Tecimer et al. Ann Heart 2017, 2(1):14-20
DOI: 10.36959/652/384 | Volume 2 | Issue 1

Annals of Heart

Research Article Open Access

The Role of Cardiotrophin-1 in the Evaluation of Myocardial Ischemia in Patients Undergoing Off-Pump and On-Pump Coronary Artery Bypass Surgery

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Abstract

Purpose: The purpose of this study was to investigate the availability of cardiotrophin-1 in the evaluation of myocardial ischemia in patients undergoing off-pump and on-pump coronary artery bypass surgery.

Methods: Between July 2012 and July 2013, a total of 40 patients undergoing isolated coronary artery bypass surgery were divided into two groups as off-pump (Group 1) and on-pump (Group 2) groups, and groups were compared each other in this prospective study. Preoperatively and postoperatively at 6th hour serum levels of cardiotrophin-1, creatine kinase, creatine kinase-myocardial band, cardiac troponin-I and electrocardiogram were obtained in all patients, and correlation analysis for cardiac ischemia and cardiotrophin-1 levels were performed. Octogenarians, patients with severe left ventricular dysfunction (left ventricular ejection fraction < 30%), patients who underwent concomitant cardiac procedures, patients who had liver and kidney failure, chronic inflammatory disease, presence of acute infections and malignancies, and patients who had emergency or redo surgery were excluded from this study.

Results: In this study, 34 patients were male; the mean age was 64.0 ± 9.7 years. The statistical analysis revealed significant correlation of postoperative cardiotrophin-1 with creatine kinase, creatine kinase-myocardial band, and cardiac troponin-I in Group 1. Also significant correlation of postoperative cardiotrophin-1 with creatine kinase and cardiac troponin-I levels was noticed in Group 2. In both groups, postoperative cardiotrophin-1 values were found to be increased significantly compared to preoperative values.

Conclusion: It was demonstrated that postoperative cardiotrophin-1 showed a positive correlation with other biochemical markers of cardiac ischemia, and it can be used as an alternative biomarker in patients undergoing isolated coronary artery bypass surgery.

Keywords

Cardiotrophin-1, Myocardial ischemia biomarker, Coronary artery bypass surgery

Introduction

Cardiovascular diseases are the leading cause of mortality in the middle and older age and they account for more than 30% of the worldwide deaths [1]. Similar to many other countries in the world, the prevalence and incidence of the Coronary Artery Disease (CAD) in our country vary between 4-5% and 0.3-0.4%, respectively [2].

The regional ischemia-reperfusion is occurred in both on-pump and off-pump Coronary Artery Bypass Grafting (CABG) operation techiques for CAD, there-

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Received: February 02, 2017: **Accepted:** May 11, 2017: **Published online:** May 13, 2017

Citation: Tecimer ME, Yuksel A, Bicer M, et al. (2016) The Role of Cardiotrophin-1 in the Evaluation of Myocardial Ischemia in Patients Undergoing Off-Pump and On-Pump Coronary Artery Bypass Surgery. Ann Heart 2(1):14-20

fore various degrees of myocardial damage may occur with both techniques. Cardiac biomarkers are used for evaluating myocardial damage. Although routinely used cardiac biomarkers show variability, most commonly used biomarkers are Creatine Kinase-Myocardial Band (CK-MB) and cardiac Troponins (cTNs) for the assessment of myocardial damage. The some isoforms of CK-MB and cTNs are sensitive and specific biomarkers of myocardial damage [3-5]. Although these biomarkers are sensitive and specific, they also have some disadvantages. For example, isoforms of CK-MB like total Creatine Kinase (CK), CK-MB, and myoglobin are not cardiac specific markers because they are found in both skeletal and myocardial muscle. Their levels are not so easily obtained, and there is much subjectivity in how results are interpreted [4]. Moreover, cTNs have the feature of late clearance from blood which makes it difficult to determine a recurrent myocardial infarction [5].

