

Evaluation of Heart-Type Fatty-Acid-Binding Protein for Early Detection of Intraoperative Cardiac Damage

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ABSTRACT

Myocardial injury occurs in patients undergoing coronary artery bypass grafting (CABG) with and without cardiopulmonary bypass (CPB) (on-pump CABG) and (off-pump CABG) respectively. The extent of damage in both groups can be evaluated by the use of heart-type fatty-acid-binding protein (hFABP) and creatine kinase-MB (CK-MB) release. Also, cardiac surgery with the use of extra corporeal circulation (ECC) is associated with oxidative stress. The present study aims to evaluate myocardial injury and oxidative stress in these two groups, comparing between the two parameters indicating cardiac damage, also oxidative stress status was assessed by estimating serum levels of isoprostane during these major operations. Fifty adult patients of either sex were distributed to 1 of 2 groups: on-pump (n= 25), in which coronary revascularization was done with the use of CPB and moderate hypothermia; and off-pump (n=25), in which surgery was performed without the use of CPB. Twenty five healthy control subjects were also enrolled in the study. The current study showed a significant increase in the mean serum levels of h-FABP in on- pump and off pump groups compared to the control group. (133.60 ± 49.41 , 58.29 ± 16.67 and 4.33 ± 2.97 ng/ml respectively, $p < 0.001$), and in the on-pump CABG group compared to off-pump CABG group (133.60 ± 49.41 vs 58.29 ± 16.67 ng/ml, $P < 0.001$). The total amount of CK-MB released was significantly higher in the on-pump group compared to the off-pump and control groups (210.80 ± 32.47 , 20.19 ± 4.22 and 13.70 ± 1.64 U/ml respectively, $P < 0.001$). While there was no significant difference in the serum levels of CK-MB between both off pump and control groups (20.19 ± 4.222 and 13.70 ± 1.64 U/ml. There was a significant increase in the mean levels of serum isoprostane in on- pump and off pump groups compared to the control group (431.14 ± 51.525 , 329.83 ± 24.620 and 132.34 ± 15.57 ng/ml respectively, $p < 0.001$), and in the on-pump group compared to the off pump group (431.14 ± 51.52 vs 329.83 ± 24.62 ng/ml $P < 0.001$). The lower levels of hFABP in the off-pump CABG group indicate that on-pump CABG with cardioplegic arrest causes more myocardial damage than does off-pump CABG. While normal CK- MB levels in the off -pump group indicate that this marker cannot detect the minor damage in that group, a finding which was detected by hFABP which increased significantly in the off-pump CABG group compared to the controls. So, hFABP could be considered a better marker for early intraoperative detection of minimal cardiac damage.

Key Words: Coronary artery bypass grafting, on-pump CABG, off-pump CABG, hFABP, CK-MB, oxidative stress.

INTRODUCTION

Perioperative myocardial infarction (PMI) with cellular damage is one of the most serious complications after coronary artery bypass grafting (CABG) that occurs with an incidence of 5–20% and is associated with highly increased perioperative morbidity and mortality⁽¹⁾.

The pathogenesis of PMI is based on a variety of different mechanisms during surgery, including inadequate cardioplegic perfusion and myocardial protection, incomplete revascularization, and distal coronary microembolization due to surgical manipulation⁽²⁾. Cardiopulmonary bypass and cardioplegic arrest enable the performance of coronary artery anastomosis in a still and bloodless field. However, early results of off-pump CABG suggest that better preservation of left ventricular contraction and mitochondrial function is attained than when cardioplegic arrest is used⁽¹⁾. Myocardial ischemia during cardiac surgery results in functional and structural changes and end by release of proteins from injured cardiomyocytes. These proteins vary in their release patterns and their cardiospecificity⁽³⁾. The occurrence of new Q-waves in the electrocardiogram (ECG) as well as elevated serum levels of cardiac markers for myocardial damage are used to establish the diagnosis of PMI⁽⁴⁾. Creatine kinase and its isoform, creatine kinase-MB (CK-MB), have been the most frequently used tools to diagnose myocardial ischemia⁽⁵⁾.

