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Predictive role of preoperative hemoglobin A1c levels on atrial fibrillation developing after coronary artery bypass graft surgery

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Research Article

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ABSTRACT

Objective: Atrial fibrillation (AF) is the most common cardiac arrhythmia seen after coronary artery bypass(CABG) surgery. Hemoglobin A1c (HbA1c) levels known to have correlation with the developement of post operative atrial fibrillation (POAF) after CABG surgery. In our study we investigated the predictability of preoperative HbA1c levels for postoperative POAF developement in patients who underwent isolated on-pump CABG operation in our clinic.

Method: We retrospectiveley studied 85 isolated on-pump CABG patients. Male to female ratio was 3:1 and mean age was 63-year old. All patients monitored in intensive care unit and than service for the occurance of AF. Relationship between HbA1c levels and developement of AF after surgery was evaluated.

Results: This study designed as cross-sectional array and performed in our clinic. 85 patients included in the study. Mean age of cohort was 63.5 years and ratio of the male to female found 3:1. During postoperative monitoring period, 22 patients (25.8%) developed POAF (p>0.05) . HbA1c levels found significiantly high in POAF-positive group (p=0.003).

Conclusions: According to our data, preoperative HbA1c levels could be used as a predictor of post operative AF in patients undergoing CABG surgery.

Keywords: Hemoglobin A1c, Coronary artery bypass graft operation, post operative atrial fibrillation

Koroner bypass cerrahisi sonrası gelişen atrial fibrilasyonda preoperatif hemoglobin a1c seviyelerinin belirleyici rolü

ÖZ

Amaç: Atrial fibrilasyon koroner bypass cerrahisi sonrası en sık görülen kardiyak aritmidir.Hemoglobin A1c seviyelerinin koroner bypass cerrahisi sonrasında atrial fibrilasyon gelişmesiyle ilişkili olduğu bilinmektedir.Biz kliniğimizde izole koroner bypass cerrahisi geçiren hastalarda post operative atrial fibrilasyon gelişmesi riskinde preoperative Hemoglobin A1c seviyelerinin öngörücü rolünü araştırmayı planladık

Yöntem: 85 izole koroner bypass operasyonu geçiren hasta retrospektif olarak incelendi.Ortalama yaş 63, erkek-kadın oranı 3:1 olarak hesaplandı.Preoperative Hemoglobin A1c seviyeleri ve operasyon sonrası atrial fibrilasyon gelişimi çalışıldı.

Bulgular: Çalışma kesitsel olarak dizayn edildi. Bu dizayn temelinde 85 izole koroner bypass hastası çalışmaya dahil edildi.Ortalama yaş 63.5, erkek-kadın oranı 3:1 olarak tespit edildi.Post operatif periodda 22 hastada (%25.8) atrial fibrilasyon (p>0.05) gelişti. Post operatif atrial fibrilasyon gelişen grupta Hemoglobin A1c seviyeleri belirgin yüksek bulundu (p=0.003).

Sonuç: Bulgularımız ışığında, preoperatif Hemoglobin A1c seviyelerinin postoperatif atrial fibrilasyon gelişiminin tahmininde kullanılabileceği kanaatindeyiz

Süreç

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Anahtar sözcükler: Hemoglobin A1c, Koroner bypass cerrahisi, postoperatif atrial fibrilasyon

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Introduction

Postoperative atrial fibrillation (POAF) after CABG surgery is a frequent serious problem and is associated with an increase in the length of hospital stay, morbidity and mortality [1]. The rate of POAF has been reported to a range from 10% to 45% in various studies [2-6]. As AF results in increased adverse outcomes after cardiac surgery [7], recognition of its risk factors and predictors have been known for POAF including older age, obesity, heart rate variability, hyperglycemia, hypertension (HT), left atrial size and function, lack of statin use and preoperative AF [3,8-15].