Due to the similarity of aminoacid structure, Cardiotrophin-1 (CT-1) is an inflammatory cytokine belong to the Interleukin-6 (IL-6) family. CT-1 is found both in atria and ventricles, and upregulated in cardiac cells in response to mechanical, humoral, metabolic and hypoxic stress. It promotes cell survival in acute stress, but if stressful signals persist, its chronic upregulation causes to cardiomyocyte hypertrophy and eventually left ventricular dysfunction. CT-1 plays an important role in the pathogenesis of ischemic heart disease. The expression of CT-1 increases in ischemic status and protects myocytes from ischemia-reperfusion injury and apoptosis. It has been shown that pro-oxidants and physiologic hypoxia increase CT-1 secretion. CT-1 is also released in vascular endothelial cells and has direct vascular effects, resulting in atherogenesis, vascular dysfunction, arterial stiffness, and increased blood pressure. CT-1 is considered as a potent profibrotic agent for the heart and vessels [6-8]. Furthermore, CT-1 has an important cardioprotective effect on the myocardial damage [9]. In this study, we aimed to investigate the availability of CT-1 in the evaluation of myocardial ischemia in patients who underwent isolated on-pump and off-pump CABG.

Materials and Methods

Ethical declaration

The study protocol was approved by the Medical Research Ethics Committee of Uludag University with the decision number of 2012-12/15 at the date of June 05, 2012. The study was conducted in accordance with the principles of the Declaration of Helsinki. All participants were informed about the study, and their informed consent forms were obtained before the operation.

Study design

Between July 2012 and July 2013, a total of 40 patients who underwent primary isolated CABG in Hospital of Uludag University Faculty of Medicine were included in this prospective study. Patients were divided into two groups according to the surgical technique as off-pump CABG (Group 1) and on-pump CABG (Group 2) groups, and groups were compared each other. Detailed anamnesis was obtained and physical examination was performed to all of patients. Octogenarians, patients with severe left ventricular dysfunction (left ventricular ejection fraction < 30%), patients who underwent concomitant cardiac procedures, patients who had liver and renal failure, chronic inflammatory disease, presence of acute infections and malignancies, and patients who had emergency or redo surgery were excluded from the study.

Venous blood samples were obtained from the participants for routine hematologic and biochemical tests following a 12-hour fasting period before CABG and 6 hours after CABG. Blood samples of the participants were studied to determite serum levels of CT-1, hemogram, urea, creatinine, Aspartat Aminotransferase (AST), Alanine Aminotransferase (ALT), CK, CK-MB, cardiac Troponin-I (cTN-I). Additionally, 2-3 mL of blood samples of the participants were put into tubes with EDTA, and stored at -20 °C until analysis of the CT-1, which was measured using a CT-1 PicoKine™ Enzyme-Linked Immunosorbent Assay (ELISA) kit maintained at 4 °C. All patients were examined using electrocardiogram to determine their cardiac rhythm (sinus rhythm, atrial fibrillation, etc) preoperatively and postoperatively. The correlation analysis for cardiac ischemia and CT-1 levels were performed.

Surgical approach

The surgical approach to be applied was decided a day before the operation. The final decision was given after evaluation of coronary anatomy and the palpation of aorta at the time of operation. Twenty patients had undergone off-pump coronary bypass surgery (beating heart without cardiopulmonary bypass) and the other twenty patients had undergone conventional on-pump coronary bypass surgery (with cardiopulmonary bypass).

Statistical analysis

Continuous variables were expressed as median ± standard deviation (minimum and maximum). Categorical variables were expressed as frequency and percentages. Intergroup comparisons were made, and preoperative and postoperative results of groups were compared according to the distribution of continuous variables using the Student T, Mann-Whitney U, and Kruskal-Wallis tests. Categorical variables were compared using the

Table 1: Clinical and demographic data of patients.