In recent years, structural myofibrillar proteins, such as troponin T and troponin I and their cardiospecific isoforms, have entered the clinical field and have been used in routine diagnostics, as well as in scientific clinical research⁽⁶⁾. However, the delay between surgical damage and the detection of a measurable amount of protein in peripheral blood renders difficulty in the rapid evaluation of the degree of myocardial injury.

Heart-type fatty-acid-binding protein (hFABP), an intracellular molecule engaged in the transport of fatty acids through the myocardial cytoplasm, is a rapid marker of myocardial infarction⁽⁷⁾.

The fatty-acid-binding proteins (FABP) are a family of cytosolic proteins that shows a large degree of structural homology⁽⁸⁾. They are called FABP because they exhibit a high affinity for the non-covalent binding of fatty acids. There are several types, and all have low molecular mass (12–15 kDa), but they differ markedly in tissue distribution, concentration within tissue, isoelectric point (PI), binding capacity, and binding specificity⁽⁹⁾. The heart and the liver contain the highest concentrations of these proteins⁽¹⁰⁾. Fatty acids are the major energy source of the heart⁽¹¹⁾, they are transported bound to albumin, or as part of the lipoproteins complex⁽¹²⁾. Heart-FABP may constitute the intracellular equivalent of albumin for the intracellular transport of the insoluble fatty acids within the cells. These proteins are truly cytoplasmic, they do not exist anywhere else under normal conditions⁽¹³⁾. Recent work has

suggested more complex regulatory functions for these proteins beyond lipid transport, but the precise physiological functions of these abundant proteins are not fully understood⁽¹⁴⁾.

hFABP is a small (15 kDa) soluble non-enzyme protein. It is composed of 132 amino acids⁽¹⁵⁾. It is one of the most abundant proteins in the heart, and comprises 5–15% of the total cytosolic protein pool in the aqueous cytoplasm. This is equal to 0.5 mg/g wet weight of tissue⁽¹⁶⁾. The gene is located on chromosome 1⁽¹⁷⁾. hFABP binds two molecules of fatty acids, and is involved with the delivery of fatty acyl coenzyme A for oxidation with the generation of energy in the mitochondria⁽¹⁸⁾. Some reports have suggested the presence of a protective role for h-FABP, as scavengers of free radicals that are present in the heart during ischemia⁽¹⁹⁾.

The rationale for the use of hFABP as a marker for the early diagnosis of myocardial injury is based on the following features: (i) the presence of that soluble protein in the myocardium in high concentration; (ii) virtual confinement to the cytoplasmic space; (iii) small molecular size; (iv) relative tissue specificity, with a relative distribution of hFABP outside the heart similar to that of creatine kinase muscle brain (CK-MB)⁽¹⁶⁾, and (v) early release into plasma and urine (within 2 h) after onset of myocardial injury. Moreover, *de Groot et al., (2001)*⁽²⁰⁾ concluded that h-FABP is potentially a more suitable cardiac marker than myoglobin.

Despite improvements in surgical techniques, anesthesia and

postoperative care, cardiac surgery with the use of extra corporeal circulation (ECC) is associated with oxidative stress⁽²¹⁾. Measurements of parameters for oxidative stress are a well-accepted technique to express the extent of cell damage⁽²¹⁾. Their involvement is known to be substantial when the on-pump technique is used⁽²²⁾. Off-pump coronary artery bypass grafting has become a well-accepted and safe technique⁽²³⁾. Isoprostane iPF₂-III is a new marker reflecting oxidative stress; it has emerged as the most reliable marker of oxidative stress status in vivo⁽²⁴⁾.

Aim of the work:

The present study aimed to investigate the competency of hFABP and CK-MB serum levels in early detection of intraoperative cardiac damage, also, to evaluate the degree of oxidative stress through estimation of serum levels of iPF₂-III in both on-pump and off-pump surgeries and if there was a possible correlation of each of the measured parameters with the mean levels of ejection fraction in the studied groups.

PATIENTS & METHODS

Patient selection criteria

Fifty adult patients of either sex who were scheduled to undergo CABG at NHI were randomly distributed to 1 of 2 groups: on-pump (n= 25), in which coronary revascularization was done with the use of CPB and moderate hypothermia; and off-pump (n=25), in whom surgery was performed without the use of CPB. Samples from 25

healthy control subjects were obtained.

