CARDIAC SURGERY

Evaluation of myocardial injury by serum levels of creatine kinase MB, myoglobin, and cardiac troponin I following off-pump and on-pump coronary artery bypass

Off-pump ve on-pump koroner arter bypass cerrahisi sonrası miyokard doku hasarının serum kreatin kinaz MB, miyoglobin ve kardiyak troponin I düzeyleriyle değerlendirilmesi

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Background: We evaluated myocardial tissue injury by measuring serum levels of creatine kinase MB (CK-MB), myoglobin, and cardiac troponin I (cTnI) after off-pump coronary artery bypass grafting (CABG) and conventional on-pump CABG.

Methods: Thirty patients undergoing first-time elective CABG were randomly assigned to on-pump (n=15) or off-pump (n=15) CABG. Blood samples were taken before surgery (m1), after induction of anesthesia (m2), 30 minutes after aortic unclamping in the on-pump CABG group or 30 minutes after the last distal anastomosis in the off-pump CABG group (m3), and at postoperative 12 hours (m4) and 24 hours (m5). Serum CK-MB activity was measured by the immunoinhibition method, and myoglobin and cTnI were measured by direct chemiluminometric technology.

Results: The mean duration of cross-clamping in the on-pump group was 74.9±17.0 minutes and the mean ischemic period due to target coronary artery occlusion in the off-pump group was 25.7±9.1 minutes. The number of grafts used was significantly higher in the on-pump CABG group (p=0.041). There were no deaths and no significant differences were observed with regard to adverse clinical events. Although serum CK-MB activity did not differ significantly in the off-pump group except for one patient, increases at m3, m4, and m5 were significant in the on-pump group. The two groups differed significantly at m3 (p<0.001), m4 (p<0.01), and m5 (p<0.01). Myoglobin activity showed significant increases at all times in both groups, but this showed significance only at m3 between the two groups (p<0.001). Serum cTnI activity reached peak values at m4 in both groups. Increases remained within the normal range in the off-pump group, whereas they were beyond normal at m3, m4, and m5 in the on-pump group, showing significant differences with the off-pump group (p<0.001).

Conclusion: Of the two techniques, off-pump CABG is associated with less myocardial tissue injury.

Key words: Biological markers; cardiopulmonary bypass/methods/adverse effects; coronary artery bypass; creatine kinase/blood; myocardial ischemia/blood; troponin I/blood.

Amaç: O*ff-pump* ve konvansiyonel *on-pump* koroner arter bypass greftlemeden (KABG) sonra oluşan miyokard doku hasarı, serum kreatin kinaz MB (CK-MB), miyoglobin ve kardiyak troponin I (cTnI) düzeyleri ölçülerek değerlendirildi.

Çalışma planı: İlk kez elektif KABG planlanan 30 hasta rastgele seçimle iki gruba ayrıldı: *on-pump* (n=15) ve *off-pump* (n=15) KABG. Tüm hastalardan beş kez kan örneği alındı: Ameliyat öncesinde (m1), anestezi indüksiyonu sonrasında (m2), *on-pump* KABG grubunda aortik klemplerin çıkarılmasından 30 dakika sonra, *off-pump* KABG grubunda ise son distal anastomozdan 30 dakika sonra (m3), ameliyat sonrası 12. saatte (m4) ve 24. saatte (m5). Serum CK-MB aktivitesi immüninhibisyon yöntemiyle, miyoglobin ve cTnI aktivitesi direkt kemiluminometrik teknikle değerlendirildi.