	Group 1 (n:20)	Group 2 (n:20)	p value
Age[a]			
< 65 years	11 (55%)	11 (55%)	1
> 65 years	9 (45%)	9 (45%)	1
Gender[a]			
Female	2 (10%)	4 (20%)	0.66
Male	18 (90%)	16 (80%)	0.66
Risk factors[a]			
Hypertension	16 (80%)	15 (75%)	1
Diabetes mellitus	8 (40%)	11 (55%)	0.527
Hyperlipidemia	7 (35%)	10 (50%)	0.522
Obesity	5 (25%)	5 (25%)	1
Smoking	12 (60%)	13 (65%)	1
History of family	14 (70%)	13 (65%)	1
Preoperative medications[a]			
Beta-blocker	11 (55%)	12 (60%)	1
Statin	5 (25%)	7 (35%)	0.73

[a]n (%).

Table 2: Preoperative values of both groups.

Parameters	Group 1 (n:20)	Group 2 (n:20)	p value
EF (%)[a]	60 (45-68)	50 (47-64)	0.001
WBC (per/mm3)[a]	7.6 (6.2-11.9)	9.8 (6.1-15)	0.014
Creatinine (mg/dl)[a]	0.9 (0.6-1.3)	0.8 (0.6-1.2)	0.398
Urea (mg/dl)[a]	33.5 (18-57)	30.5 (13-60)	0.799
AST (IU/L)[a]	23 (13-55)	20.5 (6-81)	0.327
ALT (IU/L)[a]	22.5 (10-55)	20.5 (6-81)	0.265
Hgb (g/dl)[a]	14.1 (11.9-17.3)	13.1 (9.6-15.9)	0.072
CT-1 (pg/ml)[a]	122 (5.9-457)	99.8 (0-387)	0.314
CK (U/L)[a]	72.5 (30-192)	104 (11-900)	0.261
CK-MB (ng/ml)[a]	10 (6-40)	18.5 (5-152)	0.028
cTN-I (ng/ml)[a]	6.5 (0.01-1004)	13.3 (0.03-281)	0.013

[a]Median (minimum-maximum); EF: Ejection Fraction; WBC: White Blood Cell; AST: Aspartate Transaminase; ALT: Alanine Transaminase; Hgb: Hemoglobin; CT-1:Cardiotrophin-1; CK: Creatine Kinase; CK-MB: Creatine Kinase-Myocardial Band; cTN-I: Cardiac Troponin-I.

Chi-square test. The relationships among continuous variables were analysed by using correlation analysis and Spearman correlation coefficient was calculated. All the statistical analysis were performed using the IBM Statistical Package for Social Sciences (SPSS) program version 21.0 (SPSS Inc, Chicago, IL, USA), and p value < 0.05 was considered statistically significant.

Results

Demographics and basic clinical features of patients are summarized in (Table 1). The median age of patients was 64.0 ± 9.7 years (range: 56-78 years), and 34 (85%) patients were male. There were no statistically significant differences between groups according to the age, gender, and other basic clinical and demographic features. When preoperative laboratory values of both groups were compared, it was found that there were no statistically significant differences in urea, creatinine, ALT, AST, Hemoglobin (Hgb), CT-1, CK levels; however, there were statistically significant elevation in Ejection Fraction (EF) in Group 1, and White Blood Cell (WBC), CK-MB, cTN-I levels in Group 2 (Table 2). When postoperative values of both groups were compared, it was found that there were no statistically significant differences in EF, urea, creatinine, AST and ALT levels; however, there were statistically significant elevations in WBC, Hmg, CT-1, CK in Group 1, and CK-MB, cTN-I levels in Group 2 (Table 3).

The median preoperative and postoperative laboratory values of all study population were listed in (Table 4). There were no statistically significant differences in creatinine, urea and ALT values between preoperative and postoperative period. On the other hand, white blood cell, AST, CK, CK-MB, cTN-I and CT-1 values were significantly higher in postoperative period compared to preoperative period. In postoperative period, the most common complication was new-onset atrial fibrillation which was observed in 9 (22.5%) patients. The median postoperative length of intensive care unit and hospital stay were 1.3 ± 0.6 days (range: 1-3 days) and 5.1 ± 1.2

Table 3: Postoperative values of both groups.