Although various interventions have been used for the prevention of POAF and other complications after CABG [16], the role of predisposing factors and their modification for preventing the occurance of POAF is noticable. It has been shown that diabetes mellitus (DM) can trigger AF, which signifies the importance of glycemic control for the prevention of AF [8]. Also some studies have reported that elevated HbA1c levels preceding surgery are linked to the severity of adverse outcomes after CABG like AF [17,18]. However, the association between preoperative HbA1c levels and development of POAF and its predictability for POAF have not been fully understood and proven yet.

In our study, we aimed to determine the predictability of POAF after CABG surgery by using the levels of preoperative HbA1c levels in patients who underwent isolated on-pump CABG patients in our center.

Material and Methods

Patients

We retrospectively studied 85 consecutive patients, mean age 63, who underwent isolated on-pump CABG in our clinic between September 2018 and May 2019. Informed consent was obtained from all patients. Ethic commitee permission was taken from Suleyman Demirel University Ethical Commitee with 72867572-050*.01.04-105*974 number and *04.06.2020* date. Study was designed according to World Medical Association Declaration of Helsinki.

Exclusion criteria were; [1] isolated valve surgery, CABG concomitant valve surgery, aortic surgery; [2] redo surgery; [3] emergent surgery; [4] history of AF or preoperative AF; [5] history of any chronic disease or malignancy; [6] chronic hepatic disease; [7] hypertyroidism.

Diabetic and non-diabetic patients included in the study. Patients divided into two groups as; POAF -Negative and POAF- Positive. Preoperative HbA1c levels studied for the predictability on AF after isolated on-pump CABG surgery.

Detailed medical history, physical examination and routine blood tests, echocardiogram, electrocardiogram, carotid doppler ultrasonography (CDU), chest radiograms and respiratory function tests, body-mass index (BMI), European System for Cardiac Operative Risk Evaluation (EuroSCORE) were performed for all patients that were planned to have an isolated CABG surgery. Patients who continue smoking till the day of coronary angiography determined as smoker. Endocrinology clinic consultation was requested for patients who had a previous diagnosis of DM and patients who did not have a diagnosis of DM but had fasting blood glucose was >126 mg/dl. Patients who had previously received antihypertensive treatment and those who had >130/85 mm/Hg blood pressure during clinical follow-up were considered as hypertensive. Patients on routine hemodialysis program were evaluated as chronic kidney failure (CKF). All patients that had a history of Chronic Pulmonary Obstructive Disease (COPD) were evaluated by a chest physician with pulmonary function tests or by arterial blood gas examination (ABG) and physical examination those who could not perform pulmonary function tests. Patients who had a history of myocardial infarction (MI) in last 3 months evaluated as recent MI. For determining the ejection fraction (EF) and evaluating the cardiac valves, echocardiography performed for each patient (Applio 500, Toshiba; Japan) by the same cardiologist preoperatively.

Biochemical and Hematological Parameters

After 12 hours of overnight fasting, a venous blood samples for biochemical and hematologic parameter measurement were drawn from the antecubital vein at the first day after hospital admission. Biochemical analysis included the serum levels of HbA1c (Varyant 2-Turbo, Bio-Rad; Japan), urea, creatinine (Advia 2400, Siemens; Germany), C-reactive protein (CRP) (BN 2,Siemens; Germany) and complete blood count included hemoglobin, white blood cell, neutrophile, monocyte, lymphocyte, platelet counts (Advia 2120, Siemens; Ireland) evaluated.