Bulgular: *On-pump* grubunda ortalama kros-klemp süresi 74.9±17.0 dakika, *off-pump* grubunda hedef koroner arter oklüzyonuna bağlı ortalama iskemik süre 25.7±9.1 dakika idi. Kullanılan greft sayısı *on-pump* grubunda anlamlı derecede fazla idi (p=0.041). İki grupta da ölüm olmadı; olumsuz kardiyak olay açısından da iki grup arasında anlamlı farklılık görülmedi. Serum CK-MB aktivitesi *off-pump* grubunda bir hasta dışında anlamlı farklılık göstermezken, *on-pump* grubunda m3, m4 ve m5'te anlamlı artışlar görüldü. Bu düzeyler *off-pump* grubuyla da anlamlı farklılık gösterdi (sırasıyla, p<0.001, p<0.01 ve p<0.01). Miyoglobin aktivitesi iki grupta da tüm ölçümlerde anlamlı derecede arttı; ancak, iki grup arasındaki farklılık sadece m3'te anlamlı idi (p<0.001). Serum cTnI aktivitesi en üst değerlere iki grupta da m4'te ulaştı. Artışlar *off-pump* grubunda normal sınırlar içinde kalırken, *on-pump* grubunda m3, m4 ve m5'te anlamlı idi. Bu zamanlarda ölçülen değerler *off-pump* grubuyla da anlamlı farklılık gösterdi (p<0.001).

Sonuç: İki teknik karşılaştırıldığında, *off-pump* KABG'de daha düşük düzeyde miyokard doku hasarı meydana gelmektedir.

Anahtar sözcükler: Biyolojik belirteçler; kardiyopulmoner bypass/yöntem/yan etki; koroner arter bypass; kreatin kinaz/kan; miyokard iskemisi/kan; troponin I/kan.

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Conventional coronary artery bypass grafting (CABG) is effective, safe and has an acceptable mortality rate. Cardiopulmonary bypass (CPB), global cardiac arrest and hypothermia still cause significant morbidity and ischemic myocardial injury.[1-4] Although these adverse effects of CPB are mostly reversible, avoiding the use of CPB is thought to be associated with lesser postoperative morbidity. Minimally invasive CABG and off-pump CABG with median sternotomy have been shown to be beneficial and associated with reduced myocardial injury.[3-7]

Off-pump CABG is performed on beating heart without the use of CPB and global cardiac arrest. However, there is still a risk for ischemic myocardial injury that results from the normothermic and metabolically active myocardium during the occlusion of the target coronary artery.

The aim of this prospective study was to evaluate myocardial tissue injury by measuring serum levels of creatine kinase MB (CK-MB), myoglobin, and cardiac troponin I (cTnI) after two types of surgical myocardial revascularization: off-pump CABG by median sternotomy and conventional on-pump CABG.

MATERIALS AND METHODS

Patients. After obtaining written informed consent, 30 patients undergoing first-time elective CABG were randomly assigned to two groups: on-pump CABG (n=15), and off-pump CABG (n=15). The exclusion criteria were the presence of unstable angina, acute myocardial infarction of less than a-month duration, ejection fraction of less than 40%, and concomitant valvular disease or skeletal muscle disease. In addition, patients with electrocardiographically confirmed myocardial infarction in the immediate postoperative period and showing significant increases in cardiac enzymes were also excluded. The study was designed only to demonstrate the contribution of the two types of CABG surgery to myocardial tissue injury without further evaluation of major adverse outcomes. Preoperative and perioperative data on the patient groups are summarized in Table 1.

On-pump CABG. In all the cases surgical access was gained via a median sternotomy. After harvesting bypass grafts, heparin was administrated (300 U/kg) before aortic cannulation. Anticoagulation was maintained during CPB and monitored with activated clotting time measurements (Hemochron 801, International Technique Corp, Edison, NJ, USA). We performed moderate systemic hypothermia (30 °C-32 °C) in all the patients. A roller pump, a nonheparinized circuit and a hollow-fiber oxygenator (Bentley, Univax Membrane Oxygenation Module, Baxter Healthcare Corp, Bentley Laboratory Division, Irvine, CA, USA) were used. The pump flow was kept between 2.0-2.5 L/min/m^2 body surface area to maintain a mean arterial pressure of 50 to 70 mmHg. Myocardial protection was achieved by an initial antegrade infusion of the St. Thomas' crystalloid cardioplegia and then continued with intermittent antegrade cold blood cardioplegia. Distal and proximal anastomoses were constructed during one period of aortic cross-clamping.

