The plasma galectin-3 level has high specificity and sensitivity for predicting postoperative atrial fibrillation after coronary artery bypass surgery

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Abstract. – OBJECTIVE: Postoperative new-onset atrial fibrillation (POAF) commonly occurs after coronary artery bypass graft (CABG) surgery. This study aimed to determine the utility of the preoperative netrin-1 and galectin-3 levels for predicting POAF following CABG surgery, as well as that of postoperative serial measurement for assessing these markers' patterns of expression.

PATIENTS AND METHODS: This prospective cohort study included 50 patients that underwent CABG surgery. The plasma netrin-1 and galectin-3 levels were measured via enzyme-linked immunosorbent assay (ELISA) before surgery (baseline) and at 6, 12, and 24 h after surgery. The patients were divided into two groups according to the occurrence of POAF; the POAF (+) group and the POAF (–) group.

RESULTS: In total, 26 patients developed POAF, whereas 24 remained in sinus rhythm. Baseline galectin-3 levels were higher in the POAF (+) group than in the POAF (–) group (30.7 ± 10.1 pg mL-1 and 15.7 ± 3.6 pg mL–1, respectively). The post-CABG surgery galectin-3 level increased in both the POAF (+) and POAF (–) groups at 6 h (46.2 ± 26.3 pg mL-1 and 24.9 ± 5.9 pg mL-1, respectively), 12 h (45.2 ± 24.1 pg mL-1 and 26.6 ± 9.3 pg mL-1, respectively), and 24 h (54.2 ± 33.5 pg mL-1and 28.6 ± 7.7 pg mL-1, respectively). The plasma netrin-1 level did not differ between groups at baseline or at 6, 12, and 24 h post CABG surgery.

CONCLUSIONS: Whereas netrin-1 does not appear to have any utility as a marker for the development of POAF in CABG surgery patients, the plasma galectin-3 level has high specificity and sensitivity for predicting POAF following CABG surgery and could be considered a marker for predicting POAF.

Key Words:
  Postoperative atrial fibrillation, Coronary artery bypass graft, Galectin-3, Netrin-1.

Introduction

Postoperative atrial fibrillation (POAF) is defined as new-onset atrial fibrillation that occurs during the immediate postoperative period[1]. POAF is the most common type of secondary atrial fibrillation (AF), with an incidence of 25%-40%. It occurs most frequently within 5 d after coronary artery bypass graft (CABG) surgery, with a peak incidence 2-3 d after the procedure. Although POAF is commonly regarded as benign, transient, and self-limited, it is associated with an increased risk of morbidity and mortality[2]. In addition, POAF following heart surgery is independently associated with approximately 5 d of excess hospitalization and increased hospitalization costs[3].

The pathophysiology of POAF is not fully understood; however, the mechanisms are thought to be multifactorial, and include such predisposing, and perioperative factors and triggers as preexisting atrial fibrotic remodeling, inflammation of atrial tissue, advanced age, increased sympathetic activity, oxidative stress, volume and pressure overload, and fibrosis[4-6]. Numerous biomarkers of inflammation have been studied as predictors of POAF post cardiac surgery[7-10]. POAF corresponds with changes in inflammatory markers and elevated preoperative plasma levels of cytokines, but such biomarkers' ability to predict POAF risk with high accuracy is limited[11].

Netrins are a family of laminin-like proteins, which were initially identified as axonal guidance marks during embryogenesis[12]. The role of netrin-1 in cardiovascular disease and inflammation is an emerging topic of research[13,14]. Netrin-1 has been identified as a modulator of atherosclerosis, but its

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specific role in atherosclerosis is controversial (deleterious or protective)[13,15,16]. Recently, a high serum netrin-1 level was associated with poor prognosis in elderly females and proposed as a prognostic indicator of acute coronary syndrome[14].

Galectin-3 is a fibrosis biomarker that is highly expressed in fibrotic tissues and is associated with such fibrosis-related diseases as heart failure and AF[17-19]. Atrial fibrosis is a hallmark of atrial structural remodeling and plays an essential role in the persistence of AF[20,21]. Two recent studies[10,22] reported conflicting conclusions regarding the effectiveness of the serum galectin-3 level in predicting the risk of POAF in CABG surgery patients, and there are no data regarding the postoperative expression patterns of galectin-3. In addition, to the best of our knowledge, the literature does not include any studies on the netrin-1 level's association with the development of POAF in CABG surgery patients. As such, the present study aimed to determine the utility of the preoperative netrin-1 and galectin-3 levels for predicting POAF following CABG surgery, as well as that of postoperative serial measurement for assessing these markers' patterns of expression.

