Original Article

Evaluation of the Effects of Ischemic Preconditioning with a Short Reperfusion Phase on Patients Undergoing a Coronary Artery Bypass Graft

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Purpose: This study was conducted to evaluate the effects of ischemic preconditioning (IP) with a short period of reperfusion (2 min) during brief ischemic preconditioning (6 min) on patients undergoing coronary artery bypass grafting (CABG).

Methods: In a randomized controlled trial, 40 patients undergoing on-pump CABG with cold blood cardioplegia were allocated into two groups, one IP and one control. IP was induced by 2 cycles of ascending aorta clamping (2 min for each) followed by two reperfusion phases (1 min for each). Left ventricular ejection fraction (LVEF) was measured before and after surgery. Creatine phosphokinase (CK) and CK-MB were measured 12 hrs before surgery, immediately after aortic clamping, and 24 hrs after CABG. Postoperative myocardial infarction (MI), ventricular arrhythmia, duration of inotropic support, and hemodynamic parameters were also noted.

Results: More patients in the control group needed inotropic support (65% vs. 40%, P<0.05). Moreover, duration of inotropic support was longer in the control group (9 ± 1.2 vs. 3.8 ± 1.4 hrs, P<0.05). There were no significant differences between two groups regarding development of ventricular arrhythmia, MI, values of CK, CK-MB, and postoperative LVEF. No patient needed an intra-aortic balloon pump, and no deaths occurred.

Conclusion: A short period of reperfusion phase declined post-CABG inotrope requirements; however, it did not reduce the cardiac enzymes. Our results suggested that reperfusion should be longer than 2 min to be capable of reducing cardiac enzymes. (Ann Thorac Cardiovasc Surg 2010; 16: 248–252)

Key words: coronary artery bypass graft, ischemic preconditioning, cardiac enzymes

Introduction

The protective effects of ischemic preconditioning (IP) on human heart after cardiac surgeries are well defined.[1)] Initially, the ability of short periods of ischemia to limit infarct size was referred to IP.[2)] It was then extended to include beneficial effects on ischemia and reperfusion-induced arrhythmias[3)] and on myocardial stunning.[4)] Moreover, it has been suggested that IP reduces postoperative inotropic requirements and has a preventive role in

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postoperative myocardial dysfunction.[5-7)]

Despite a variety of IP timings that have been employed during cardiac surgeries in different studies, the minimum duration of the ischemia, reperfusion, and total IP that are able to protect the heart have not yet been well defined.

Because IP is an acceptable approach to cardiac protection during heart surgeries, determination of the minimum durations of ischemia and reperfusion phases, thus shortening the total duration of IP, can help cardiac surgeons to use an effective IP duration while they avoid time-consuming methods. To the best of our knowledge, the shortest period of ischemia phase (1 min) and IP (6 min) has been reported by Illes and colleagues.[5)] Although they failed to show a reduction in postoperative cardiac enzymes, it seems that they have reached the lowest duration of ischemic phase and total duration of IP. In contrast, the shortest period of reperfusion phase to enable improved cardiac hemodynamics without decline in postoperative cardiac enzymes has not yet been recognized. The shortest period of reperfusion phase was 4 min, which resulted in a reduction in postoperative cardiac enzymes.[6)]

The present study aimed to evaluate the effects of a brief IP with a short period of reperfusion on multiple postoperative parameters in patients undergoing coronary artery bypass grafting (CABG). For this purpose, we selected the shortest period of IP (6 min) that had been reported.[5)] Furthermore, because the shortest ischemic time that reduced postoperative cardiac enzymes was 4 min,[6–9)] this duration was selected for the ischemia period in our study. Moreover, we reduced the duration of reperfusion phase to 2 min, which differentiates our protocol from previous reports.[5,6,10–13)] The favorable outcome was an improvement in postoperative hemodynamics.

Patients and Methods

This randomized controlled trial was carried out at Shariati hospital. An ethics committee of human research of Tehran University of Medical Sciences approved the study, and all patients gave an informed consent before enrollment.

Forty patients who were candidates for elective CABG, aged 40–60 years, entered the study. Exclusion criteria were patients with left ventricular ejection fraction (LVEF) of less than 30%; severe calcification of the ascending aorta; history of unstable angina within the past two weeks or recent (≤3 months) myocardial infarction (MI); additional cardiac disease (e.g., prominent valvular heart diseases) or noncardiac disorders (e.g., pulmonary hypertension and renal failure); cardiac reoperation; and need for an emergency operation.

The patients were randomly divided into two groups of IP and control, using a random table of numbers. They all underwent on-pump CABG with cold-blood cardioplegia.

In the IP group, IP was induced by two cycles of ascending aorta clamping (2 min for each), followed by two reperfusion phases (1 min for each) before cross-clamping. The control group received no IP.

