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Research

# Myocardial Ischemia Serum Markers in Coronary Artery Bypass Grafting by On-pump and Off-pump Techniques

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## Abstract

***Background*: Coronary Artery Bypass Grafting (CABG) is usually performed with Cardio Pulmonary Bypass (CPB). However CPB has been associated with several adverse effects. Recently off-pump CABG technique is offered as an alternative to the standard on-pump technique. The purpose of this study was to evaluate the safety of the technique by estimating and comparing serum markers of myocardial ischemia; CK, CK-MB, LDH, AST, Cardiac Troponin 1 and some peri and postoperative complications after two types of surgical procedures.**

***Patients and Methods*: Seventy-three patients (58 males and 15 females) with angiographically defined CAD admitted to the hospital for CABG were selected. The off-pump technique was performed in 38 patients with mean age of 60±10.5 years. In 35 other patients with mean age of 55±10.4 years, the on-pump technique was applied. CK, CK-MB, LDH and AST activities and Cardiac Troponin 1 concentration were measured pre and postoperatively into first 24 hours. Characteristics of the patiaents and some pre and postoperative data regarding incidence of complications were also recorded.**

***Results*: The activities of cardiac enzymes; CK, CK-MB, LDH and AST after on-pump CABG technique were higher than those of off-pump technique ($P<0.05$ in all cases). The levels of Troponin I were significantly higher after on-pump CABG throughout the entire measurement period ($P<0.01$). In other groups of the patients no preoperative myocardial infarction was observed. In the off-pump technique procedure time was shorter and transfusion of blood and blood products was less than those of on-pump technique, but no differences were noticed among the other recorded data.**

***Conclusion*: Significantly lower release of the enzymes and Troponin 1 during operation by off-pump technique suggests that the technique causes less myocardial injury. On the basis of little change in the activities of cardiac enzymes and Troponin 1 and presented data including a marked decrease in blood transfusion and shorter procedural time it is concluded that off-pump CABG is a safe and effective technique in selected patients with appropriate coronary lesions.**

**Key words:** On-pump CABG, Off-pump CABG, CK, CK-MB, LDH, AST, Troponin 1.

## Introduction

The use of Cardio Pulmonary Bypass (CPB) has been linked to a systemic inflammatory response that may play a role in undesirable patient outcomes. Recently off-pump coronary artery bypass grafting (off-pump CABG) has developed and became noticeably important.[2] The technique was offered as an alternative to the standard on-pump technique in selected and suitable cases. Comparing to the on-pump CABG procedure, this technique avoids CPB and

cardioplegia with global cardiac arrest [3] but there is a potential risk of ischemic myocardial injury resulting from normothermic, metabolically active myocardium during the temporary occlusion of the corresponding coronary arteries.[4]

Off-pump CABG procedure need much patience skill, than conventional CABG. The technique was introduced many years ago, but has been abandoned with the advent of CPB and cardioplegic arrest.[5,6] Off-pump CABG operation enable a better investigation of the role of CPB for myocardial protection during coronary bypass operation. It allows to compare global ischemia reperfusion associated with a CABG procedure using CPB, cardioplegia, and global cardiac arrest versus local ischemia reperfusion due to temporary occlusion of one of the coronary arteries as performed by off-pump CBG.

The aim of this study was to evaluate the safety of the technique by measuring the markers of myocardial ischemia including the activities of serum cardiac enzymes and levels of cardiac specific protein release in the serum after on-pump and off-pump CABG procedures. Myocardial injury occurs in essentially 100% of cases following cardiac bypass surgery. Following the injury activities of cardiac enzymes and level of cardiac specific protein increase in the serum. The amount of increase is generally higher for CK-MB than for Troponin 1; it has been suggested that Troponin 1 may be a better marker for distinguishing myocardial infarction from "normal" preoperative injury.[7,8] Incidence of peri and postoperative complications in off-pump and on-pump CABG was also estimated and compared with each others.