Operative Technique

Median sternotomy was applied under general anesthesia in all patients. Cardiopulmonary bypass was performed by using aortocaval cannulation technique in all patients following systemic heparin administration (300 IU/kg). Cardiac arrest was achieved by using hypothermic, hyperkalemic blood cardioplegia and topical hypothermia. Surgery was performed under moderate systemic hypothermia (32° C). Cardiopulmonary bypass flow was maintained at 2.2–2.5 L/min/m^2, mean perfusion pressure was maintained between 50 and 80 mm Hg, and hematocrit level was maintained at 20–25% during cardiopulmonary bypass. Cardiac arrest maintained by using intermittent antegrade cold blood cardioplegia infusions. In patients that had low ejection EF, multivessel disease (MVD) and poor ventricular function, continuous retrograde cold blood cardioplegia infusion was given in addition to antegrade intermittent cold blood cardioplegia. Left internal mammary artery (LIMA) was used in all patients for revascularization of left anterior decending artery. Saphenous vein graft was used for grafting of other coronary arteries. Warm blood cardioplegia was given in all patients just before removing the cross-clamp. All proximal anastomosis were performed by using side clamp. All early postoperative

patient follow ups were done in third degree cardiovascular surgery intensive care unit.

POAF

All patients were monitored in cardiovascular intensive care unit after surgery with a 5-lead monitoring system (Philips IntelliVue MX800; Philips, Boeblingen, Germany) using the standard lead II configuration. After discharge from intensive care unit, patients were taken to service follow up. Following surgery, subsequent 12-lead electrocardiograms were obtained daily from each patient until discharge postoperatively, and also if a patient manifested with symptoms of palpitations or an irregular pulse, a 12-lead electrocardiography (Mindray Bene Heart R12 -Shenzhen Mindray Bio-Medical Electronics Co. Ltd., Shenzhen, China) was performed to diagnose the possible arrhythmia. New-onset POAF was described as AF (according to the established Society of Thoracic Surgeons definition) occurring during hospitalization after CABG in a patient with no history of AF.

Statistical Analysis

The statistical analyses of the study were performed by SPSS 20.0 (IBM Inc, Chicago, IL, USA). The descriptive statistics were presented as frequency (percentage) for categorical variables and mean±SD (median, min, max where necessary) for numerical variables. The normality of the continuous variables was checked by Kolmogorov-Smirnov test. However, none of the variables were distributed normally. Therefore, the comparison between two independent groups was performed by Mann-Whitney U test, and Monte Carlo Exact Chi-square test was used to determine the relations between the categorical variables. ROC analysis was performed to determine the diagnostic values of HbA1C for post-op AF occurrence. Univariate logistic regression analysis was established for prognostic factors of biochemical measurements on patients with post-op AF. For correlations between HbA1c and other measurements, the Spearman's Rho correlation analysis was performed. In all analyses, $p<0.05$ value was considered as statistically significant result for 5% Type-I error.

The power analysis was performed by GPower 9.1.2 (Universitaet Kiel, Germany). The analysis was based on one-tailed t-test, and the effect size was calculated as 0.79 using a priori HbA1c values for AF negative and positive groups. The requirements of the analysis were considered as 5% error rate, 0.90 (actual power 0.908) power and 3 allocation ratio (N1:N2) since the number of negative post-op AF was higher in the hospital. Therefore, the minimum sample size was calculated as 19 for positive AF and 55 for negative AF patients.

Results

This study designed as cross-sectional array and performed in our clinic. Eighty five patients included in the study. Mean age of cohort was 63.5 and ratio of the male to female found 3:1. During postoperative monitoring period, 22 patients (25.8%) developed POAF (*p>0.05)*. HbA1c levels found significantly high in POAF-positive group (*p=0.003*). HbA1c levels in POAF- negative and positive group found to be 7.00±1.16 mg/dL and 8.41±2.21 mg/dL, respectively (Figure 1). Mean body mass index (BMI) of the patients found 28.99±4.37 kg/m^2 and no statistical significance was evaluated among patients for BMI (*p=0.443*). There was no difference found between comorbidities but DM found to be high in POAF-positive group (*p=0.095*). Smoking ratios were similar in two groups. By-passed vessel count median value was equal (3 vessels), cross clamp times were nearly equal and total cardiopulmonary bypass time was avarage 115 minute (*p=0.752*) (Table 1). Glomerular filtration rate (GFR) found significiantly low in POAF-positive group (*p=0.029*) (76.86±17.15 *ml/min/1.73m^2)*. Euroscore was found significantly high in POAF-positive group (1.87±1.50) than POAF-negative group (1.38±0.93) (*p=0.048*). Neutrophil/Lymphocyte ratio (*p=0121*) and Platelet/Lymphocyte ratio (*p=0.557*) found high in POAF-positive group but found statistically not significant. Platelet/Neutrophile ratio found higher in POAF-negative group but is also statistically not significiant (*p=0.273*). No inflammation was found among two groups (p_{CRP}=0.907*).* Detailed results shown in Table 2.

