

ATRIAL FIBRILLATION AND GAMA GLUTAMYL TRANSFERASE; OF-PUMP VERSUS ON-PUMP CORONARY ARTERY BYPASS SURGERY

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Abstract: Introduction: Atrial fibrillation (AF) which can be seen as a complication of the open heart surgery, may cause serious problems on post operative period. The exact pathophysiology of AF is unknown but it is thought that factors such as oxidative stress might cause AF. **Material and methods:** We retrospectively surveyed the serum gamma glutamyl transferase (GGT) levels which is accepted as a mediator of oxidative stress, for the Post Operative Atrial Fibrillation (POAF) that occur after of-pump versus on-pump Coronary Artery Bypass Graft (CABG) surgery. Our study included 183 cases (101 male, 72 female; median age 63 ± 4.3 years) of which CABG was performed. **Results:** Echocardiography, routine blood tests, electrocardiography (ECG), test for the serum GGT levels were performed in preoperative and postoperative period to all participants. AF developed in 34 patients (35 %) in Group I and 19 patients (20 %) in Group II. There were no significant differences between two groups (of-pump versus on-pump) in terms of gender, cardiovascular risk factors and the severity of the coronary artery disease. In patients who has developed AF in postoperative period had significantly higher serum GGT levels. **Conclusion:** This study has shown that serum GGT levels were found to be significantly higher in patients whom AF has developed after on-pump CABG surgery.

Keywords: Coronary artery bypass graft, Serum gamma glutamyl transferase, atrial fibrillation.

INTRODUCTION

Atrial fibrillation (AF) is the most common pathologic arrhythmia among clinical arrhythmias and can be seen in coronary artery disease, hypertension, mitral valve diseases and hyperthyroidism. AF can also be seen idiopathically. Recently, in addition to these risk

factors, obesity, metabolic syndrome, chronic alcoholism and atherosclerosis have been reported as other etiological factors of AF (1). Oxidative stress is thought to be an important physiopathological mechanism in the development of POAF since antioxidant agents such as ascorbic acid is found to be important in the prevention of the development of POAF (2, 3). Serum gamma glutamyl transferase (GGT) enzyme is important in the homeostasis of the glutathione which is responsible for the protection of the cells from the free oxygen radicals. GGT is related with hepatobiliary diseases and alcohol consumption. There are studies in which the use of the serum concentrations of GGT as a marker for increased oxidative stress (4). It has also been postulated that increased serum GGT levels and cardiovascular diseases and the metabolic syndrome are closely related (5, 6). Because of these facts we investigated the relationship of serum GGT which is a marker for increased oxidative stress with POAF.

MATERIALS AND METHODS

Our study included 183 cases of which CABG was performed in Gaziantep Dr. Ersin Arslan Education and Research Hospital between 2012 and 2017. Patients who had chronic liver disease, preoperative AF, wide left atrium (> 5 cm) and patients who had indications for emergency CABG were excluded from this study. Echocardiography, routine blood tests, electrocardiography (ECG), test for the serum GGT levels were performed in preoperative and postoperative period to all participants.

Biochemical analysis

A venous blood specimen (5 mL) was collected at 6:00 a.m. to 7:00 a.m. Serum was separated by centri-

fugation at $1500 \times g$ for 15 min. All laboratory analysis were performed at the department of central bio chemistry labarotry. Serum GGT levels were measured spectrophotometrically with the Beckman DXC800 automatic biochemical analyzer (USA). Reference range for GGT was 7-49 U/L.

Surgical Technic

Off-pump and On-pump CABG procedures were performed through a median sternotomy approach. Octopus and Starfish (Medtronic, USA) was used to stabilize the target coronary vessel in all off-pump CABG cases . Revascularization in on-pump CABG was performed by standard surgical technique with moderate systemic hyperthermia (30-32°C). Conduits for both off-pump and on-pump CABG included the internal

mammary artery or saphenous veins, or a combination of the two. All patients were continuously monitored in the intensive care unit (ICU) postoperatively. A 12-lead ECG recording was performed to confirm the AF episodes. POAF was defined as the characteristic arrhythmia lasting for more than 5 minutes. POAF was treated by amiodarone and replacement of potassium and magnesium. Patients were periodically examined in our outpatient clinics especially who had POAF. All continuous variables were presented as mean \pm SD. Student t-test was used for analysis of continuous variables and Chi-squared test was used.