Anesthesia and surgical techniques

The anesthetic and surgery techniques were the same in all cases. Anesthesia was induced using sufentanil, midazolam, and pancuronium. Cardiopulmonary bypass (CPB) with nonpulsatile perfusion flow (2.2 L/min/m^2) was established using membrane oxygenators with arterial line filtration. No hypothermia was induced. CPB was performed using aortic root and 2-stage single venous cannula. A retrograde, self-inflating coronary sinus cardioplegia cannula with a pressure-monitoring port was guided into place. For antegrade cardioplegia, the aortic root was catheterized using a 9-gauge cannula. Distal anastomoses were carried out as right coronary artery, circumflex artery, left anterior descending artery, and proximal anastomoses. In all subjects, grafting of the left internal thoracic artery to the left anterior descending artery was performed. For induction of cardioplegia, a solution with a 21% hematocrit and potassium concentrations of 21 mmol/L and 9 mmol/L in the initial and subsequent successive doses was used. Blood from the pump reservoir was mixed with crystalloid serum in a ratio of 4:1. The temperature of the mentioned solution was maintained at 4ºC. The pressures of cardioplegia were respectively 80 mmHg and 30 to 50 mmHg during antegrade and retrograde deliveries. The flow was at least 200 mL/min. Using a high-potassium solution, we performed 1.5-min antegrade cardioplegia and then a 2.5-min retrograde cardioplegia. After each distal anastomosis, cardioplegia solution was administered retrograde for 1 min to grafts of the right coronary and left circumflex arteries. Lastly, retrograde warm cardioplegia (37°C) was administered about 3 min before cross-clamping removal.[14)]

Postoperative care

All patients were mechanically ventilated until achieving stable hemodynamics and recovering from the anesthesia. To maintain filling pressure at least at the preoperative level, an infusion of volume was perfumed. After the patients had been weaned from the ventilator, they were given β-blockers. If arrhythmias developed, cardiological

Table 1. Preoperative characteristics of patients in IP and control groups

Variables	IP group (n = 20)	Control group (n = 20)	P value
Age (years)	48 ± 7.8	45 ± 5.8	0.72
Sex (female)	8 (40%)	5 (25%)	0.5
Preoperative LVEF fraction	49.5 ± 8.6	44.2 ± 9.8	0.092
Previous MI	8 (40%)	11 (55%)	0.52
NYHA class (2, 3)	(8,12)	(7,13)	0.9
Hyperlipidemia	5 (25%)	11 (55%)	0.102
Hypertension	7 (35%)	4 (20%)	0.48

LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association

counseling was requested for pharmacological and interventional management.

Measurements

LVEF was measured using echocardiography before and after surgery. Creatine phosphokinase (CK) and CK-MB were obtained 12 hrs before surgery, immediately after cross-clamping and 24 hrs later. Required data were recorded for each patient. They included demographics; pre- and postoperative LVEF, CK, and CK-MB levels; duration of cardiopulmonary bypass (CPB) (needing postoperative inotropic support and its length); duration of ICU stay; myocardial infarction; occurrence of ventricular arrhythmia; and intra-aortic balloon pump (IABP) requirements.

Perioperative infarction was diagnosed if any new Q waves appeared with one-third of QRS height and for longer than 0.04 sec, or if CK-MB passed beyond 100 IU/L.[15]

Statistical analysis

Data were expressed as mean ± SD or numbers. A statistical analysis was done using a statistical package (SPSS Inc., Chicago, IL, USA; Version 11.5). Fischer's exact test, χ^2, independent samples t-test, and a paired samples t-test were used to analyze data. P value <0.05 was considered statistically significant.

Results

According to inclusion and exclusion criteria, 40 patients (20 in each group) were enrolled in the study. There were no significant differences between the two groups regarding preoperative parameters. Table 1 shows the preoperative characteristics of the patients in each group.

Neither were any significant differences observed regarding the postoperative values of CK and CK-MB (Figs. 1 and 2). Also, postoperative LVEF was significantly higher in the IP group when compared to the control group (P = 0.001). More patients in the control group needed inotropic support compared to the IP group, and the duration of inotropic support was significantly longer in the control group (Table 2). No patient needed an intra-aortic balloon pump, and no deaths occurred.

Discussion

Our results showed that a reduction of reperfusion phase to 2 min significantly reduced the inotropic support need; however, despite an appropriate ischemic period, it was unable to make significant differences between IP and control groups regarding most postoperative factors.