ROC analysis was performed for evaluating the predictive value of HbA1c levels on developing POAF (Figure 2). Area under the curve found significant (*AUC=0.714; p=0.003).* Cut-off value for HbA1c was found 6.65%. As a result of cross comparison according to this value, the differential diagnosis rates were found to be acceptable, although the specifity was little low. The accuracy of the test was determined as 56.98% (Table 3). In the post- operative period, binary logistic regression model was created to determine prognostic factors and effects in patients with AF. Only two features were identified that made a significant contribution to the model; increased HbA1c levels were associated with increased AF development in post post-operative period (*OR=1.923 (1.264-2.924); p=0.002*) and platelets determined to decrease AF development in post-operative period in low predictive value (OR=-1.026 (1.000-1.052); *p=0.047*).

Table 1. Demographical characteristics of patients with AF at post-operative period

Variables	Categories	Post-op AF[a] Negative	Post-op AF[a] Positive	
		N (%)		*p*
Gender	*Male*	46 (73.0)	19 (86.4)	*0.207*
	Female	17 (27.0)	3 (13.6)	
Diabetes Mellitus	*None*	27 (42.9)	5 (22.7)	*0.095*
	Yes	36 (57.1)	17 (77.3)	
Hypertension	*None*	36 (57.1)	9 (40.9)	*0.192*
	Yes	27 (42.9)	13 (59.1)	
COPD[b]	*None*	35 (55.6)	11 (50.0)	*0.654*
	Yes	28 (44.4)	11 (50.0)	
Smoking	*None*	50 (79.4)	18 (81.8)	*0.806*
	Yes	13 (20.6)	4 (18.2)	
Variables	**Units**	**Post-op AF[a] negative (n=63)**	**Post-op AF[a] Positive (n=22)**	
		Mean±SD (Median, Min, Max)		*p*
Age	*year*	62.56±9.70	66.36±9.26	*0.143*
BMI[c]	*kg/m²*	28.81±4.55	29.60±4.95	*0.443*
Number of Bypassed vessels		3.16±0.83 (3.0, 1.0, 5.0)	3.09±0.75 (3.0, 2.0, 5.0)	*0.603*
Cardiopulmonary Bypass Time	*minute*	116.05±34.39	113.18±27.36	*0.752*

(a-Atrial Fibrillation, b-Chronic Obstructive Pulmonary Disease, c-Body-Mass Index)

Table 2. Clinical features of patients with AF at post-operative period

Variables	*Units*	Post-op AF[a] negative (n=63)	Post-op AF[a] Positive (n=22)	
		Mean±SD (Median, Min, Max)		*p*
HbA1C	*mg/dL*	7.00±1.16	8.41±2.21	***0.003****
EF[b]	*%*	55.37±8.31	51.09±9.81	*0.082*
GFR[c]	*ml/min/1.73m²*	86.28±14.69	76.86±17.15	***0.029****
Euro Score		1.38±0.93	1.87±1.50	***0.048****
X-Clamp	*minute*	68.70±22.52	67.09±21.41	*0.718*
Hemoglobin	*g/dL*	13.19±1.60	13.58±1.64	*0.200*
WBC	*10^3/ µL*	7.73±2.25	7.89±2.17	*0.511*
Neutrophil	*10^3/ µL*	4.73±1.79	5.08±1.72	*0.356*
Lymphocyte	*µL*	2.13±0.90	1.90±0.63	*0.272*
Monocytes	*10^3/ µL*	0.48±0.15	0.51±0.24	*0.671*
Platelet	*10^3/ µL*	242.43±59.80	228.14±58.46	*0.257*
NLR[d]	---	2.46±1.31	2.75±1.11	*0.121*
PLR[e]	---	122.40±41.91	132.17±45.88	*0.557*
PNR[f]	---	56.20±22.25	52.09±21.02	*0.273*
CRP	*mg/L*	1.10±1.25	1.19±1.23	*0.907*