RESULTS

183 cases were divided into two groups; Group I included the patients (n: 96) who had on-pump CABG,

Table 1. Demographic data

VARIABLES	ON-PUMP (n: 96)	OFF-PUMP (n: 87)	significance
Age	56 \pm 2.3	54 \pm 2.3	N.S.
Sex	f: 46 (48%) m: 50 (52%)	f: 41 (47%) m: 46 (53%)	N.S.
Positive Familiy History	63 (65%)	53 (60%)	N.S.
Smoking	66 (68%)	61 /70%)	N.S.
Hypertension (BP > 139/89 mmHg)	46 (48%)	41 (47%)	N.S.
Carotid Artery Disease	13 (13%)	11 (12%)	N.S.
Peripheric Artery Disease	21 (21%)	17 (19%)	N.S.
Angina Pectoris	54 (56%)	43 (49%)	N.S.
Myocardial Infarction	25 (26%)	22 (25%)	N.S.
COPD	26 (27%)	23 (26%)	N.S.

COPD: Choronic Obstructive Pulmonary Disease, f: female, m: male

Table 2. Preoperative biochemical markers

VARIABLES	ON-PUMP (n: 96)	OFF-PUMP (n: 87)	significance
WBC (3.5-10 X 10 ⁶ /L)	5.600	6.100	
Hg (11.5-16.5 g/dl)	10.7	10.3	
Hct (%)	32	30	
Platelet (100-400 X 10 ⁶ /L)	221.000	213.000	
Cr (0.7-1,3 mg/dl)	1,0	1,1	
BUN (6-20 mg/dl)	12,7	13,3	
Glucose (< 200 mg/dl)	107	111	
AST (0-37 U/L)	19	23	
ALT (0-41 U/L)	16	13	
LDH (210-425 U/L)	337	411	
GGT(10-	36	31	

WBC: White Blood Cell, Hg: Hemoglobin, Hct: Hemotocrit, Cr: Creatinine, BUN: Blood Urea Nitrogene, AST: Aspartate Transferease, ALT: Alanine Transferase, LDH: Lactic De Hydrogenase, GGT: Gama Glytamil Transferase.

Table 3. Postoperative biochemical markers

VARIABLES	ON-PUMP (n: 96)	OFF-PUMP (n: 87)	significance
WBC (3.5-10 x 10 ⁶ /L)	12.300	7.100	
Hg (11.5-16.5 g/dl)	8,7	9,8	
Hct (%)	26	28	
Platelet (100-400 x 10 ⁶ /L)	143.000	227.000	
Cr (0.7-1.3 mg/dl)	1,3	0,8	
BUN (6-20 mg/dl)	33	17	
Glucose (< 200 mg/dl)	156	124	
AST (0-37 U/L)	53	18	
ALT (0-41 U/L)	119	26	
LDH (210-425 U/L)	1048	768	
GGT	89	33	

WBC: White Blood Cell, Hg: Hemoglobin, Hct: Hemotocrit, Cr: Creatinine, BUN: Blood Urea Nitrogene, AST: Aspartate Transfe-
 rase, ALT: Alanine Transferase, LDH: Lactic De Hydrogenase, GGT: Gama Glytamyl Transferase.

Table 4. Operative and postoperative data

VARIABLES	ON-PUMP (n: 96)	OFF-PUMP (n: 87)	significance
Mean Number Of Diseased Coronary Artery	2.3	2.1	
Mean Number of Revascularized Coronary Artery	2.1	2.0	
Preoperative EF	46%	48%	
Postoperative EF (3 Months Later)	43%	49%	
Postoperative AF	34 (35 %)	19 (20 %)	
Postoperative AF (3 Month later)	11 (11 %)	7 (8 %)	
3 months later GGT	74	36	

EF: Ejection Fraction, AF: Atrial Fibrillation, GGT: Gama Glutamyl Transferase

Group II included the patients (n: 87) who had of-pump CABG. There were statistically no significant difference between two groups in terms of demograp-
 hic data and preoperative clinical conditions (Table 1, 2). AF developed in 34 patients (35 %) in Group I and 19 patients (20 %) in Group II. Also despite the anti AF therapy 3 months later AF persisted in 11 patients (11 %) in Group 1 and in 7 patients (8 %) in Group II. No significant differences between two groups were fo-
 und in terms of pre-operative blood tests. No signifi-
 cant differences between two groups were found in terms of post-operative blood tests except for the AST and the GGT. AST in Group I was 23.44±12.89 mg/dl and in Group II 38.48 ± 51.89 mg/dl. GGT which is considered to be a marker for increased oxidative stress was found to be significantly different; in Group I: 47.57 ± 29.44, in Group II:35.13 ± 18.77, (p < 0.05).

DISCUSSION

POAF is the mostly encountered arrhythmic com-
 plication of CABG which is estimated to 5-30 % (7A).

