Role of Ischemic Preconditioning in myocardial protection during CABG

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Abstract

Background: Remote ischemic preconditioning (RIPC) is a biologic phenomenon in which a brief ischemia followed by reperfusion of an organ makes a distant organ more resistant against sustained ischemic insult. In order to assess whether RIPC can protect myocardium in CABG patients against ischemia, we conducted this study.

Methods and materials: Elective coronary artery bypass grafting (CABG) patients were randomized to either receive RIPC (group A=145) or not (group B=145) after anesthesia. RIPC induction was by inflating a blood pressure cuff on the upper arm. The outcome was evaluated by comparison between serum troponin levels at various times after surgery.

Results: Mean serum troponin level at various times after surgery (6, 12, 24, 72 hours after the operation) in group A was significantly lower than group B ($p<0.05$). In addition decreasing trend of post operative serum troponin level was more significant in group A than group B ($p<0.0001$).

Conclusion: RIPC can protect myocardium in CABG patients against ischemia and can be recommended for clinical use during open cardiac surgeries in order to decrease the incidence of myocardial ischemic injury following cardioplegic arrest.

Key words: Coronary artery bypass grafting, myocardial ischemia, myocardial reperfusion injury troponin

Introduction

Preconditioning is the biological process of adaptation in which, if the heart (and possibly other tissues) had a short period of ischemia followed by reperfusion, heart may then be able to re-establish itself more tolerant to subsequent longer period of ischemia. At remote type of this phenomenon which is also called inter organ, induction of ischemia in one organ is able to withstand other organs against subsequent ischemia (1, 2). Therefore, a better understanding of this phenomenon, including the creation or duration of ischemia, ischemic interval between initial and subsequent ischemia and the relationships among ischemic organs, is an interesting subject to study that may result into reducing the adverse effects of tissue ischemia and reperfusion injury in different tissues, especially heart tissue. The first successful application of remote

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ischemic preconditioning (RIPC) on clinical situation was reported by Cheung et al (3). Inflation of the manometer cuff around the upper or lower limbs of human samples also can be used as a remote, non-invasive stimulant of RIPC due to the induction of transient ischemia of the extremities (4). Moreover, the occurrence of ischemic post conditioning (iPost) concept, stating that the interference can be made during reperfusion of the myocardium after the incidence of myocardial ischemia, which may lead to better myocardial protection, performs a new role in the treatment of coronary heart disease in post myocardial infarction phase (5, 6). Also the protection of myocardium against myocardial ischemia during cardiac surgery is one of the important aspects of these surgeries which are directly related to the outcome of the patients. The complications following myocardial ischemia or myocardial stunning in these patients including hemodynamic impairment and arrhythmia have significant effects on the incidence of morbidity and mortality.

Methods and materials

After the approval of the study protocol had been granted by the institutional review board and ethic committee of Tehran University of medical sciences and written informed consent had been obtained from each patient, 290 patients underwent elective on-pump coronary artery bypass grafting (CABG) at Rajaie Cardiovascular Medical & Research Center from 2010 to 2012 were enrolled in this randomized clinical trial. All patients were indicated for elective CABG based on their clinical and angiographic findings with the inclusion criteria of preoperative serum troponin level < 0.01 µg/L. The patients who suffered from concomitant diseases such as liver, renal or respiratory failure, unstable angina or myocardial infarction within the last 4 weeks, peripheral vascular disease of the upper extremities and the cases who underwent concomitant non-coronary surgeries including valvular surgeries, emergency surgery, redo surgery or off-pump CABG were excluded from the study. The cases were randomly divided into 2 groups. For group A; 145 cases, remote ischemic preconditioning was induced and group B patients; 145 cases underwent the surgery with no remote preconditioning induction. All patients underwent CABG by the same surgical team and technique with the aid of cardioplegic arrest and cardiopulmonary bypass (CPB). In group A, in order to induce remote ischemic preconditioning, manometer cuff was applied around the upper limb (the site without the arterial line) and inflated to 200 mm/Hg 3 times for 5 minutes with 5 minutes rest between each inflation (a total of 25 minutes). This process was performed after induction of anesthesia, before CPB and during the time interval of left internal mammary artery (LIMA) and saphenous vein harvesting. In group B, manometer cuff was applied around the upper limb (the site without the arterial line) without inflation for 25 minutes. In order to evaluate the serum levels of troponin I and T, blood samples were collected before induction of anesthesia, 6, 12, 24 and 72 hours after the operation. In case the serum level of troponin of the first blood sample was more than 0.01 ng/dL, the patient was excluded from the study. The required data were collected and Statistical analyses were performed with SPSS software version 15. Clinical data are expressed as mean values ± standard deviation. Differences were analyzed with student's T-test and Chi-square test. In order to compare the trend between 2 groups Anova repeated measurement was used. A value of $P<0.05$ was considered statistically significant.