The groups' demographic and clinical profiles are presented in table (1). There were no significant differences between the 2 groups in age, sex, weight, height, or medications.

According to cardiac catheterization data, the numbers of diseased vessels were comparable in the 2 population groups. All patients were eligible for either off-pump or on-pump revascularization. Informed consent from all patients and approval of the ethical committee were obtained before starting the study.

Table (1): Demographic and clinical data of the studied groups

Variables	On-pump CABG	Off- pump CABG	Control group
Number of subjects	25	25	25
Male population	21	19	17
Age in years (means \pm SD)	55.28 \pm 9.131	59.94 \pm 9.212	56.4 \pm 8.8
Preo. ejection fraction (%) (means \pm SD)	59 \pm 8.7	59.9 \pm 9.7	61.76 \pm 7.87
Number of diseased vessels (means \pm SD)	2.8 \pm 0.4	2.8 \pm 0.5	//////////

CABG = Coronary Artery Bypass Grafting

Preo. = Preoperative

Patient exclusion criteria

Patients with aortic incompetence, poor ventricular function (ejection fraction \leq 0.30), concomitant heart valve disease, unstable angina, renal disease, or chronic obstructive pulmonary disease were excluded, as were those on steroid therapy and those undergoing reoperation.

Biochemical Analysis:

Blood samples were collected from each patient, immediately on arrival to ICU (nearly after 3 hours of the start of surgery). Samples were immediately cooled to 4°C and centrifuged at 3,000 rpm for 10 minutes. Serum was stored at -80°C until assay.

Serum levels of hFABP were measured by ELISA technique⁽²⁵⁾ (Kit provided by Biocheck, Inc.).

Serum levels of CK-MB were measured by immunoinhibition assay⁽²⁶⁾ (Kit provided by RANDOX Laboratories Ltd., United Kingdom).

Isoprostane serum levels were measured by a competitive enzyme immunoassay⁽²⁷⁾ using the kit provided by Oxis Research, U.S.A. Prior to analysis of the samples, a solid phase extraction procedure was performed on. The procedure requires C18 and silica columns (C18 and Silica Sep PakTM). The former column was prewashed with ethanol and 1mM HCl and the sample was loaded. The column was then washed with HCl and heptane and the sample was eluted with ethyl acetate:heptane (1:1). The latter column was prewashed with methanol and ethyl acetate and the ethyl acetate:heptane eluate from C18 Sep PakTM was

loaded. The column was then washed with ethyl acetate and the sample was eluted with ethyl acetate: methanol (1:1), evaporated under nitrogen gas and the residue was dissolved in the diluted buffer prior to analysis.

Surgical Technique

On-Pump Group.

All patients in the on-pump group underwent surgery on CPB by means of aortoatrial cannulation and moderate systemic hypothermia. The extracorporeal device consisted of a roller pump, a reservoir, and a membrane oxygenator. The circuit was primed with 1,500 mL of Ringer's lactate, containing 0.5 g/kg of mannitol and 5,000 IU of heparin. The pump flows were adjusted to maintain a cardiac index of more than 2.4 L/min/m. Myocardial protection was achieved by intermittent antegrade administration of a warm-blood, cardioplegic solution.

Off-Pump Group.

In the off-pump group, colloids were administered and body positions and gravity support (Trendelenburg, and right and left table rotation) were changed to stabilize the patient's hemodynamics. The distal anastomoses were performed first. Lesions of the left anterior descending coronary artery were bypassed with internal thoracic pedicle grafts first. Lesions of the rest of left coronary artery were bypassed using only one long saphenous vein in sequential technique. Lesions of the right coronary artery were bypassed using only one long saphenous vein in sequential technique if needed. In general, the sequence of graft construction was as follows: 1) left anterior descending with left internal

thoracic artery; 2) distal circumflex, 2nd, 3rd obtuse marginal vessels 3) ramus intermedius artery; 4) diagonal artery; 5) posterior descending artery and 6) main right coronary artery. Target artery immobilization and regional myocardial control were achieved through a commercially available Octopus III stabilizer-suction system (Octopus Tissue Stabilizer, Medtronic, Inc.; Eden Prairie, Minn). Twelve-lead electrocardiography was performed preoperatively, immediate postoperatively on arrival to ICU, and then daily for at least the first 3 postoperative days. All patients had continuous electrocardiographic monitoring until they were discharged from the ICU.

