0.136

Table 3. Outcome Comparison Among Diabetic Patients in Both Groups

Risk Factors	Diabetics in the RIPC Group	Diabetics in the Control Group	P Value
Diabetes (N = 88)			0.018
Negative cTnI after PCI	49 (55.68)	34 (38.64)	
Positive cTnI after PCI	1 (1.14)	4 (4.54)	

5. Discussion

The results of this study showed that RIPC reduces the release of cTnI after elective PCI in patients with diabetes. Two studies on human subjects showed contradictory results. Xu et al. found that markers of myocardial injury are decreased with RIPC but MI type IV-a and high-sensitivity cTnI (hscTnI) were not affected in patients with CHD comorbid with diabetes mellitus (DM) who had drug-eluting stent (DES) implantation (14). Moreover, Jensen et al. reported that O-linked N-acetylglucosamine (O-GlcNAc) levels involved in the resistance of insulin in muscle cells and adipocytes are influenced by humoral agents; cardioprotection is mediated by RIPC and is chronically activated in the myocardium of diabetic patients, which prevents the myocardium from more protection caused by RIPC; therefore, RIPC may have less cardioprotective effects in diabetics (15). Contrary to the findings of our study, according to the two aforementioned studies, diabetics respond worse to the RIPC.

The results of studies on non-human subjects have also proved to be contrary to the results of our study. Hu et al. demonstrated that the RIPC is highly effective in both non-diabetic and diabetic rats at reducing incidence and duration of all classes of post-ischemic ventricular tachyarrhythmias; however, atrioventricular block (AVB) was highly responsive to RIPC in non-diabetic rats and unresponsive to RIPC in diabetic rats (16).

In addition, in a canine model study by Kersten et al. it was shown that ischemic preconditioning significantly reduces the extent of infarction in normal, but non-diabetic dogs. Put it differently, ischemic preconditioning did not protect against infarction in diabetic dogs (17). Different results of the reviewed literature may be because of the difference in cardiac procedures, inclusion and exclusion criteria, sample size, and demographic characteristics of patients.

5.1. Conclusions

The results of this study show the beneficial effects of RIPC on preventing myocardial injury and release of cTnI in special subgroups of patients with diabetes. However, we did not observe significant changes in cTnI in all the patients, which necessitates the need for further investigations in multicenter prospective studies to confirm these results and to assess long-term outcomes in patients undergoing the PCI.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Acknowledgments

Hormozgan University of Medical Sciences has funded this research. Devoted efforts of the executives, the coordinators, the researchers, the patients, and the Cardiology Research Center of Shahid Mohammadi Hospital are highly appreciated.

Footnotes

Clinical Trial Registration Code: This research has been registered at www.irct.ir (IRCT code: IRCT20180306038978N1).

Conflict of Interests: No conflicts of interests have been declared by the authors.

Ethical Approval: This study received ethics approval on November 29, 2017 (ethics code: HUMS.REC.1396.93).

Funding/Support: This study was financially supported by Hormozgan University of Medical Sciences.