Results

The number of patients participating in this study was 290 patients, including 145 patients in group A (116 males and 29 females, with mean age of 62.03 ± 10.106 years) and 145 cases in group B (110 males and 35 females with mean age of 61.92±10.007 years). The mean body mass index (BMI) of the patients in group A was 25.88±2.618 versus 26 ±2.698 in group B. There were no significant differences between two groups of the study regarding age, gender, BMI, number of grafts, type of the graft, aortic cross clamping time and cardiopulmonary bypass time. The mean ejection fraction (EF) before surgery in group A was 42.03% ± 8.63% versus group B 43.27% ± 7.82% with no significant difference. However, the mean EF after surgery was significantly different between groups (44.93 % ± 8.31 % in group A versus 41.44% ± 8.22% group B, $p<0.05$). The mean level of creatinine before the operation was 1.02 ±0.25 in group A versus 0.97 ±0.21 in group B and the mean level of creatinine after the operation was 1.05±0.34 in group A versus 1.07 ± 0.35 in group B. There were no significant differences regarding preoperative and postoperative level of creatinine between groups. The mean levels of troponin 6, 12, 24 and 72 hours after the surgery was compared between groups and the results have been demonstrated in ta-

ble 1.Figure 1 shows the decreasing trend of troponin level in each group. The mean level of serum lactate after the surgery in group A was 3.28 ± 1.74 versus 3.56 ± 1.76 in group B with no significant difference. The mean required inotrope was 0.021 ± 0.039 in group A versus 0.021 ± 0.057 in group B with no significant difference. Electrocardiographic changes before and after the surgery was compared between groups and no significant difference was reported. One-hundred and twenty six cases were admitted in ICU for 3 days in group A versus 127 patients in group B, 17 patients stayed in ICU for 4 days in group A versus 16 cases in group B and 2 cases stayed in ICU for 5 days in group A the same as group B. No significant differences were reported regarding the duration of ICU stay. Twelve patients in group A and 8 cases in group B required intra-aortic balloon pump (IABP) with no significant difference.

Discussion

Remote ischemic preconditioning (RIPC) is a biologic phenomenon in which a brief ischemia followed by reperfusion of an organ makes a distant organ more resistant against sustained ischemic insult. In order to assess whether RIPC can protect myocardium in CABG patients against ischemia we conducted this study. Thielmann et al (7) studied 53 non-diabetic cases underwent CABG with cross-clamp fibrillation technique and concluded that with the aid of RIPC, the level of serum troponin I was significantly decreased. Therefore, this technique may protect myocardium from ischemia. In this study we reached the same conclusion in spite of different technique; antegrade technique with cold- blood cardioplegin in our study versus cross-clamp fibrillation technique in mentioned study. Ali N et al (8) used CPK (MB) as a predictor of myocardial ischemia and they also concluded that RIPC may result into significant decrease in the incidence of myocardial ischemic injury during cardioplegic arrest. Venugopal et al (9) studied 23 patients who underwent on pump CABG with the aid of antegrade technique with cold- blood cardioplegin. They evaluated the level of serum troponin during the process and similar to our study they concluded that by performing RIPC, the incidence of myocardial ischemic injury may decrease .Hong et al (10) studied the patients who underwent off pump CABG and evaluated the effect of RIPC. In contrast with our study the level of serum troponin I was not significantly decreased after the surgery in their study. Mean postoperative troponin levels in our study has been considered as a direct indicator of myocardial ischemia and compared between groups A and B at different times of 6, 12, 24, and 72 hours after surgery .These criteria were significantly lower in group A patients. The decreasing trend of serum troponin after the surgery was also more significant in group A. Two other indicators including required inotrope and IABP in our study were considered in order to compare the ischemic insult to the myocardium during cardioplegic arrest. The required inotrope and IABP were not significantly different between groups. Based on this result, we concluded that RIPC may have the effect on laboratory measurements of serum cardiac enzymes with no significant effect on clinical approach to the patients. We also compared postoperative level of serum creatinine and lactate in order to assess the systemic perfusion of extremities and the incidence of low cardiac output .No significant differences were observed between 2 groups regarding these criteria. Also, there were no significant differences regarding the electrocardiographic changes

Table 1: The comparison of serum troponin levels at different times after the surgery between 2 groups of patients

Serum Troponin level (ng/dl)	Group A	Group B	p.value
6 hours after surgery	1.53±1.03	2.13±0.78	<0.05
12 hours after surgery	1.28± 1.17	1.77±0.80	<0.05
24 hours after surgery	0.83±0.73	1.31±0.67	<0.05
72 hours after surgery	0.26±0.33	0.47±0.42	<0.05

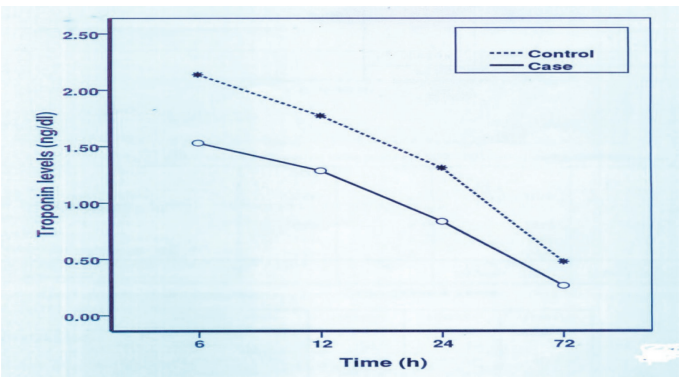

Figure 1: The comparison of decreasing trend of serum troponin levels at different times after the surgery between 2 groups of patients

and the duration of ICU stay between groups. However, due to various factors involved in judging these aspects it is better to assign more specific studies in order to reach to a conclusion.

Conclusion

RIPC can protect myocardium in CABG patients against ischemia and can be recommended for clinical use during open cardiac surgeries in order to decrease the incidence of myocardial ischemic injury following cardioplegic arrest.

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