A single cardiologist, who was blinded to the study, performed transthoracic 2-dimensional echocardiography for all patients to evaluate left ventricular function, before discharge.

Statistical Analysis:

The data were coded, entered and analyzed using the statistical package SPSS version 15. The descriptive statistics were computed to summarize the mean and standard deviation for quantitative variables and percent for qualitative variables. The Chi-Square test was used to assess difference between qualitative variables, while t test and ANOVA (analysis of variables) followed by post hoc LSD test (multiple comparison) were used for normally distributed quantitative variables. Non parametric Mann-Whitney test and Kruskal-Wallis H test, were used for quantitative variables without distribution other than normal. $P\text{-value} < 0.05$ was

considered significant. Linear Correlations were done to detect the relation between variances.

RESULTS

The present study showed a significant increase in the mean levels of serum hFABP in on- pump and off- pump groups compared to the control group. (133.60 ± 49.41 , 58.29 ± 16.67 and 4.33 ± 2.97 ng/ml respectively, $p < 0.001$). Also, the mean concentrations of hFABP released was significantly higher in the on-pump CABG group than in the off-pump CABG group (133.60 ± 49.41 vs 58.29 ± 16.67 ng/ml, $P < 0.001$), **Table (2), Fig.(1)**.

The total amount of CK-MB released was significantly higher in

the on-pump group compared to the off-pump and control groups (210.80 ± 32.47 , 20.19 ± 4.22 and 13.70 ± 1.64 U/ml respectively, $P < 0.001$). While there was no significant difference in the serum levels of CK-MB between both off pump and control groups (20.19 ± 4.22 and 13.70 ± 1.64 U/ml, **Table (2) , Fig.(2)**.

There was significant increase in the mean levels of serum isoprostane in on- pump and off- pump groups compared to the control group. (431.14 ± 51.52 , 329.83 ± 24.62 and 132.34 ± 15.57 ng/ml respectively, $p < 0.001$). Also, the total amount of isoprostane was found to be significantly higher in the on-pump group compared to the off pump group (431.14 ± 51.52 vs 329.83 ± 24.62 ng/ml $P < 0.001$), **Table (2)**.

Table (2): Mean values of chemical parameters estimating the extent of myocardial damage (hFABP, CK- MB) and oxidative stress (Isoprostane) in on and off pump groups.

Parameter/Group	On- pump	Off- pump	Control	P value
hFABP, ng/ml	133.60 ± 49.41	58.29 ± 16.67	4.33 ± 2.97	$P1 < 0.001^*$ $P2 < 0.001^*$ $P3 < 0.001^*$
CK- MB, U/ml	210.80 ± 32.47	20.19 ± 4.22	13.70 ± 1.64	$P1 < 0.001^*$ $P2 > 0.05$ (NS) $P3 < 0.001^*$
Isoprostane, ng/ml	431.14 ± 51.52	329.83 ± 24.62	132.34 ± 15.57	$P1 < 0.001^*$ $P2 < 0.001^*$ $P3 < 0.001^*$

(*) = Significant.

(NS) = Not significant

P1= between on pump and control groups.

P2= between off pump and control groups.

P3= between on pump and off pump groups.

