



Adenosine Preconditioning versus Ischemic Preconditioning in Patients undergoing Off-Pump Coronary Artery Bypass (OPCAB)

Seyed Khalil Forouzannia, MD¹, Mohammad Hassan Abdollahi, MD¹, Seyed Jalil Mirhosseini, MD¹, Mehdi Hadadzadeh, MD¹, Rouholla Zarepur, MD¹, Ehsan Zarepur, MD¹, Omid Beiki, MD, PhD², Mohammadtaghi Sarebanhassanabadi, MSc^{1*}

¹Yazd Cardiovascular Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

²Kermanshah University of Medical Sciences, Kermanshah, Iran.

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Abstract

Background: During off-pump coronary artery bypass (OPCAB), the heart is subjected to ischemic and reperfusion injury. Preconditioning is a mechanism that permits the heart to tolerate myocardial ischemia. The aim of this study was to compare the effects of Adenosine preconditioning with ischemic preconditioning on the global ejection fraction (EF) in patients undergoing OPCAB.

Methods: In this single-blind, randomized controlled trial, sixty patients undergoing OPCAB were allocated into three equally-numbered groups through simple randomization: Adenosine group, ischemic group, and control group. The patients in the Adenosine group received an infusion of Adenosine. In the ischemic group, ischemic preconditioning was induced by the temporary occlusion of the left anterior descending coronary artery twice for a 2-minute period, followed by 3-minute reperfusion before bypass grafting of the first coronary vessel. The control group received an intravenous infusion of 0.9% saline. Blood samples at different times were sent for the measurement of creatine kinase isoenzyme MB (CK-MB) and cardiac troponin I (cTnI). We also recorded electrocardiographic indices and clinical parameters, including postoperative use of inotropic drugs and preoperative and postoperative EF.

Results: History of myocardial infarction, hyperlipidemia, diabetes mellitus, kidney disease, preoperative arrhythmias, and utilization of postoperative inotrope was the same between the three groups. The incidence of postoperative arrhythmias was not significant between the three groups. Also, there were no significant differences in preoperative and postoperative EF and the serum levels of enzymes (cTnI and CK-MB) between the groups.

Conclusion: Based on the findings of this study, there was no significant difference in the postoperative EF between the groups. Although the incidence of arrhythmias was higher in the ischemic preconditioning group than in the other groups, the difference between the groups did not constitute statistical significance.

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Keywords: Coronary artery bypass, off-pump • Ischemic preconditioning • Reperfusion injury

*Corresponding Author: Mohammadtaghi Sarebanhassanabadi, Yazd Cardiovascular Research Center, Afshar Hospital, Jomhuri Boulevard, Yazd, Iran. 891794556. Tel: +98 351 5231421. Fax: +98 351 5253335. E-mail: mtsareban@gmail.com.

Introduction

Despite the use of conventional measures to provide myocardial protection, perioperative myocardial ischemia and dysfunction remain commonplace after cardiac surgery. Preconditioning is an entity; it requires exposure to a form of stress or stimulus in order for the entity to be more resistant against a future encounter with the same stimulus. Myocardial preconditioning is a powerful, endogenously regulated means of myocardial protection that may also have some clinical benefit for patients undergoing cardiac surgery.

There are several types of preconditioning: (1) ischemic preconditioning (IPC). In IPC, ischemia induces endogenous release of Adenosine, opiates, and bradykinin which activates G-protein coupled pathways; (2) Adenosine preconditioning (APC). In APC, Adenosine induces the activation of A1 and A3 receptors and Adenosine triphosphate (ATP) sensitive potassium channels; and (3) excitotoxic (pharmacologic) preconditioning (EPC). In EPC, pharmacologic agents induce the stimulation of N-methyl-D-aspartate (NMDA) receptors, nitric oxide, and ATP-sensitive potassium channels.