If AF is untreated it is one of the leading cause of post-
 operative morbidity and mortality (7). It usually is seen on 2nd or 3th postoperative day (8). There are many studies of-pump CABG lowers the incidence of PO-
 AF(9,10), but also there are authors on the contrary (11, 12). In our study POAF is seen with significantly higher incidence in on-pump CABG compared to of-pump CABG. This is the main postulate of this study. There are multifactorial mechanisms are questi-
 oned for POAF. It could be of either slow atrial con-
 duction nature or dispersion of atrial refractoriness (13). Especially Archobold stated that; a combination of prolonged signal-averaged P-wave duration (SAPD), advanced age, and male sex identifies patients at high risk for development of POAF (13). AF is accepted to be reentrant in origin, so sustained AF requires that the depolarizing wave fronts continuously encounter exci-
 table tissue, a circumstance favored by slow atrial con-
 duction and a short atrial refractory period (14). It has been found that atrial myositic calcium load and elec-
 trophysiological remodelling of the atrial tissue is fo-

und to be responsible for the development of POAF (15). Plasma peroxidase levels were found to be increased after aortic cross clamping, in patients whom CABG operation was performed (7, 16). POAF can develop in an environment in which there is increased oxidative but there isn't enough anti oxidants present. Violi reports on experimental and clinical studies exploring the role of Reactive oxygen species (ROS) in eliciting the occurrence or recurrence of AF and the potential efficacy of a treatment by antioxidant vitamins (17). Stanger states that Ischemia-reperfusion has been reported to be associated with augmented oxidative stress in the course of surgery, which might be causally involved in the onset of atrial fibrillation (AF), the most common arrhythmia after cardiac surgery. So he hypothesized that supplementation of antioxidants and n-3 polyunsaturated fatty acids (n-3 PUFAs) might lower the incidence of AF following coronary artery bypass graft (CABG) surgery. And finally he concludes that the administration of vitamins attenuates post-operative oxidative stress in the course of CABG surgery (18). GGT is the enzyme for the separation of gamma glutamyl from glutathione which itself is an important antioxidant. Because of the close relationship between serum GGT levels and inflammation and atherosclerosis (8) the development of POAF which occurs in a similar fashion is found to be significantly related with the serum GGT levels as well. GGT as an enzyme that is derived from the liver is postulated to have an independent relationship between postoperative AF (19). The mean age is found to be significantly higher in Group I in which postoperative AF occurred ($p < 0.05$) and thus the age group in this study is considered to be appropriate. Postoperative AF is found to be more

often in the second and third postoperative days and serum GGT levels are found to be increased in the first postoperative day. This might affect the statistical analysis but since history of MI was among the exclusion criteria elevated levels of serum GGT may be an independent risk factor for AF.

CONCLUSION

The leading etiological factors for the development of postoperative AF are inflammation and oxidative stress. Thus it is imperative to perform the tests for inflammatory markers and the markers of oxidative stress in the preoperative period in order to develop preventive treatment protocols for such complications of CABG operation.

Abbreviations

AF — Atrial fibrillation
GGT — gamma glutamyl transferase
POAF — Post Operative Atrial Fibrillation
CABG — Coronary Artery Bypass Graft
EKG — electrocardiography
ROS — Reactive oxygen species

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Sažetak

ATRIJALNA FIBRILACIJA I GAMA GLUTAMIL TRANSFERAZA; AORTOPULMONALNO PREMOŠĆAVANJE SA I BEZ UPOTREBE PUMPE ZA VANTELESNU CIRKULACIJU

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Uvod: Atrijalna fibrilacija (AF), koja se može javiti kao komplikacija operacija na otvorenom srcu, može izazvati ozbiljne probleme u postoperativnom periodu. Tačna patofiziologija AF je nepoznata. Smatra se da faktori kao što je oksidativni stres mogu izazvati AF.

Materijal i metode: Retrospektivno smo ispitali nivo serumske gama glutamil transferaze (GGT), kao medijatora oksidativnog stresa, kod postoperativne atrijalne fibrilacije (POAF) koja se javila posle aortokoronarnog premošćavanja (CABG) uz pomoć i bez

upotrebe pumpe za vantelesnu cirkulaciju. Naša studija je uključila 183 slučaja (101 muškarac, 72 žene; prosečne starosti 63 ± 4.3 godine) kod kojih je izvedeno aortokoronarno premošćavanje.

Zaključak: Ova studija je pokazala da je značajno viši nivo serumske GGT nađen kod atrijalne fibrilacije nakon aortokoronarnog premošćavanja sa upotrebom pumpe za vantelesnu cirkulaciju.

Gljučne reči: aortokoronarno premošćavanje, serumska gama glutamil transferaza, atrijalna fibrilacija.