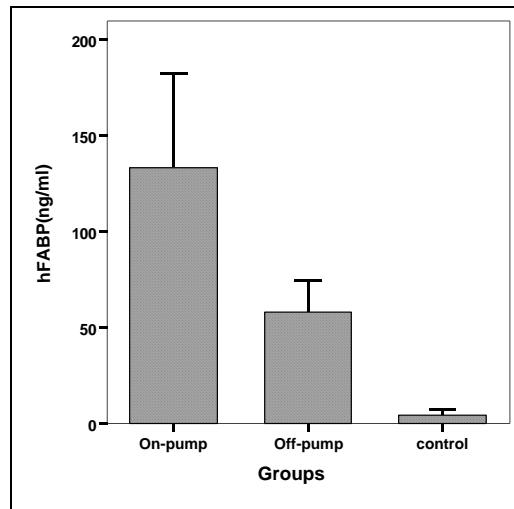


Fig.(1): Mean serum hFABP level in all studied groups

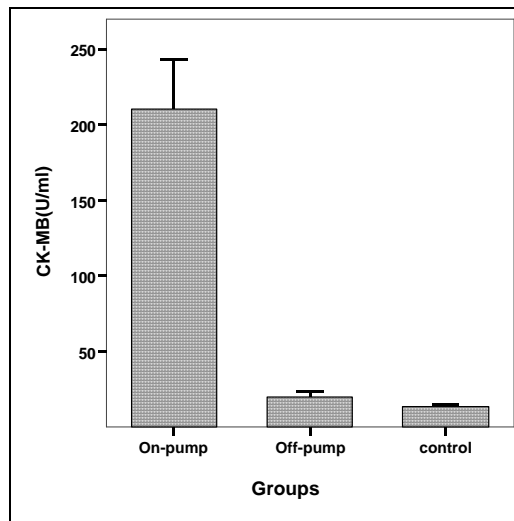


Fig.(2): Mean serum CK-MB level in all studied groups

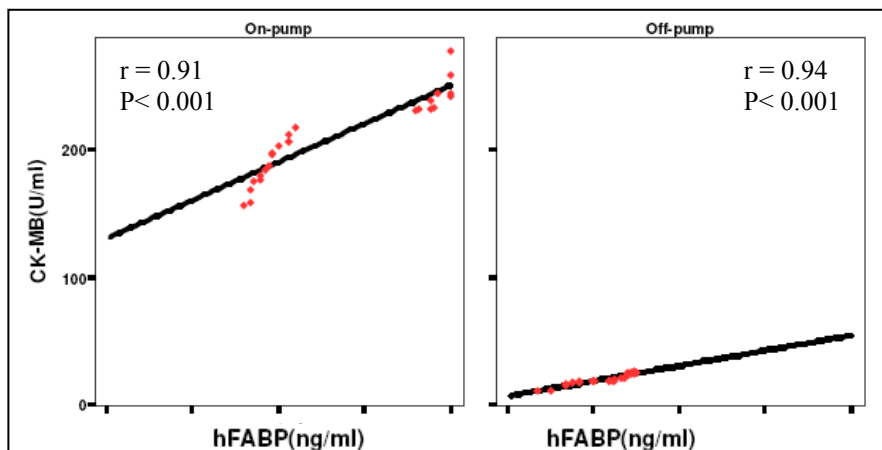


Fig.(3):Correlation between hFABP and CK-MB levels in on-pump and off-pump groups.

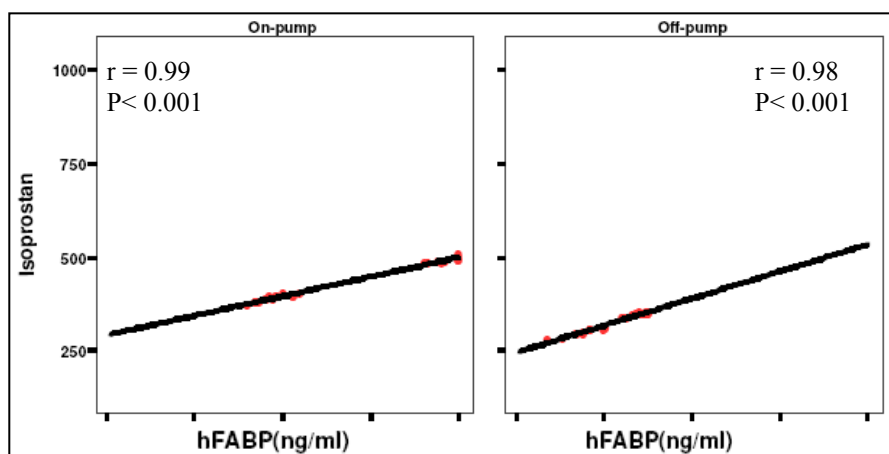


Fig.(4):Correlation between hFABP and Isoprostane levels in on-pump and off-pump groups