IPC was first identified in 1986 by Murry et al.¹ The protective effect of IPC has two windows of protection: the first lasts between 4-6 hours and is named classical or early preconditioning (local action of Adenosine, opiates, and bradykinin) and the second beings at 24 hours and lasts up to 72 hours after ischemia and reperfusion stimulus. IPC is endogenous myocardial protection triggered by exposure to brief periods of ischemia for the adaptation of the myocardium so as to tolerate ischemic stress.² Several proposed mechanisms are responsible for IPC, including the activation of several myocardial G protein-coupled receptors, most notably A1 Adenosine and α 1-adrenergic receptors. Protein kinase C appears to be a key cellular mediator of IPC, in part through the activation of ATP-sensitive potassium channels.³ Adenosine is most distinguished for its potent vasodilation of the vasculature. However, it also promotes glycolysis and activates potassium-sensitive Adenosine triphosphate (KATP) channels. Adenosine also strongly inhibits neutrophil function such as superoxide anion production, protease release, and adherence to coronary endothelial cells. Consequently, Adenosine attenuates ischemic injury as well as neutrophil-mediated reperfusion injury. There are three Adenosine receptors: (1) A1 receptors, which are located on cardiomyocytes and vascular smooth muscle cells; 2) A2 receptors, which are situated on endothelial and vascular smooth muscle cells; and 3) A3 receptors, which are located on ventricular myocytes. Adenosine has also been implicated in the cardioprotective phenomenon of IPC. Experimental studies have demonstrated that Adenosine reduces post-ischemic injury when administered before ischemia and at the onset of reperfusion. Clinical studies have demonstrated that Adenosine has cardioprotective properties. A large number of experimental studies have reported that Adenosine turns

on the protein kinase C (PKC)-mediated pathway, which accounts for the cardioprotection conferred by IPC contrasts. Nevertheless, there is a scarcity of clinical data documenting the preconditioning-like protective effect of Adenosine during cardiac operations in humans.⁴ Adenosine plays an important role in different protective and adaptive responses to ischemia and has been suggested to induce IPC.⁵

The aim of this study was to compare the effects of exogenous APC with IPC on the global ejection fraction (EF) in patients undergoing off-pump coronary artery bypass (OPCAB).

Methods

In this single-blind, randomized controlled trial study, sixty patients undergoing OPCAB were allocated into three equally numbered groups through simple randomization: Adenosine group, ischemic group, and control group. The patients were unaware of exact intervention in each group. The method of surgery and anesthesia was the same in all the patients. Also, the surgeon and anesthesiologist were similar for all the patients. An Octopus (Octopus® 4.3 code: 29403, Medtronic) device was fixed to expose and stabilize the obtuse marginal artery of the heart, and the intracoronary shunt was used for all the patients. Anesthesia was performed with Thiopental sodium (5 mg/kg), Pancuronium (0.01 mg/kg), and Fentanyl (10 mic/kg) and maintained with Propofol (10 mic/kg/min) and Fentanyl.

The patients in the Adenosine group were given an infusion of Adenosine through a central venous catheter via the internal jugular vein. The initial infusion rate was 50 mic/kg/min, the infusion speed was increased every minute to the dose of 150 mic/kg/min, and the total duration of Adenosine infusion lasted for 10 minutes. IPC was induced by occluding the left anterior descending coronary artery (LAD) twice for a 2-minute period, followed by a 3-minute LAD reperfusion, before bypass grafting of the first coronary vessel. The patients of the control group received an intravenous infusion of 0.9% saline instead during the infusion period. Five minutes after the completion of Adenosine or saline infusion protocol, revascularization was commenced. Blood samples were collected at the following time points: T0 (before incision), T1 (60 minutes), and T2 (24 hours after revascularization).

Levels of MB isoenzyme of creatine phosphokinase (CPK-MB) and cardiac troponin I (CTnI) were measured (RAMP Troponin I Assay). Normal level of cTnI was < 0.1 ng/ml. Electrocardiographic indices, including premature atrial contractions, atrial fibrillation, premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation, were followed up for 24 hours. Clinical parameters such as the postoperative use of inotropic drugs and preoperative and postoperative EF were recorded.