References

1. Gregg EW, Williams DE, Geiss L. Changes in diabetes-related complications in the United States. *N Engl J Med*. 2014;**371**(3):286–7. doi: 10.1056/NEJMc1406009. [PubMed: 25014698].
2. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;**339**(4):229–34. doi: 10.1056/NEJM199807233390404. [PubMed: 9673301].
3. Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: A population-based retrospective cohort study. *Lancet*. 2006;**368**(9529):29–36. doi: 10.1016/S0140-6736(06)68967-8. [PubMed: 16815377].
4. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia*. 2001;**44 Suppl 2**:S14–21. [PubMed: 11587045].
5. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *J Am Coll Cardiol*. 2007;**50**(22):2173–95. doi: 10.1016/j.jacc.2007.09.011. [PubMed: 18036459].
6. Zhou FZ, Song W, Yin LH, Song ZF, Yang S, Yang FB, et al. Effects of remote ischemic preconditioning on myocardial injury and endothelial function and prognosis after percutaneous coronary intervention in patients with acute coronary syndrome. *Eur Rev Med Pharmacol Sci*. 2017;**21**(20):4642–8. [PubMed: 29131250].
7. Hausenloy DJ, Yellon DM. Remote ischaemic preconditioning: Underlying mechanisms and clinical application. *Cardiovasc Res*. 2008;**79**(3):377–86. doi: 10.1093/cvr/cvn114. [PubMed: 18456674].
8. Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation*. 1993;**87**(3):893–9. [PubMed: 7680290].
9. Sivaraman V, Pickard JM, Hausenloy DJ. Remote ischaemic conditioning: Cardiac protection from afar. *Anaesthesia*. 2015;**70**(6):732–48. doi: 10.1111/anae.12973. [PubMed: 25961420]. [PubMed Central: PMC4737100].
10. Yang L, Wang G, Du Y, Ji B, Zheng Z. Remote ischemic preconditioning reduces cardiac troponin I release in cardiac surgery: A meta-analysis. *J Cardiothorac Vasc Anesth*. 2014;**28**(3):682–9. doi: 10.1053/j.jvca.2013.05.035. [PubMed: 24103716].
11. Zhou C, Liu Y, Yao Y, Zhou S, Fang N, Wang W, et al. beta-blockers and volatile anesthetics may attenuate cardioprotection by remote preconditioning in adult cardiac surgery: A meta-analysis of 15 randomized trials. *J Cardiothorac Vasc Anesth*. 2013;**27**(2):305–11. doi: 10.1053/j.jvca.2012.09.028. [PubMed: 23276595].
12. Thielmann M, Kottenberg E, Kleinbongard P, Wendt D, Gedik N, Pasa S, et al. Cardioprotective and prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: A single-centre randomised, double-blind, controlled trial. *Lancet*. 2013;**382**(9892):597–604. doi: 10.1016/S0140-6736(13)61450-6. [PubMed: 23953384].
13. Hausenloy DJ, Candilio L, Laing C, Kunst G, Pepper J, Kolvekar S, et al. Effect of remote ischemic preconditioning on clinical outcomes in patients undergoing coronary artery bypass graft surgery (ERICCA): Rationale and study design of a multi-centre randomized double-blinded controlled clinical trial. *Clin Res Cardiol*. 2012;**101**(5):339–48. doi: 10.1007/s00392-011-0397-x. [PubMed: 22186969].
14. Xu X, Zhou Y, Luo S, Zhang W, Zhao Y, Yu M, et al. Effect of remote ischemic preconditioning in the elderly patients with coronary artery disease with diabetes mellitus undergoing elective drug-eluting stent implantation. *Angiology*. 2014;**65**(8):660–6. doi: 10.1177/0003319713507332. [PubMed: 24163121].
15. Jensen RV, Zachara NE, Nielsen PH, Kimose HH, Kristiansen SB, Botker HE. Impact of O-GlcNAc on cardioprotection by remote ischaemic preconditioning in non-diabetic and diabetic patients. *Cardiovasc Res*. 2013;**97**(2):369–78. doi: 10.1093/cvr/cvs337. [PubMed: 23201773]. [PubMed Central: PMC3584969].
16. Hu Z, Chen M, Zhang P, Liu J, Abbott GW. Remote ischemic preconditioning differentially attenuates post-ischemic cardiac arrhythmia in streptozotocin-induced diabetic versus nondiabetic rats. *Cardiovasc Diabetol*. 2017;**16**(1):57. doi: 10.1186/s12933-017-0537-3. [PubMed: 28446231]. [PubMed Central: PMC5406986].
17. Kersten JR, Toller WG, Gross ER, Pagel PS, Warltier DC. Diabetes abolishes ischemic preconditioning: Role of glucose, insulin, and osmolality. *Am J Physiol Heart Circ Physiol*. 2000;**278**(4):H1218–24. doi: 10.1152/ajpheart.2000.278.4.H1218. [PubMed: 10749717].