A significant positive correlation between serum levels of h-FABP and CK-MB was found in on pump and off pump groups ($r=0.9$, $P< 0.001$), **Fig.(3)**. Also a significant positive Correlation between serum levels of h-FABP and isoprostane was found in on pump and off pump groups ($r=0.9$, $P<0.001$), **Fig.(4)**. Also there was a

significant positive correlation between serum levels CK-MB and isoprostane ($r = 0.9$, $P<0.001$) in on pump and off pump groups. There was no significant difference in the mean levels of ejection fraction between all studied groups, (59.08 ± 8.73 , 59.90 ± 9.71 and 61.76 ± 7.87 respectively).

DISCUSSION

The main findings in the present study were marked elevation in hFABP serum levels in both on-pump and off-pump groups as compared to the control one, and in the on-pump group as compared to the off-pump one. Also, CK-MB serum levels were significantly higher in the on-pump group as compared to both off-pump and control groups. Those results are concomitant with those of *Malik et al. (2006)*⁽²⁸⁾ who found higher levels of hFABP and CK-MB in the on-pump group than in the off-pump group. These findings indicate more myocardial injury in the on-pump group, despite optimal cardiac protection, compared with the off-pump group and they stated that, one probable cause of the discrepancy is that on-pump CABG results in global ischemia, whereas off-pump CABG results in localized ischemia. *Petzold and coworkers, (2001)*⁽²⁹⁾ investigated hFABP for diagnosis of perioperative myocardial infarction during conventional CABG. They studied the release patterns of hFABP, CK-MB at intervals of 5 and 60 minutes after declamping and 1, 2, and 10 days thereafter. They concluded that hFABP is a rapid marker of myocardial damage and peaks earlier than CK-MB. Meanwhile, *Hasegawa and colleagues, (2004)*⁽³⁰⁾ concluded that elevated serum hFABP levels might be a rapid and potentially useful prognostic indicator of myocardial damage and clinical outcome in pediatric cardiac surgery. On the other hand, a new finding of the present study, is that CK-MB levels could not detect subtle myocardial damage in

the off-pump group (where the damage is less than the on-pump one) as there were almost similar levels in off-pump and control groups, whereas hFABP levels were significantly higher in the off-pump group compared to the control group; which denotes that it can detect such subtle damage. This finding has not been clarified by any research till present; thus estimation of CK-MB levels may not be the investigation of choice for early detection of minor cardiac damage, whereas hFABP levels could be. Moreover, hFABP concentrations peaked earlier in both groups, compared with CK-MB concentrations. All these observations may deviate our attention towards the use of that marker, hFABP for rapid and early detection of peri and post-operative cardiac injury following CABG so that early intervention can be possible.

The present study's results also indicate that patients undergoing off-pump CABG surgery had only mild signs of oxidative stress compared with patients undergoing on-pump CABG surgery (serum isoprostane levels: 329.83 ± 24.62 vs 431.14 ± 51.52 ng/ml $P < 0.001$), that finding was shown by the study done by *Gerritsen and his colleagues, (2006)*⁽³¹⁾, they used Malondialdehyde as a marker of oxidative stress, and found that its serum levels were higher in on-pump group as compared to the off-pump one. *Cavalca et al. (2006)*⁽²⁴⁾ studied such stress in both groups by estimation of urinary isoprostane levels and they found that it is significantly increased during surgery and returned at baseline 24 hours later, thus they concluded that,

off pump CABG revealed less perioperative oxidative stress, as reflected by lack of excretion of iPF₂-III in urine, lack of increase of plasma free malondialdehyde, and by lower decrease in plasma total antioxidant status.

Moreover, the significant positive correlation found between serum levels of hFABP and isoprostane in on pump and off pump groups ($r=0.9$, $P<0.001$), Fig.4 may permit to use serum isoprostane as a perioperative measure to give an idea about the extent of cardiac damage.