Parameters	Group 1 (n:20)	Group 2 (n:20)	p value
EF (%)[a]	60 (45-66)	50 (30-63)	0.210
WBC (per/mm3)[a]	11.2 (7.2-13.9)	11 (6.5-17)	0.002
Creatinine (mg/dl)[a]	0.8 (0.6-1.1)	0.8 (0.6-1.4)	0.072
Urea (mg/dl)[a]	30 (13-45)	41 (17-80)	0.144
AST (IU/L)[a]	33.5 (15-79)	39.5 (19-110)	0.080
ALT (IU/L)[a]	19 (6-42)	26 (8-92)	0.177
Hgb (g/dl)[a]	10.8 (8.5-14.2)	9.5 (8.6-11.4)	0.000
CT-1 (pg/ml)[a]	349 (21-887)	330 (154-985)	0.000
CK (U/L)[a]	656 (96-1183)	(248-4257)	0.000
CK-MB (ng/ml)[a]	26 (8-89)	31.5 (12-110)	0.008
cTN-I (ng/ml)[a]	94 (0.05-1142)	243 (0.19-516)	0.002

[a]Median (Minimum-Maximum); EF: Ejection Fraction; WBC: White Blood Cell; AST: Aspartate Transaminase; ALT: Alanine Transaminase; Hgb: Hemoglobin; CT-1: Cardiotrophin-1; CK: Creatine Kinase; CK-MB: Creatine Kinase-Myocardial Band; cTN-I: Cardiac Troponin-I.

Table 4: Preoperative and postoperative laboratory values of patients.

Parameters	Preoperative values	Postoperative values	p value
WBC (per/mm^3)	8.7 (6.1-15)	11.1 (6.5-17)	< 0.05
Creatinine (mg/dL)	0.9 (0.6-1.3)	0.8 (0.6-1.4)	0.116
Urea (mg/dL)	32.1 (13-60)	35.6 (13-80)	0.178
AST (IU/L)	21.8 (6-81)	36.5 (15-110)	< 0.05
ALT (IU/L)	21.5 (6-81)	22.7 (6-92)	0.396
Hgb (g/dL)	13.6 (9.6-17.3)	10.2 (8.5-14.2)	< 0.05
CK (U/L)	88.3 (11-900)	557.3 (96-4257)	< 0.05
CK-MB (ng/mL)	14.2 (5-152)	28.8 (8-110)	< 0.05
cTN-I (ng/mL)	9.9 (0.01-1004)	168.5 (0.05-1142)	< 0.05
CT-1 (pg/mL)	111 (0-457)	339 (21-985)	< 0.05

ALT: Alanine Aminotransferase; AST: Aspartat Aminotransferase; CK: Creatine Kinase; CK-MB: Creatine Kinase-Myocardial Band; cTN-I: Cardiac Troponin-I; CT-1: Cardiotrophin-1; Hgb: Hemoglobin; WBC: White Blood Cell.

**The values were given as median (minimum and maximum).*

Table 5: Correlation analysis between postoperative CT-1 values and postoperative values of other ischemia biomarkers in Group 1.

CT-1	CK	CK-MB	cTN-I
r value	0.471	0.532	0.448
p value	0.036	0.016	0.048

CABG: Coronary Artery Bypass Grafting; CK: Creatine Kinase; CK-MB: Creatine Kinase-Myocardial Band; cTN-I: Cardiac Troponin-I; CT-1: Cardiotrophin-1.

Table 6: Correlation analysis between postoperative CT-1 values and postoperative values of other ischemia biomarkers in Group 2.

CT-1	CK	CK-MB	cTN-I
r value	0.467	0.344	0.149
p value	0.044	0.149	0.042

CABG: Coronary Artery Bypass Grafting; CK: Creatine Kinase; CK-MB: Creatine Kinase-Myocardial Band; cTN-I: Cardiac Troponin-I; CT-1: Cardiotrophin-1.

days (range: 4-10 days), respectively. No death was observed during postoperative period.