## Patients and Methods

*Subjects*: The study included 73 patients ( 58 males and 15 females) with a mean age of 58±10.3 years referred to Shahid Madani Hospital, Tabriz-Iran, who were scheduled for surgical revascularization. The off-pump CABG group comprised 38 patients with a mean age of 60±10.5 years with one-vessel (n=5), two-vessels (n=11), three-vessels (n=20) and four-vessels (n=2) coronary artery disease (CAD). The on-pump CABG group included 35 patients with a mean age of 55±10.4 years with one-vessel (n=3), two vessels (n=6), three-vessels (n=20) and four-vessels (n=6) CAD. Characteristics of the patients and some pre and postoperative data were recorded. To ensure equivalency between the two groups, patients appropriate for either procedure had to be included. Both groups of the patients underwent by-pass grafting through a sternotomy incision.

*Sampling*: The tests were carried out on peripheral venous blood samples collected in simple tubes. The samples obtained before and 6,9,12 and 24 hours after operation.

*Measurements*: Catalytic activities of CK, LDH and AST in serum samples were determined by using commercial reagents (Boehringer Mannheim, Mannheim, Germany) in an automated chemical analyzer (Cobas Mira) at 25 C and results reported as IU/L. CK-MB isoenzyme activity was detected by immunoinhibition with commercial agents (Boehringer Mannheim) in the same analyzer at 25 C. Cardiac Troponin 1 concentration in the serum samples were assayed by using Troponin 1 enzyme immunoassay test kit (Diagnostic Automation Inc. Calabasas, CA 91302 USA) in Awareness stat Fax 2600 analyzer. The ELISA test is based on the principle of solid phase Enzyme Linked Immunosorbent Assay.

Statistical analysis of data was accomplished by means of the SPSS 100 statistical software package. Regression analysis was calculated for correlation between parameters. A P-value of less than 0.05 was considered significant. All data are expressed as the mean ±SD.

## Results

There was no hospital mortality, no neurolgic accidents, pulmonary insufficiency or incidences of myocardial infarction in the on-pump and off-pump CABG technique ($P \leq 0.05$). Blood transfusion in on-pump CABG group was required more frequently than off-pump CABG group and the differences was marked ($P \leq 0.05$). Ionotrop requirement in both procedures were almost similar ($P \geq 0.05$). The cardiac enzymes activities; CK, CK-MB, LDH and AST were measured in the serum samples obtained before and after operation and the results are reported asIU/L. Comparison of the enzymes activities obtained by different procedure are shown in table 1.

Before operation the activities of CK in both groups were almost similar ($P>0.05$) but after surgery increased in both groups of the patients. Peak values for CK were measured at 12 hours. The elevation of the enzyme in on-pump technique was significantly higher than that of off-pump technique in

**Table : 1: The Mean ±SD Values of Cardiac Enzymes Activities in Serum Before and After Operation by Off-pump and On-pump Procedures at Different Times .**

| Enzymes IU/L | Before Operation Off-pump/On-pump No. No | After Operation Off-pump/On-pump No. No. | | | Differences |
|---|---|---|---|---|---|
| | | 6 hours | 12 hours | 24 hours | |
| CK | 131±96/122±60 (38) (35) | 841±84/1324±63 (38) (35) | 1960±990/2042±885 (38) (35) | 1851±1020/1917±985 (38) (35) | * |
| CK-MB | 17±6/20±4 (38) (35) | 38±16/45±12 (38) (35) | 31±14/53±17 (38) (35) | 29±18/38±18 (38) (35) | * |
| LDH | 413±130/451±111 (38) (35) | 470±140/666±141 (38) (35) | 673±220/801±141 (38) (35) | 693±231/850±205 (38) (35) | * |
| AST | 26±8/24±6 (38) (35) | 36±10/55±12 (38) (35) | 68±17/87±14 (38) (35) | 73±18/97±12 (38) (35) | * |

in all off the postoperative samples ($P<0.05$ in all cases). The activities of CK-MB isoenzyme before operation were at normal range and increased after operation with a peak at 6 and 12hr samples in off-pump and on-pump procedures respectively. Meaningful differences were noticed between two groups ($P<0.05$). The activities of two other enzymes; LDH and AST were also measured in all samples. After operation the activities of LDH and AST increased and peak activities appeared a 12 hr samples and remained elevated till 24hr samples. Activities of both enzymes in on-pump procedure were significantly higher than off-pump procedure in all cases ($P<0.05$) .