It has been shown that IP improves postoperative hemodynamic parameters after cardiac operation.[16] In a study by Illes et al.,[5] IP induced by 1 minute of aortic cross-clamping followed by 5 min of reperfusion during normothermic cardiopulmonary bypass, immediately before cardioplegic arrest. The results of this study showed that ischemic preconditioning significantly improves heart function after cardiac operations and decreases the need for inotropic support, but they failed to show a reduction in postoperative cardiac enzymes. Consistent with the mentioned study, in spite of a reduction in postoperative inotropic support, our method could not show significant decline in cardiac enzymes. Thus it seems that a short period of IP (6 min) reduces postoperative inotropic support in spite of no significant reduction in cardiac enzymes. And similar to the study by Illes and associates,[5] the cardiac enzymes levels were even slightly higher in the IP group, which may suggest some protective effects of IP mediated through apoptotic dependent mechanisms.[17]

Our findings showed that brief IP improves postoperative

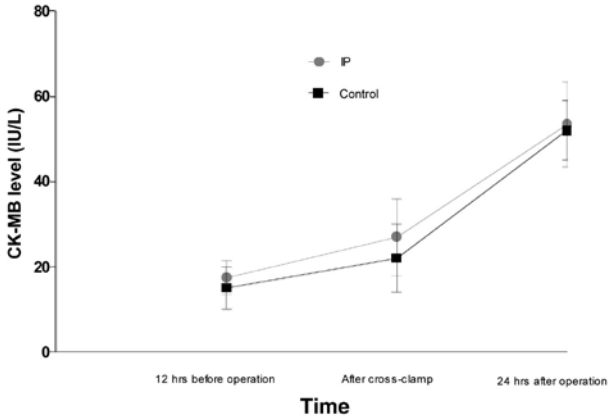

Fig. 1. Comparison of CK-MB values in IP and control groups during the 12 hrs before surgery, immediately after cross-clamping, and 24 hrs after surgery. There were no significant differences between CK-MB values in the IP group or equivalent time in the control group (P>0.05).
IP, ischemic preconditioning.

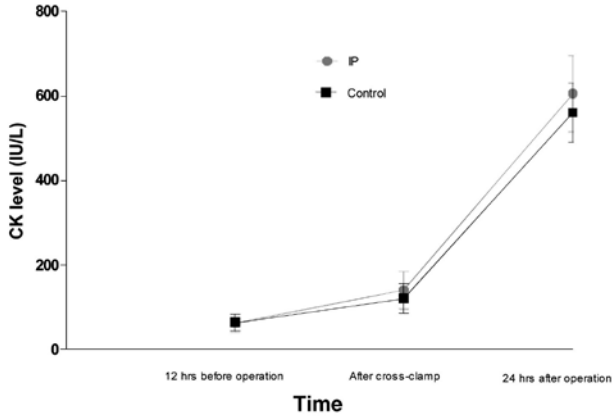

Fig. 2. Comparison of CK values in IP and control groups in 12 hrs before surgery, immediately after cross-clamping, and 24 hrs after surgery. There were no significant differences between CK values in the IP group and equivalent time in the control group (P>0.05).
IP: ischemic preconditioning

Table 2. Comparison of postoperative parameters between IP and control groups

Variables	IP group (n = 20)	Control group (n = 20)	P value
Cross-clamping time (min)	61.9 ± 18	65.4 ± 29	0.65
Cardiopulmonary bypass time (min)	103.3 ± 29	99.6 ± 21.7	0.52
Need for inotropics (n)	8 (40%)	13 (65%)	0.20
Postoperative MI	1 (5%)	3 (15%)	0.60
Duration of ICU stay (hr)	20.5	21.2	0.37
Duration of inotropic support (hr)	3.8 ± 1.4	9 ± 2.1	<0.01
Ventricular arrhythmia	1 (5%)	3 (15%)	0.60
Postoperative LVEF (%)	48.2 ± 1.45	42.5 ± 3.17	0.001

MI, myocardial infarction; LVEF, left ventricular ejection fraction

LVEF and inotropic requirement. Improvements in ventricular function following IP have been shown in several studies using either cardiac index[5,6] or LVEF.[18] Also, several studies have suggested a reduction in postoperative inotropic requirement.[5,19] Because preoperative LVEFs and other baseline characteristics were not significantly different between the IP and control groups, the difference between the two groups regarding inotropic support could not be related to these factors. This phenomenon can be explained in part by the preventive effects of IP on stunning.[5]

According to previous reports, IP suppresses postoperative arrhythmias.[14,19] In line with these reports, we found a lower number of patients developing ventricular arrhythmias in the IP group, but there were no significant differences between the two groups. In their study, Wu et al.[14] found that ventricular tachycardia (VT) decreased within 2 hrs and over the period of 24 to 48 hours after reperfusion, but not during 2 to 24 hrs. This may explain why we could find no significant differences between the two groups regarding the development of VT. In our study, VT was recorded when the patients were under Holter monitoring in ICU, which usually was not longer than 24 hrs postoperatively. Also, we could find no significant association between ICU stay and IP, as previously reported by other studies.[5,19]

The present study had several limitations. We did not use cardiac troponin, a more-specific biomarker of cardiac injury compared to CK-MB.