In correlation analysis between postoperative CT-1 values and postoperative values of other ischemia biomarkers and some parameters including age, number of bypass grafts, length of hospital stay in Group 1, it was found that there were statistically significant correlation between an increase in postoperative CT-1 values and increases postoperative CK, CK-MB and cTN-I values (Table 5). There were no statistically significant correlation with age, number of bypass grafts, length of hospital stay. In Group 2, there were statistically significant correlation between an increase in postoperative CT-1 values and increases postoperative CK and cTN-I values, but not CK-MB values (Table 6). There were no statistically significant correlation with age, number of bypass grafts, and length of hospital stay. In both groups, postoperative CT-1 values were found to be increased significantly compared to preoperative values ($p < 0.05$).

Discussion

In recent years, the requirement of coronary revascularization is increased because of incidence of ischemic heart disease is increased. Coronary revascularization is the standard treatment method for ischemic heart disease that is unresponsive to medical treatment [10]. Surgical treatment (CABG) is an option for coronary revascularization that decreases angina pectoris, increases life

span, and achieves this with a low rate of mortality and morbidity nowadays. Although reliability of operations that are performed by using CPB is approved, off-pump coronary bypass technique is utilized more nowadays, because this technique without CPB is more physiologic, causes less myocardial damage and postoperative complications as we see in many studies [11-13]. Occurrence of myocardial damage is one of the severe complications following CABG surgery. Although myocardial protection measures and advances in surgery, various degrees of myocardial ischemia may occur. In 5-15% of the cases, the ischemia may progress even to the myocardial necrosis [14]. Several studies demonstrated that the patients suffered perioperative Myocardial Infarction (MI) had lower survival expectation at mid- and long-term follow-up [15,16].

Along with CK, CK-MB and AST; the biomarkers with higher specificity and sensitivity like cTn are also utilized for detecting myocardial damage [17]. Studies about sensitive and specific biomarkers which may allow early diagnosis has become focus of attention due to the higher mortality, postoperative complications and length of hospital stay of perioperative MI. The serum values of CK, CK-MB begin to increase between 8th and 12th hour of MI, peak between 24th and 72th hour and continue at high levels between 2nd and 5th day. Steuer and colleagues [18] reported that the fact that serum levels of AST, CK, CK-MB are higher in patients who underwent CABG shows myocardial damage and this fact is related with postoperative early and late period mortality. The serum levels of these biomarkers are not specific, because they may also increase in heart failure, myocarditis, paroxysmal tachycardia attacks, aortic dissection, liver diseases, pancreatitis and musculoskeletal system injury, and these biomarkers are utilized less nowadays. In Sabzi and colleagues' study [19], abnormal serum levels of liver function tests are observed in the majority of cases following CABG, these increases usually occur at postoperative first 3 days and they decrease to normal level in a short time. It was emphasized that the increases of liver function tests level have not only hepatocellular origin. The authors also stated that the perioperative myocardial damage may be related with erythrocyte destruction after hemolysis and musculoskeletal trauma. In Teoh and colleagues' study [20], the authors showed that the permeability of ischemic myocardium increased during cold cardioplegic arrest, and depending on that, serum AST level can increase independently from liver damage. In our study, the serum levels of AST, CK, CK-MB were increased significantly at the postoperative period. This increase can depend on either cardiac myocyte damage or mechanic trauma and erythrocyte destruction, because we analysed postoperative 6th hour serum levels.

CT-1 is a member of IL-6 cytokine family. This family is known as gp130 group cytokines due to show their effects by transmembrane protein gp130 [21]. CT-1 is found both in atria and ventricles. In previous studies, it was shown that CT-1 inhibits cardiomyocyte apoptosis, plays role on sustaining survival and proliferation of embryonic cardiomyocytes. CT-1 protects cardiomyocytes against ischemic damage with the deposition of heat-shock proteins [22,23]. Talwar and colleagues [24] demonstrated that serum levels of CT-1 and N Terminal pro-Brain Natriuretic Peptide (NT-proBNP) increase correlatively in unstable angina pectoris, however instable angina pectoris only serum levels of CT-1 increase. In unstable angina, it is thought that regional wall stress that increases after ischemy triggers CT-1 expression. In Khan and colleagues' study [25] in which 291 patients have acute MI, authors reported that CT-1 and NT-proBNP are higher in patients that develops heart failure and death, and they also reported that like NT-proBNP, CT-1 may predict death and heart failure independently of age, sex, previous MI, serum level of creatinine and Killip classification. In the prediction of the development of death and heart failure, it was emphasized that combined levels of CT-1 and NT-proBNP were more informative than either marker alone after an acute MI.