Off-pump CABG. After a median sternotomy and harvesting the bypass grafts, heparin (150 U/kg) was administered. The Octopus Tissue Stabilizer (Octopus-3 28400, Medtronic, Cardiac Surgical Products, MI, USA) was used for the stabilization of the target coronary artery. First, the proximal anastomosis of the vein grafts was constructed by the help of a partially occluding aortic-side clamp. In all the cases, the left anterior descending (LAD) artery was the first coronary artery to be revascularized. The target coronary artery was stabilized and occluded proximally with the help of a bulldog clamp and then the distal anastomosis was performed. No coronary shunts were used during the distal anastomosis. Heparin was antagonized with protamin sulphate until the activated clotting time decreased below 200 seconds.

Table 1. Comparison of preoperative and operative data

	On-pump CABG	Off-pump CABG	*p**
No. of patients	15	15	
Age (mean)	59.5±10.8	59.6±9.5	
Gender (female/male)	10/5	11/4	
Prior myocardial infarction	5	7	
Ejection fraction (%)	51.2±8.7	52.1±8.5	
Presence of hypertension	8	6	
Presence of diabetes mellitus	4	3	
Aortic clamping (min)	74.9±17.0	……	–
Use of left internal mammary artery	14	13	
No. of grafts used	3.1±0.8	2.4±0.7	0.041

p*: Nonsignificant *p* values were omitted.

Blood sampling. As parameters of myocardial injury, we measured creatine kinase MB (CK-MB), myoglobin, and cardiac troponin I (cTnI) levels. Blood samples were taken sequentially from the patients before surgery (m1), after induction of anesthesia (m2), 30 minutes after aortic unclamping in the on-pump CABG group or 30 minutes after the last distal anastomosis in the off-pump CABG group (m3), and at postoperative 12 hours (m4) and 24 hours (m5).

Determination of serum CK-MB activity was made by the immunoinhibition method (Dade-Behring Dimension RxL, Germany). Myoglobin and cTnI measurements were made by direct chemiluminometric technology (Automated Chemiluminescence System: ACS-180, Chicron Diagnostics, East Walpole, MA, USA). The ACS system detects free cTnI in addition to the complex forms.

Statistical analysis. Statistical analyses were performed using the SPSS statistical software (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as mean±standard deviation. Analyses were made with Kruskal-Wallis, Mann-Whitney U-, chi-square, and Fischer's exact tests. Mann-Whitney U-test was used for comparison of changes in levels (changes in comparison to the initial serum levels) of biochemical parameters between the two groups. A p value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Preoperative variables of the patients were comparable in both groups (Table 1). The mean duration of cross-clamping in the on-pump group was 74.9±17.0 minutes and the mean ischemic period due to target coronary artery occlusion in the off-pump group was 25.7±9.1 minutes.

The number of grafts used was significantly higher in the on-pump CABG group (3.1±0.8 *vs* 2.4±0.7; p=0.041, Table 1). In the off-pump group, the target coronary arteries grafted other than LAD were diagonal (n=3), circumflex (n=7), and right coronary (n=11) arteries. There were no deaths in both groups. Adverse clinical events did not differ significantly between the two groups (Table 2).

Parameters of myocardial injury. Serum concentrations of myoglobin which were initially within the normal range rose with the initiation of the operation and reached peak values with the beginning of reperfusion (m3) in the on-pump group, and at postoperative 12 hours (m4) in the off-pump group. In both groups, increases in myoglobin concentrations at m2, m3, m4, and m5 were significant compared to baseline levels, but this showed a statistical significance only at m3 when the two groups were compared (786±185 ng/ml *vs* 213±51 ng/ml; p<0.001). This may possibly be due to diverse time intervals of culmination in serum myoglobin concentrations in the two groups (Fig. 1).