The concentration of Troponin 1 was measured pre and postoperatively. As shown in Table2, before operation the levels of Troponin I in serum was very low and sometime non-detectable, but after operation its concentration increase in both techniques and the maximum of Troponin 1 concentration was detected at 9 and 12 hr after operation in off-pump and on-pump procedure respectively. Comparing the results of both groups, the concentration of Troponin 1 in all the postoperative samples of on-pump technique was higher than that of off-pump procedure ($P<0.05$).

To increase specificity of studied parameters the relationship between the numbers of grafts and the enzyme activities or protein levels at postoperative samples with maximum activities or levels were estimated. The patients in both groups were subdivided into four subgroups according to number of received graft and performing Pearson's correlation coefficient the relationship between the number of the grafts and the variables was assessed. As shown in Tables 3a and 3b in both techniques the regression analysis demonstrated a positive correlation between the number of vessels grafted and levels of Troponin 1, but in the case of CK-MB the correlation was only positive and significant in off-pump group. In spite of higher activities of the other enzymes in the samples obtained after on-pump technique there was no correlation between the number of grafts and the procedures.

## Discussion

Open-heart surgery, such as aortic surgery and Coronary Artery Bypass Grafting (CABG) is usually accompanied by ischemic or mechanical damage to the heart tissues. Post-operative cardiac failure due to myocardial necrosis still remain the major complication in cardiac surgical procedures and the main cause of increased morbidity and mortality. Significant myocardial injuries associated with cardiac surgery result in significant (up to 10 fold) increases in the two-year complication rates[10]. In recent years new surgical designs in the treatment of coronary artery disease have generated controversy and debate[11,12]. Early results suggest that off-pump coronary artery revascularization with excellent short-term results and minimal morbidity[13].However, the safety and efficacy of the procedure are still to be determined. The main object of this prospective study was to compare postoperative kinetic and patterns of cardiac Troponin 1 and CK, CK-MB LDH and AST activities after off-pump CABG versus conventional on pump CABG. We found no

**Table 2: The Mean Levels of Troponin T in the Serum of Patients Before and After Operation by Off-pump and On-pump techniques**

| Procedures | *Mean ±SD Levels of Troponin I (ng/ml)* | | | | |
|---|---|---|---|---|---|
| | *Before Operation* | *After Operation* | | | |
| | | *6 hours* | *9 hours* | *12 hours* | *24 hours* |
| Off-pump | 0.75±0.28 | 3.55±0.28 | 3.34±0.31 | 3.25±0.54 | 2.15±0.52 |
| On -pump | 0.63±0.33 | 6.46±2.35 | 9.21±1.95 | 6.85±1.55 | 4.8±2.30 |

**Table 3a: Correlation Between the Number of Vessels Grafted and the Variables; CK, CK-MB, LDH, AST and Troponin 1 After Off-pump Operation**

| Variables | Number of Vessels Grafted | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | r | 1 p | r | 2 p | r | 3 p | r | 4 p |
| CPK | 0.22 | 0.41 | 0.380 | 0.24 | 0.415 | 0.33 | 0.357 | 0.28 |
| CK-MB | 0.44 | 0.03 | 0.59 | 0.019 | 0.620 | 0.031 | 0.389 | 0.016 |
| LDH | 0.197 | 0.88 | 0.53 | 0.29 | 0.133 | 0.45 | 0.221 | 0.18 |
| AST | 0.549 | 0.43 | 0.49 | 0.16 | 0.312 | 0.22 | 0.292 | 0.32 |
| Troponin I | 0.203 | 0.016 | 0.33 | 0.032 | 0.292 | 0.009 | 0.312 | 0.012 |