These results indicate more myocardial injury in the on-pump group, despite optimal cardiac protection, compared with the off-pump group. Myocardial cellular damage associated with cardiac surgery can be caused by different mechanisms (graft related and non graft related), the graft related mechanisms include direct myocardial trauma by surgical manipulations, focal damage caused by inadequate cardioplegic perfusion, and inadequate myocardial protection⁽²⁾. Myocardial damage could also be induced by coronary artery microembolization and result in focal inflammation and regional contractile myocardial dysfunction⁽³²⁾. The non graft related mechanisms contribute in myocardial injury are, graft occlusion, graft kinking or overstretching, subtotal anastomotic stenosis, or graft spasm⁽⁴⁾. These aetiologies of myocardial damage can all result in myocardial necrosis and therefore lead to the elevations of cardiac biomarkers and enzymes⁽³³⁾.

Conclusion:

The present study nominates serum hFABP as a competent intraoperative marker detecting early and minor cardiac damage (off-pump group) in patients undergoing CABG operations, in other words hFABP estimation may be superior to CK-MB particularly in case of off pump operation as its levels are significantly elevated with the lesser cardiac damage (compared to on-pump surgery) accompanying this surgery while CK-MB non significant elevation may provide a false sense of security during the off-pump surgery. Also the results of this study confirm the increased oxidative stress (observed by the increased Isoprostane serum levels) accompanying the on-pump surgeries.

Recommendations:

As we are speaking about the non invasive prevention of a serious and fatal condition (perioperative myocardial infarction); further studies are recommended on larger and different populations.

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تقييم البروتين الرابط للأحماض الدهنية- نوع القلب- للكشف المبكر عن تلف عضلة القلب أثناء العمليات الجراحية

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عمليات ترقيع الشرايين التاجية سواء كانت (علي المضخة) أو (خارج المضخة) تحدث تلفا في عضلة القلب كما تحدث أيضا إجهاد تأكسدي .
 يمكن تقييم درجة التلف في كلتا الحالتين عن طريق قياس البروتين الرابط للأحماض الدهنية- نوع القلب- وإنزيم منشط الكرياتين-إم بي في مصل الدم.
 تهدف هذه الدراسة لتقييم درجة التلف في عضلة القلب في كلتا المجموعتين وذلك عن طريق المقارنة بين مستويات المواد السابق ذكرها ،بالإضافة إلي تقييم الإجهاد التأكسدي وذلك بقياس مستوي الأيزوبروستين في مصل الدم أثناء هذه العمليات الكبرى .
 تضمنت الدراسة خمسين مريضا تم توزيعهم في مجموعتين:
 المجموعة الأولى :علي المضخة (٢٥ مريضا)
 المجموعة الثانية:خارج المضخة (٢٥ مريض)
 بالإضافة إلي ٢٥ شخصا اصحاء كمجموعة ضابطه.
 وقد أوضحت الدراسة ان هناك ارتفاع ذو دلالة إحصائية في مستويات البروتين الرابط للأحماض الدهنية- نوع القلب- في مصل الدم في المجموعة الأولى(علي المضخة) مقارنة بالمجموعة الثانية (خارج المضخة) وبين كل من المجموعتين مقارنة بالمجموعة الضابطه .
 كما وجد ارتفاع ذو دلالة إحصائية في مستويات إنزيم منشط الكرياتين-إم بي في المجموعة الأولى مقارنة بالمجموعة الثانية بينما لم يكن هناك أي إختلاف في تلك المستويات بين المجموعة الثانية (خارج المضخة) مقارنة بالمجموعة الضابطه.
 وأيضاً وجد ارتفاع ذو دلالة إحصائية في مستويات الأيزوبروستين في المجموعة الأولى مقارنة بالمجموعة الثانية وبين كل من المجموعتين مقارنة بالمجموعة الضابطه.
 ونستنتج من هذه الدراسة أن عمليات القلب (علي المضخة) تكون مصاحبه بقدر أكبر من تلف عضلة القلب والإجهاد التأكسدي.
 كما اوضحت هذه الدراسة ان قياس مستويات البروتين الرابط للأحماض الدهنية- نوع القلب- في مصل الدم يعد افضل من قياس إنزيم منشط الكرياتين-إم بي كمؤشر للكشف المبكر عن بداية التلف في عضلة القلب أثناء العمليات الجراحية.