Table 2. Peri- and postoperative adverse events

	On-pump	Off-pump
Inhospital mortality	0	0
Perioperative myocardial infarction	1	1
Stroke	1	0
Wound infection	1	1
Postoperative atrial fibrillation	4	3
Intraaortic balloon pump	1	0

Baseline CK-MB levels were within the normal ranges. Serum concentrations began to rise with the operation and reached peak values at m3 and m4 in the on-pump and off-pump groups, respectively. Compared to initial levels, serum CK-MB values did not differ significantly at all times in the off-pump group except for one patient who did not manifest any ECG change. However, increases were significant at m3, m4, m5 in all the patients in the on-pump group. When the two groups were compared, CK-MB was significantly elevated in the on-pump group at m3 (52.0±11.6 U/L *vs* 24.3±8.6 U/L; p<0.001), m4 (48.4±10.0 U/L *vs* 24.6±10.2 U/L; p<0.01), and m5 (37.7±7.0 U/L *vs* 22.2±9.5 U/L; p<0.01) (Fig. 2).

Preoperative cTnI concentrations were within the normal range and raised with the operation, reaching peak values at m4 in both groups. Increases remained within the normal range in the off-pump group at all measurements, whereas they were beyond the normal range after reperfusion (m3), and remained higher at m4, and m5 in the on-pump group. Comparison of the two groups showed significantly higher values in favor of the on-pump group after reperfusion (m3) (4.0±1.9 ng/ml *vs* 0.3±0.5 ng/ml; p<0.001), at m4 (13.2±4.1 ng/ml *vs* 0.4±0.5 ng/ml; p<0.001) and m5 (8.5±2.4 *vs* 0.4±0.3 ng/ml; p<0.001) (Fig. 3).

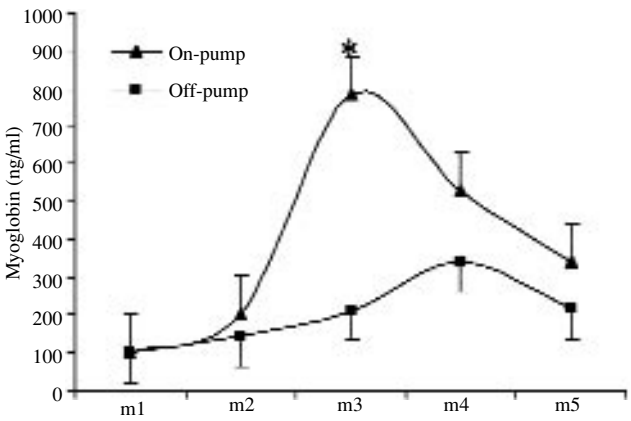

Fig. 1. Changes in myoglobin concentrations. *: p<0.001.

DISCUSSION

Creatine kinase MB, myoglobin, and cardiac troponins are specific markers for myocardial injury and are widely used during CABG surgery.[3-5,7-10]

Conventional CABG causes some degree of intraoperative myocardial tissue injury during global cardioplegic arrest, resulting in elevations in CK-MB, myoglobin, and cTnI levels even in patients with an uneventful recovery.[3-5,11,12]

Higher releases of serum markers showing myocardial injury during on-pump CABG with global cold cardioplegic arrest may be due to inadequate perfusion of the subendocardium and the remaining ungrafted ischemic areas, unexpected aortic regurgitation, reperfusion (whose consequences are not well-known) through the bypass grafts after unclamping, or to direct trauma to the myocardium.[10,13,14] On the other hand, off-pump CABG is considered to be associated with a potential risk for ischemic myocardial tissue damage due to normothermic, metabolically active myocardium during the occlusion of the target coronary artery.[3]

The present study reveals that the amount of myocardial injury following an uneventful off-pump CABG is less than that occurs during an uneventful course of conventional CABG; this was evident by lower releases of CK-MB, myoglobin, and cTnI during off-pump CABG. These findings may indicate that regional normothermic warm ischemia due to target coronary artery occlusion during off-pump CABG causes less myocardial injury than that seen with global cold cardioplegic arrest during conventional on-pump CABG. Our findings are consistent with two studies that demonstrated less myocardial injury with off-pump CABG.[4,5]

The cTnI levels in our study were somewhat higher than reported in some previous studies, which may be related to different assay technology and the kits used.[4] The ACS method applied in our study detects free cTnI. Similar cTnI levels were reported by Wan et al.[5] who used the same method, and by Kilger et al.[3] who used a fluorogenic sandwich enzyme immunoassay method.