REFERENCES

1. Prystowsky EN, Padanilam BJ, Fogel RI. Treatment of Atrial Fibrillation. *JAMA*. 2015; 314(3): 278-88.
2. Orenes-PiZero E, Montoro-García S, Banerjee A, Valdés M, Lip GY, Marín F. Pre and post-operative treatments for prevention of atrial fibrillation after cardiac surgery. *Mini Rev Med Chem*. 2012; 12(13): 1419-31.
3. Pavlos P, Olga A, Eleferios C, Fotini A, Charilaos K, Karaikos T et al. The role of ascorbic acid in the prevention of atrial fibrillation after elective on-pump myocardial revascularization surgery: a single-center experience-pilot study *Interact Cardiovasc Thorac Surg*. 2011; 12(2): 121-4.
4. Bulusu S, Sharma M. What does serum γ -glutamyl transferase (GGT) tell us as a cardiometabolic risk marker? *Ann Clin Biochem*. 2016; 53(Pt 3): 312-32.
5. Cho HS, Lee SW, Kim ES, Mo EY, Shin JY, Moon SD, et al. Clinical significance of serum bilirubin and gamma-glutamyl transferase levels on coronary atherosclerosis assessed by multidetector computed tomography. *Nutr Metab Cardiovasc Dis*. 2015; 25(7): 677-85.
6. Wei D, Chen T, Li J, Gao Y, Ren Y, Zhang X, et al. Association of Serum Gamma-Glutamyl Transferase and Ferritin with the Metabolic Syndrome. *J Diabetes Res*. 2015; 2015: 741731. doi: 10.1155/2015/741731. Epub 2015 Jun 21.
7. Mao Z, Zhong X, Yin J, Zhao Z, Hu X, Hackett ML. Predictors associated with stroke after coronary artery bypass grafting: A systematic review. *J Neurol Sci*. 2015; 357(1-2): 1-7.
8. Zakkar M, Ascione R, James AF, Angelini GD, Suleiman MS. Inflammation, oxidative stress and postoperative atrial fibrillation in cardiac surgery. *Pharmacol Ther*. 2015; 154: 13-20.
9. Abo-Salem E, Lockwood D, Boersma L, Deneke T, Pison L, Paone RF, et al. Surgical Treatment of Atrial Fibrillation. *J Cardiovasc Electrophysiol*. 2015; 26(9), 1027-37.
10. Patel S, Wang S, Pauliks L, Chang D, Clark JB, Kunselman AR, et al. Evaluation of a novel pulsatile extracorporeal life support system synchronized to the cardiac cycle: effect of rhythm changes on hemodynamic performance. *Artif Organs*. 2015; 39(1): 67-76.
11. Benedetto U, Ng C, Frati G, Biondi-Zoccai G, Vitulli P, Zeinah M, et al. Miniaturized extracorporeal circulation versus off-pump coronary artery bypass grafting: a meta-analysis of randomized controlled trials. *Int J Surg*. 2015; 14: 96-104.
12. Pecha S, Schäfer T, Subbotina I, Ahmadzade T, Reichen-spurner H, Wagner FM. Rhythm outcome predictors after concomitant surgical ablation for atrial fibrillation: a 9-year, single-center experience. *J Thorac Cardiovasc Surg*. 2014; 148(2): 428-33.
13. Sezai A, Nakata K, Iida M, Yoshitake I, Wakui S, Osaka S, et al. A Study on the occurrence and prevention of perioperative stroke after coronary artery bypass grafting. *Ann Thorac Cardiovasc Surg*. 2015; 21(3): 275-81.
14. Bouchot O, Guenancia C, Kahli A, Pujos C, Malapert G, Vergely C et al. Low circulating levels of growth differentiation factor-15 before coronary artery bypass surgery may predict postoperative atrial fibrillation. *J Cardiothorac Vasc Anesth*. 2015; 29(5): 1131-9.
15. El-Chami MF, Binongo JN, Levy M, Merchant FM, Halkos M, Thourani V et al. Effect of surgical atrial fibrillation ablation at the time of cardiac surgery on risk of postoperative pacemaker implantation. *Am J Cardiol*. 2015; 116(1): 88-91.
16. Li T, Sun ZL, Xie QY. Meta-analysis identifies serum C-reactive protein as an indicator of atrial fibrillation risk after coronary artery bypass graft. *Am J Ther*. 2016; 23(6): e1586-e1596. doi: 10.1097/MJT.0000000000000255.
17. Violi F, Pastori D, Pignatelli P, Loffredo L. Antioxidants for prevention of atrial fibrillation: a potentially useful future therapeutic approach? A review of the literature and meta-analysis. *Europace*. 2014; 16(8): 1107-16.
18. Stanger O, Aigner I, Schimetta W, Wonisch W. Antioxidant Supplementation Attenuates Oxidative Stress in Patients Undergoing Coronary Artery Bypass Graft Surgery. *Tohoku J. Exp. Med*. 2014; 232(2): 145-54.
19. Ndrepepa G, Xhepa E, Collieran R, Braun S, Cassese S, Fusaro M et al. Gamma-glutamyl transferase and atrial fibrillation in patients with coronary artery disease. *Clin Chim Acta*. 2017; 465: 17-21.

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