In conclusion, IP with a short period of reperfusion phase declined post-CABG inotropic support requirements; however, it did not reduce the cardiac enzymes.

Our results suggested that reperfusion should be longer than 2 min to be able to reduce cardiac enzymes. It seems that for enough cardiac protection, the duration of reperfusion phase and IP should respectively take 2 and 6 min or more. Future studies are recommended to investigate the effects of IP on serum inflammatory factor levels, such as Interleukin-6, besides specific markers of myocardial injury.

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References

1. Teoh LK, Grant R, Hulf JA, Pugsley WB, Yellon DM. A comparison between ischemic preconditioning, intermittent cross-clamp fibrillation and cold crystalloid cardioplegia for myocardial protection during coronary artery bypass graft surgery. *Cardiovasc Surg* 2002; **10**: 251–5.
2. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; **74**: 1124–36.
3. Shiki K, Hearse DJ. Preconditioning of ischemic myocardium: reperfusion-induced arrhythmias. *Am J Physiol* 1987; **253**: H1470–6.
4. Cohen MV, Liu GS, Downey JM. Preconditioning causes improved wall motion as well as smaller infarcts after transient coronary occlusion in rabbits. *Circulation* 1991; **84**: 341–9.
5. Illes RW, Swoyer KD. Prospective, randomized clinical study of ischemic preconditioning as an adjunct to intermittent cold blood cardioplegia. *Ann Thorac Surg* 1998; **65**: 748–52.
6. Wu ZK, Tarkka MR, Pehkonen E, Kaukinen L, Honkonen EL, et al. Ischaemic preconditioning has a beneficial effect on left ventricular haemodynamic function after a coronary artery biopass grafting operation. *Scand Cardiovasc J* 2000; **34**: 247–53.
7. Wu ZK, Vikman S, Laurikka J, Pehkonen E, Iivainen T, et al. Nonlinear heart rate variability in CABG patients and the preconditioning effect. *Eur J Cardiothorac Surg* 2005; **28**: 109–13.
8. Wu ZK, Tarkka MR, Eloranta J, Pehkonen E, Kaukinen L, et al. Effect of ischemic preconditioning on myocardial protection in coronary artery bypass graft patients : can the free radicals act as a trigger for ischemic preconditioning? *Chest* 2001; **119**: 1061–8.
9. Wu ZK, Tarkka MR, Pehkonen E, Kaukinen L, Honkonen EL, et al. Beneficial effects of ischemic preconditioning on right ventricular function after coronary artery bypass grafting. *Ann Thorac Surg* 2000; **70**: 1551–7.
10. Alkhulaifi AM, Yellon DM, Pugsley WB. Preconditioning the human heart during aorto-coronary bypass surgery. *Eur J Cardiothorac Surg* 1994; **8**: 270–5.
11. Cremer J, Steinhoff G, Karck M, Ahnsell T, Brandt M, et al. Ischemic preconditioning prior to myocardial protection with cold blood cardioplegia in coronary surgery. *Eur J Cardiothorac Surg* 1997; **12**: 753–8.
12. Belhomme D, Peynet J, Florens E, Tibourtine O, Kitakaze M, et al. Is adenosine preconditioning truly cardioprotective in coronary artery bypass surgery? *Ann Thorac Surg* 2000; **70**: 590–4.
13. Ghosh S, Galinanes M. Protection of the human heart with ischemic preconditioning during cardiac surgery: role of cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 2003; **126**: 133–42.
14. Wu ZK, Iivainen T, Pehkonen E, Laurikka J, Tarkka MR. Ischemic preconditioning suppresses ventricular tachyarrhythmias after myocardial revascularization. *Circulation* 2002; **106**: 3091–6.
15. Carrier M, Pellerin M, Perrault LP, Solymoss BC, Pelletier LC. Troponin levels in patients with myocardial infarction after coronary artery bypass grafting. *Ann Thorac Surg* 2000; **69**: 435–40.
16. Wu ZK, Pehkonen E, Laurikka J, Kaukinen L, Honkonen EL, et al. The protective effects of preconditioning decline in aged patients undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2001; **122**: 972–8.
17. Wu ZK, Laurikka J, Saraste A, Kyto V, Pehkonen EJ, et al. Cardiomyocyte apoptosis and ischemic preconditioning in open heart operations. *Ann Thorac Surg* 2003; **76**: 528–34.
18. Buyukates M, Kalaycioglu S, Oz E, Soncul H. Effects of ischemic preconditioning in human heart. *J Card Surg* 2005; **20**: 241–5.
19. Li G, Chen S, Lu E, Li Y. Ischemic preconditioning improves preservation with cold blood cardioplegia in valve replacement patients. *Eur J Cardiothorac Surg* 1999; **15**: 653–7.