To test for the normality of the data, we used the Kolmogorov-Smirnov test. For the analysis of the data, the chi-squared test, Fisher exact test (expanded), and analysis of variance (ANOVA) were employed. The level of significance was set at < 0.05 . For the statistical analyses, the statistical software SPSS (version 16.0) for Windows (SPSS Inc., Chicago, IL) was employed.

Results

The mean age of the patients was 61.45 ± 10.5 years. There was no significant difference in history of myocardial infarction, hyperlipidemia, diabetes mellitus, kidney disease, hypertension, and preoperative arrhythmias between the three groups (Table 1).

Forty-one patients were male and 19 were female. There was no significant difference in the number of grafts and the use of inotrope between the three groups (Table 1). There was also no significant difference in the average concentration of cTnI and CK-MB at the time points of T0, T1, and T2 between the study groups (Tables 2 and 3). There was no statistically significant difference in terms of postoperative EF between the three groups (Table 4). There was no arrhythmia in the IPC group, while 2 patients in the APC group had arrhythmias after surgery. IPC and APC both decreased the incidence of postoperative arrhythmias in OPCAB, but the reduction rate was more pronounced in the former (Table 4). However, there was no statistically significant difference regarding arrhythmias between the three groups (p value = 0.51).

Table 1. Characteristics of the patients*

	Types of preconditioning			P value
	IPC (n = 20)	ADO-PC (n = 20)	Control (n = 20)	
Age (y)	61.80±9.52	58.50±13.99	64.05±8.19	0.275
Sex				0.116
Male	13 (65)	17 (85)	11 (55)	
Female	7 (35)	3 (15)	9 (45)	
Preoperative history				
Myocardial infarction	6 (30)	3 (15)	4 (20)	0.629
Diabetes mellitus	8 (40)	4 (20)	8 (40)	0.301
Hyperlipidemia	7 (35)	8 (40)	10 (50)	0.619
Kidney disease	1 (5)	1 (5)	4 (20)	0.343
Hypertension	6 (30)	8 (40)	12 (60)	0.63
Number of grafts				0.464
1	1 (5)	4 (20)	2 (10)	
2	10 (50)	5 (25)	8 (40)	
3	9 (45)	11 (55)	10 (50)	
Use of inotropes				0.676
Yes	2 (10)	4 (20)	3 (15)	
No	18 (90)	16 (80)	17 (85)	

*Data are presented as mean±SD or n (%).

IPC, Ischemic preconditioning; ADO-PC, Adenosine preconditioning

Table 2. Mean level of cardiac troponin I (CTnI) before incision (T0) and 60 minutes (T1) and 24 hours after revascularization (T2)

	Types of preconditioning			P value
	IPC	ADO-PC	Control	
T0	0.085	0.250	0.046	0.830
T1	0.295	0.559	0.184	0.504
T2	1.377	1.992	1.193	0.714

IPC, Ischemic preconditioning; ADO-PC, Adenosine preconditioning

Table 3. Mean level of CPK-MB before incision (T0) and 60 minutes (T1) and 24 hours after revascularization (T2)

	Types of preconditioning			P value
	IPC	ADO-PC	Control	
T0	21.5	31.5	20.8	0.053
T1	34.0	44.4	27.8	0.420
T2	62.7	102.3	43.6	0.451

CPK-MB, Creatine phosphokinase-MB; IPC, Ischemic preconditioning; ADO-PC, Adenosine preconditioning

Table 4. Comparison of postoperative EF and postoperative arrhythmias between the groups

	Types of preconditioning			P value
	IPC	ADO-PC	Control	
Postoperative EF (Mean±SD)	43±8.64	44.8±8.33	43.5±10.4	0.451
Postoperative Arrhythmia [n (%)]				0.510
Yes	0	2 (10)	3 (15)	
No	20 (100)	18 (90)	17 (85)	

*Data are presented as mean±SD or n (%).