Patients and Methods

This prospective longitudinal cohort study included 80 consecutive patients that were referred to Selcuk University Hospital (tertiary center) for CABG surgery. Only patients with a negative history of AF that were scheduled for elective on-pump CABG procedures were included. In addition, patients that required mitral valve surgery were excluded because patients with mitral valve disease have a higher incidence of POAF related to dilated atria and interstitial fibrosis[23]. Other exclusion criteria included emergency surgery, a history of AF or other atrial arrhythmias, perioperative use of class 1 and 3 antiarrhythmic drugs, left ventricular ejection fraction (LVEF) >50%, advanced renal failure (GFR <30 mL×min^{-1}×1.73 m^{-2}), hypothyroidism/hyperthyroidism, and a history of heart surgery. The study was conducted in compliance with the STROBE-Statement[24], and the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Selcuk University Institutional Ethics Committee (2019/141) and written informed consent was obtained from each patient.

Continuous ECG monitoring was performed during CABG surgery and rhythm disturbances (when present) were recorded. Any episode of AF lasting >30 s was defined as POAF[25]. In addition, the duration of surgery and hospitalization were recorded. All patients underwent standard transthoracic echocardiography preoperatively and 5 h postoperatively. A trained echocardiographer performed all echocardiographic examinations. LVEF was measured using Simpson's method, and left atrial (LA) volume, right atrial (RA) volume, and systolic pulmonary artery pressure (sPAP) were calculated[26]. All echocardiographic images were examined and checked by a cardiologist for final approval.

Blood samples were obtained from all patients before surgery and at 6, 12, and 24 h following surgery. Peripheral blood samples (5 mL) were collected into EDTA tubes, rapidly sent to the laboratory, and centrifuged at 1500 x g, and then the plasma was stored at −80 C° until analysis. Analysis was performed at room temperature and measured *via* ELISA using the Galectin-3 test kit (ARCHITECT®, Abbott Diagnostics, IL, USA) for Galectin-3 and the Human Netrin-1 ELISA kit (Bioassay Technology Laboratory Co, Shanghai, China) for netrin-1.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.20.0 (IBM Corp., Armonk, NY, USA). Numerical variables are given as mean ± SD or median (interquartile range). Categorical variables are given as numbers and percentages. Data were tested for the normality of distribution *via* the Kolmogorov-Smirnov test. Student *t*-test was used for analyzing pairs of independent and normally distributed variables. The Mann-Whitney U test was used to analyze non-normally distributed and independent variances. All categorical variables were analyzed using the Chi-square test or Fisher's exact test, as appropriate. All *p*-values were 2-tailed, and values <0.05 were considered statistically significant.

Results

Patient baseline characteristics and clinical data are presented in Table I. POAF developed in 26 patients [POAF (+) group], while sinus rhythm persisted in 24 patients [POAF (−) group]. The mean age of the 50 study patients (34 male and 16 female) was 64.2 ± 9.7 years. Preoperatively 74% of the patients had hyperlipidemia, 72% had

Table I. Study population baseline characteristics and clinical data.

	All patients (n = 50)	POAF (+) (n = 26)	POAF (–) (n = 24)	p-value
Age, years	64.2 ± 9.7	64.2 ± 9.6	64.1 ± 9.9	0.97
BMI	29.5 ± 4.9	29.3 ± 4.6	29.7 ± 5.3	0.80
Female, n (%)	16 (32)	11 (42.3)	5 (32)	0.10
Hypertension, n (%)	36 (72)	19 (73.1)	17 (70.8)	0.86
DM, n (%)	13 (26)	8 (30.8)	5 (20.8)	0.42
Hyperlipidemia, n (%)	37 (74)	19 (73.1)	18 (75)	0.87
Smoking, n (%)	26 (52)	10 (38.5)	16 (66.7)	0.06
COPD, n (%)	4 (8)	3 (11.5)	1 (4.2)	0.33
PAD, n (%)	1 (2)	0	1 (3.8)	0.33
Preoperative creatinine, mg dL^{-1}	0.96 ± 0.26	0.96 ± 0.25	0.97 ± 0.35	0.95
Baseline LVEF	51.0 ± 7.7	49.6 ± 8.0	52.6 ± 7.2	0.16
Baseline LA area, cm^2	24.3 ± 3.9	25.3 ± 4.2	23.2 ± 3.3	0.06
Baseline RA area, cm^2	21.0 ± 4.4	22.1 ± 4.6	20.1 ± 4.1	0.12
Baseline sPAP, mmHg	31.9 ± 7.7	33.5 ± 7.8	30.5 ± 7.5	0.17
Aortic cross-clamp time, min	53.0 ± 17.4	50.2 ± 17.2	56.1 ± 17.6	0.24
Bypass time, min	102.0 ± 34.4	97.7 ± 31.8	106.8 ± 37.1	0.35