(a- Atrial fibrillation, b-Ejection Fraction, c-Glomerular Filtration Rate, d- Neutrophil-Lymphocyte Ratio e-Platelet-Lymphocyte ratio, f-Platelet-Neutrophile ratio9

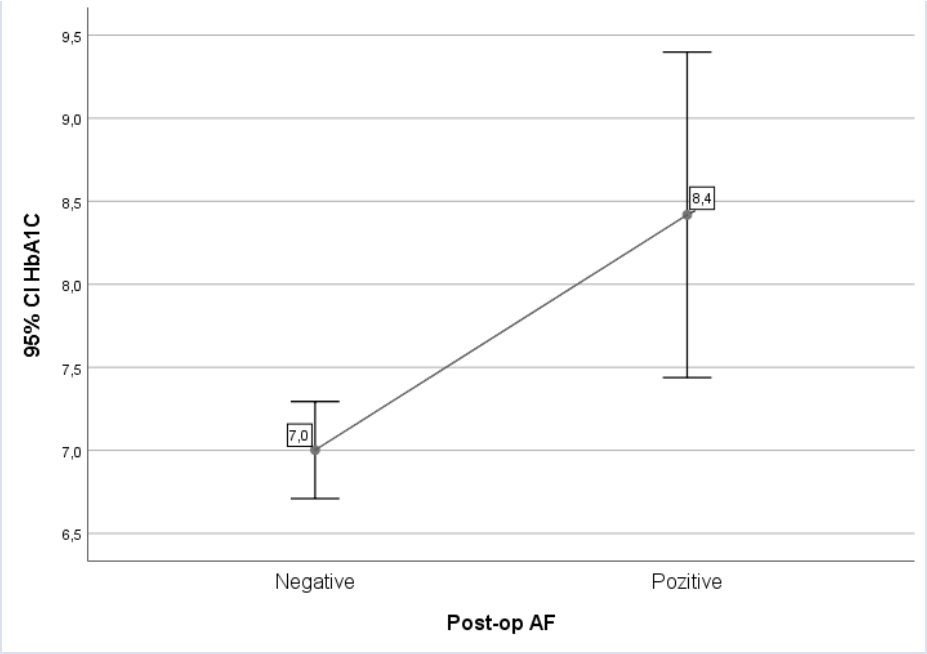

Figure 1 . HbA1c values in POAF-positive and POAF-negative patient groups *(p=0.003)*

Table 3. ROC analysis results and the diagnostic values for HbA1C of patients with AF at post-op period

AUC=0.714 (p=0.003)	**Cut-off**=6.65 *mg/dL*	0.594 – 0.835
Diagnostic Rates	**Value**	**95% CI**
Sensitivity	86.96%	66.41% - 97.22%
Specificity	46.03%	33.39% - 59.06%
Positive Likelihood Ratio	1.61	1.22 - 2.13
Negative Likelihood Ratio	0.28	0.10 - 0.84
Prevalence	26.74%	17.77% - 37.38%
Positive Predictive Value	37.04%	30.83% - 43.71%
Negative Predictive Value	90.62%	76.50% - 96.63%
Accuracy	56.98%	45.85% - 67.61%