Etievent et al.[9] showed that increases in cardiac specific serum markers of myocardial injury during coronary procedures, especially in cTnI, might be used as an indicator of the efficiency of cardioprotective procedures. Reversible myocardial ischemia can cause functional disintegrity of myocardial cell membranes and consecutive release of cytocolic molecules without cellular necrosis.[3,15] Taking this into consideration, we did not include patients who developed perioperative myocardial infarction to exclude irreversible myocardial ischemia, and still the release of cytocolic molecules from reversibly injured myocytes was significantly lower in patients undergoing off-pump CABG.

Hadjinikolaou et al. [16] investigated another specific marker for cardiac muscle, cardiac troponin T (cTnT), and found significantly higher cTnT levels in patients undergoing conventional CABG when compared with those measured for minimally invasive direct CABG. They also reported that cTnT levels in the latter group remained within the normal range just as cTnI levels measured in our study in the off-pump group.

The authors of the present study are aware that the results might have been influenced by the following limitations: the small patient size, the lesser number of grafts used in the off-pump group, and the lack of utilization of angiography to show early graft patency. These may somewhat result in comparable clinical outcomes in both groups. However, recent studies suggest that differences in clinical outcomes may only be manifest between high risk patients undergoing CABG with or without CPB.[17-19]

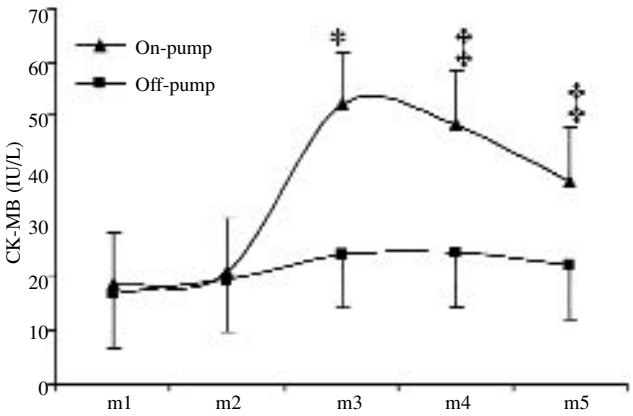

Fig. 2. Changes in CK-MB concentrations. *: p<0.001; ‡: p<0.01.

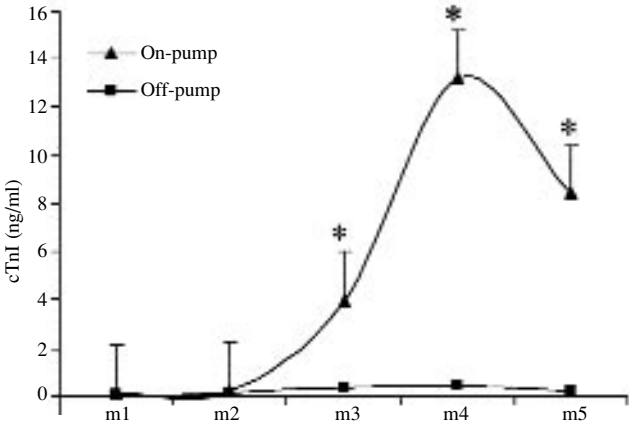

Fig. 3. Changes in cTnI concentrations. *: p<0.001.

The consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee states that the higher the value of the cardiac biomarker, the greater the amount of damage to the myocardium irrespective of the mechanism.[20]

In conclusion, normothermic regional ischemia during off-pump CABG causes less myocardial tissue injury than that resulting from on-pump CABG with global cold cardioplegic arrest, and this may be demonstrated by changes in serum levels of CK-MB, myoglobin, and cTnI. Compared to global cold ischemia induced by cardioplegia, multiregional warm ischemia during target coronary occlusion is associated with less myocardial injury.

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