CT-1 expression protects cardiomyocytes from ischemia-reperfusion damage and apoptosis in hypoxic status. Ruixing and colleagues [26] compared the effects of CT-1 on hemodynamics, cardiac function and cardiomyocyte apoptosis in rats with acute MI that develop after left coronary artery ligation. The number of apoptotic cardiomyocytes in treated group which receive CT-1 one week before coronary ligation was found less than that in control group, and it was shown that CT-1 pretreatment significantly inhibits P53, Fas and Bax, and increases Bcl-2 expression in myocardium. As a consequence, its protective effect on cardiomyocytes was provided. Freed and colleagues [27] showed that CT-1 levels were higher in rats after acute MI in infarct area. In Wei and colleagues' study [28], postoperative changes of CT-1 was not found associated with cardiac functions and levels of brain natriuretic peptide in 49 off-pump coronary bypass surgery patients, but it was found associated with the patients that have recent MI. However in our study, the patients were elective cases and these patients had no history of early MI. Therefore, postoperative CT-1 increase was not associated with MI, it was associated with perioperative hypoxia and cell injury. The fact that postoperative cTN-I levels were positively correlated with preoperative CT-1, postoperative CK, CK-MB, CT-1 levels supports this situation.

In our study, postoperative CT-1 levels were significantly increased from preoperative levels in both groups,

and it was found to be positively correlated with preoperative cTN-I, postoperative CK, CK-MB and cTN-I levels. Hypoxic and cellular-level injuries which can occur in myocytes by perioperative mechanic or inflammatory mechanisms may explain these results. Positive correlation between postoperative CK, CK-MB, cTN-I levels and postoperative CT-1 levels demonstrated that postoperative CT-1 can determine perioperative hypoxia and cellular injury like other biomarkers. However, there were no correlation between postoperative CT-1 levels and age or number of bypass grafts, therefore these results were supported clinical feasibility of CT-1 by demonstrating its immunity against these factors.

Nowadays, CABG is a common treatment modality for patients with CAD that is unresponsive to medical treatment, and it can cause damage in cardiac myocytes due to various perioperative causes (advanced age, diffuse CAD, inadequate myocardial protection, incomplete surgical revascularization, vasospasm, atheromatous embolism from aorta or previous bypass grafts, air embolism, thrombosis of a native coronary artery or a new graft, etc.). Although CK, CK-MB, cTNs have been used for determination of this injury, the cut-off values of these biomarkers have not been defined yet. It is known that serum level of CT-1 increases in hypoxic status to prevent apoptosis. On the other hand, perioperative ischemia is associated with prolonged length of ICU and hospital stay, increased costs and increased morbidity and mortality. Therefore, there is an intense interest in this field to diagnose of perioperative myocardial ischemia with higher sensitivity and specificity as well as much faster fashion. CT-1, which release hypoxic situations to protect myocytes from ischemic and reperfusion injuries and apoptosis, may be more useful than other markers in the detection of myocardial ischemia related to CABG.

When compared to results of the literature, our early-term postoperative outcomes including the rates of major complication and death were comparable. There were several limitations in the interpretation of the results of our study. The major limitations of this present study were the small number of patients in the study groups and evaluated data were limited. A larger sample could have increased the statistical power of our research.

Conclusion

It was demonstrated that CT-1 can show perioperative myocardial damage and it is positively correlated with cTN-I, therefore it can be used as an alternative biomarker to the CK, CK-MB and cTN-I in this patient group.

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