EF, Ejection fraction; IPC, Ischemic preconditioning; ADO-PC, Adenosine preconditioning

Discussion

In this single-blind, randomized controlled trial study, sixty patients undergoing OPCAB were allocated into three equally numbered groups: Adenosine group, ischemic group, and control group. The aim of this study was to compare the effects of APC with IPC on the global EF in patients undergoing OPCAB.

Zhong-Kai et al.⁶ reported that IPC constituted a potential additional myocardial protective role in multi-vessel diseased patients undergoing OPCAB. Benjamin et al.⁷ in an experimental study showed that preconditioning with Adenosine prior to elective ischemia/reperfusion was a promising strategy to decrease spontaneous atrial arrhythmias in patients undergoing OPCAB. Our results indicated that although both IPC and APC could decrease the incidence of postoperative arrhythmias in OPCAB, the former was more effective than was the latter with respect to the reduction in the incidence of postoperative arrhythmias. Nonetheless, we did not find any statistically significant difference between our study groups.

The mechanism of postoperative arrhythmias includes reentry, enhanced automaticity, and triggered activity. Transmural reentry is the most likely mechanism underlying ischemia reperfusion arrhythmias. Evidence suggests that both oxygen-derived free radicals and transient calcium overload have important pathologic roles in arrhythmogenesis after heart surgery.⁶ Postoperative arrhythmias are believed to be multifactorial, but incomplete myocardial protection is a major cause. The vulnerability to reperfusion-induced arrhythmias is critically dependent on the duration of the preceding ischemia. The cause of myocardial ischemia may be an important factor in the genesis of arrhythmias; post-cardioplegic arrhythmias are deemed one of the variables in comparing strategies for myocardial protection. Laurikka et al.⁸ reported that IPC was applicable and safe in patients undergoing OPCAB. The authors also concluded that not only did IPC reduce the immediate myocardial enzyme release, but also it prohibited the postoperative increase in the heart rate and augmented the recovery of the stroke volume index (SVI). In our study, the level of enzymes was not significantly different between the three groups.

Drenger et al.⁹ reported that perioperative coronary occlusion during OPCAB led to an increase in the production of ischemia-related metabolic products. The application of methods such as IPC or volatile anesthesia appears to reduce the metabolic deficit, free-radical production, and physiologic changes. In contrast to our study, in which IPC proved to confer better myocardial protection than did APC, Piriou and Chiari¹⁰ concluded that IPC was not necessary.

In the Sadigh et al. study,⁵ a low-dose Adenosine infusion reduced the ischemic burden and enhanced left ventricular regional systolic function in the ischemic walls of patients with exercise-induced myocardial ischemia; this confirmed that

Adenosine is a potential preconditioning agent in humans. As was previously mentioned, our results revealed that APC was not as efficient as was IPC in offering myocardial protection. Yang J and Li LH¹¹ concluded that APC could reduce the release of CK-MB and cTnI, begotten by myocardial injuries during OPCAB. Lasley et al.¹² showed that a transient rise in interstitial fluid (ISF) Adenosine could reduce the myocardial infarct size but the prescription of Adenosine alone could not fully replicate the protective effects of IPC. Belhomme et al.⁴ demonstrated that Adenosine could turn on the PKC-mediated signaling pathway involved in preconditioning but this biochemical event did not translate into reduced cell necrosis after coronary artery bypass grafting, suggesting that a preconditioning-like protocol might not be best suited for utilizing the otherwise well-documented cardioprotective effects of Adenosine. Jin et al.¹³ reported that Adenosine pretreatment was a cardioprotective agent during open-heart surgery in pediatric patients. Our study showed that the levels of cTnI and CK-MB were not different between the three groups of IPC, APC, and control group.

Conclusions

Our results showed no significant difference in the postoperative EF between the groups. Although the incidence of arrhythmias was higher in the IPC group than in the other groups, there was no significant difference between the groups during OPCAB. To compare the efficiency of the two methods, further studies with more patients and longer follow-up periods are suggested.

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