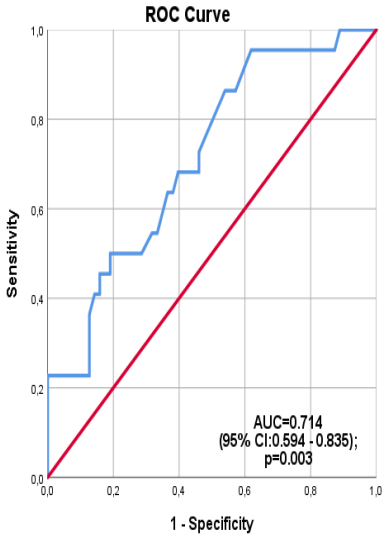

Figure 2 . ROC Curve for POAF-positive patient group

Correlation values between HbA1c and other determined values of patients were evaluated. While there was no significiant relationship between HbA1c and other demographic features and biochemical values in POAF-negative group, there was a low-level correlation found between HbA1c and EF in POAF-positive group (*R=-0.406; p=0.041*). Also a positive and moderately significant correlation was obtained with Euroscore values (*R=0.459; p=0.032*).

Discussion

AF is the most common arrythmia seen after CABG surgery. The rate of POAF has been reported to a range from 10% to 45% in various studies [2-6]. In our study, 22 patients (25.8%) developed POAF. The exact factors that cause this disorder are largely unknown. Estimated risk factors that could play a role on developing POAF including older age, hyperglisemia, obesity, heart rate variabilty, hypertension, left atrial function, lack of statin usage and preoperative AF [3,8-15]. Some studies have also reported that elevated HbA1c levels preceding surgery are linked to the severity of adverse outcomes after CABG like mortality or morbidity including wound infections,

sternal dehissence or POAF [17,18]. For this reason, HbA1c can be used both as a clinical marker of mean glycemia in patients with DM [19] and for determining individuals' risks for cardiovascular events such as POAF, regardless of the presence or absence of DM [20]. In our study, HbA1c levels studied for POAF in both diabetic and non-diabetic patients undergoing isolated CABG operation and isolated HbA1c levels found significantly high in POAF-positive group (*p=0.003*). HbA1c levels in POAF- negative and positive group found to be 7.00±1.16 mg/dL and 8.41±2.21 mg/dL respectively (Figure 1). Our results are consistent with the studies in the literature about the association between HbA1c levels and AF prevelance [21].

But the mechanism by which HbA1c may lead to the etiology of AF has remained largely unknown [22]. In recent years, serum levels of HbA1c have been studied for the correlation with the pathogenesis of AF [23]. Increased levels of HbA1c may lead to high oxygen affinity of hemoglobin and decreased synthesis of diphosphoglycerate, both of which contribute to the difficulty in oxygen dissociation, thereby resulting in aggrevated myocardial ischemia and hypoxia [24] and this may result in AF. On the other hand, it was hypothesized that long-term high levels of blood glucose could induce the activation of glycation end products (AGE) including HbA1c may play a crucial role in atrial remodeling via the induction of reactive oxygen species [25]. Inflammation and oxidative stress could have been associated with AF development [26] for this reason it may play a role in the pathogenesis of AF [27]. But we found no inflammation among two groups according to biochemical parameters in our study (p_{CRP}=0.907*)* (Table 2).

The most limiting factor of our study was the amount of the cases that included in the study. Since our cardiac surgery department is a new onset center, we were only able to examine a limited number of patients. Because of this major limitation, we think that further studies with more patients must be performed for the proof of our theory about predictability of preoperative HbA1c levels on development of POAF in patients underwent CABG. And also we will continue to collect data from our new patients and think to continue this study and re-evaluate our theory with more patients.

Conclusion

According to our data and statistical analysis, we observed that preoperative elevated HbA1c levels in both diabetic or non-diabetic patients could predict the risk of POAF and we think that HbA1c levels must added to routine preoperative blood tests of CABG patients not only for evaluating the long term blood glucose levels, but also for predicting the POAF risk. By this knowledge, precautions can be taken for preventing POAF and by this precautions morbidity and mortality rates related to this frequent arrythmia could be decreased.

Conflict of interest

There is not a conflict of interest

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