**Table 3b: Correlation Between the Number of Vessels Grafted and the Variables; CK, CK-MB, LDH, AST and Troponin 1 after on-pump operation**

| Variables | Number of Vessels Grafted | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | r | 1 p | r | 2 p | r | 3 p | r | 4 p |
| CPK | 0.549 | 0.95 | 0.434 | 0.081 | 0.610 | 0.73 | 0.440 | 0.48 |
| CK-MB | 0.221 | 0.88 | 0.133 | 0.089 | 0.341 | 0.153 | 0.770 | 0.90 |
| LDH | 0.070 | 0.182 | 0.349 | 0.331 | 0.435 | 0.10 | 0.125 | 0.18 |
| AST | 0.012 | 0.67 | 0.291 | 0.680 | 0.380 | 0.30 | 0.480 | 0.075 |
| Troponin I | 0.320 | 0.045 | 0.144 | 0.028 | 0.075 | 0.004 | 0.380 | 0.008 |

differences in the incidence of postoperative complication between the off-pump CABG and CABG with CPB groups. Because the rate of many complications in this center is in the range of 1-5 percent to show a significant difference between groups would require a sample size of well over 1000 patients. In this study we also found meaningful differences between the two groups with regard to overall length of stay, blood and blood products transfusion and length of procedure. They were all low in off-pump CABG procedure. Similar results have been reported by others.[14,15]

All patients undergoing CABG surgery with or without CPB postoperatively showed an increase of cardiac Troponin 1 levels. After uncomplicated coronary revascularization, patients with the off-pump CABG technique continuously showed lower serum Troponin 1 concentrations than those with the on-pump CABG technique. The release following CABG with or without CPG was different; Troponin 1 reach its postoperative peak value in patient with the off-pump CABG technique earlier than those with the on-pump CABG technique. Different time pattern (peak) and increased levels of the protein after CABG operation have been reported by others.[16,17] The differences may be due to length of operation and method of detection of Troponin 1 in different laboratories.

The present study reveals that an uncomplicated CABG without signs of pre-operative MI causes a moderate increase of the following enzymes: CPK, CK-MB, LDH and AST. Patients with off-pump CABG presented low activities of the enzymes than patients with on-pump. The findings are compatible with those of reported by Kilger et al.[4] Time patterns of elevation of the enzymes in both procedures were

same, except in case of CK-MB that reached to maximum in off-pump technique earlier than on-pump technique (6hr postoperatively versus 12hr). Studying specificity of the markers of myocardial ischemia by performing Pearson's correlation coefficient between the enzyme activities or protein concentration and number of vessels grafted shows positive correlations in case of Troponin I in both techniques but in case of CK-MB only in the off-pump technique was observed. The increase in the CK-MB and protein in this study, particularly Troponin I which are reliable and highly specific markers of myocardial ischemia during cardiac operation can be used to assess the efficacy of cardio protective procedures.[18] It has to be noted that reversible myocardial ischemia can cause a functional dysintegrity of cell membranes and release of cytosolic enzymes without subsequent cellular necrosis.[19] Since no patient developed MI as confirmed by ECG and echocardiography increased activities or levels of protein following open heart surgery may be due to temporary myocardial ischemia that lead to release of cytosolic enzymes or proteins from reversibly injured cardiac cells.

Significantly greater extant release of the markers in the on-pump CABG procedure may be partially due to reperfusion of heart following global cardiac arrest, oxidative stress and inflammation.[20] In view of low activities or level of the marker in patient undergoing off-pump CABG our data did not support additional release of the markers induced by myocardial injury due to Octopus devices.

Marked correlation between levels of Troponin I and the number of vessels grafted suggests that Troponin I is the best indicator of the myocardial injury. On the basis of lower release of the markers in off-pump CABG procedure it was concluded that the technique is safe and effective.

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