POAF: postoperative atrial fibrillation, BMI: body mass index; COPD: chronic obstructive pulmonary disease; GFR: glomerular filtration rate; DM: diabetes mellitus; LA: left atrium; LVEF: left ventricular ejection fraction; PAD: peripheral artery disease; RA: right atrium; sPAP: systolic pulmonary artery pressure.

hypertension, 52% were smokers, 26% had diabetes mellitus, 8% had chronic obstructive pulmonary disease, and 2% had peripheral artery disease. These perioperative risks did not differ significantly between the POAF (+) and POAF (–) groups. Baseline LVEF, LA and RA volumes, sPAP, and aortic cross-clamp and bypass times were similar in both groups. The plasma galectin-3 and netrin-1 levels are presented in Table II.

Galectin-3

Baseline galectin-3 levels were higher in the POAF (+) group than in the POAF (–) group. The galectin-3 level at 6, 12, and 24 h post-CABG surgery increased in both groups as compared to baseline; however, the increase was greater in the POAF (+). In the POAF (+) group, the galectin-3 level increased sharply 6 h after CABG surgery, remained consistent at 12 h, and again increased at 24 h. ROC curve analysis showed that galectin-3 level at baseline, and at 6 and 24 h post CABG surgery were highly specific and sensitive for the prediction of POAF (AUC: 0.967, 95% CI: 0.908-1.000, and p<0.0001, AUC: 0.858, 95% CI: 0.721-0.996, and p=0.002, and AUC: 0.839, 95% CI 0.687-0.991, and p=0.003, respectively) (Figure 1).

Netrin-1

Baseline plasma netrin-1 levels were higher in the POAF (+) group than in the POAF (–) group; however, the difference was insignificant. The plasma netrin-1 level at 6, 12, and 24 h post-CABG surgery increased similarly in both the POAF (+) and POAF (–) groups as compared to the baseline. In the POAF (+) group, the netrin-1 level increased sharply at 6 h post-CABG surgery, remained consistent at 12 h, and again increased at 24 h. In contrast, in the POAF (–) group, the netrin-1 level increased at 6 h and 12 h post-CABG surgery and then decreased at 24 h.

Discussion

The present study evaluated the serum galectin-3 and netrin-1 levels in CABG surgery patients. The findings show that patients that developed POAF after CABG surgery had a significantly higher preoperative galectin-3 level than patients with postoperative sinus rhythm. In addition, postoperative serial measurement of the galectin-3 level increased in both the POAF (+) and POAF (–) groups, although the increase was significantly higher in the POAF (+) group. The

Table II. Study population plasma galectin-3 and netrin-1 levels.

|	POAF (+) (n = 26)	POAF (−) (n = 24)	*p*-value
Galectin-3 levels			
Baseline	30.7 ± 10.1	15.7 ± 3.6	<0.001
6 h post CABG surgery	46.2 ± 26.3	24.9 ± 5.9	<0.001
12 h post CABG surgery	45.2 ± 24.1	26.6 ± 9.3	0.002
24 h post CABG surgery	54.2 ± 33.5	28.6 ± 7.7	<0.001
Netrin-1 levels			
Baseline	1381 ± 629	1130 ± 237	0.07
6 h post CABG surgery	1860 ± 1180	1397 ± 396	0.07
12 h post CABG surgery	1866 ± 1071	1799 ± 839	0.81
24 h post CABG surgery	2106 ± 1252	1642 ± 696	0.24

POAF: postoperative atrial fibrillation, CABG: coronary artery bypass graft.

preoperative netrin-1 level in the POAF (+) group was higher than in the POAF (−) group, but not significantly. Furthermore, post-CABG surgery serial measurement of the netrin-1 level showed that the pattern of increase was similar in both the POAF (+) and POAF (−) groups.

POAF is the most common arrhythmia following cardiac surgery. It is associated with poor short- and long-term outcomes, including an increased risk of stroke and mortality[27]. Preexisting atrial fibrotic remodeling, oxidative stress, active pulmonary vein sleeves, advanced age, inflammation, and pressure and volume overload are possi-

ble underlying mechanisms for the development of POAF post CABG surgery[4-6,28]. In the present study 52% of the patients developed POAF post CABG surgery, which is higher than the previously reported prevalence of 20%-40%[1]. This difference might be due to differences between the studies in the types of surgery, monitoring, and AF definitions. In the present study, there were not any differences in preoperative risk factors between the POAF (+) and POAF (−) groups.

Galectin-3 has garnered attention as a novel biomarker of cardiac fibrosis and myocardium remodeling[11]. An elevated galectin-3 level was
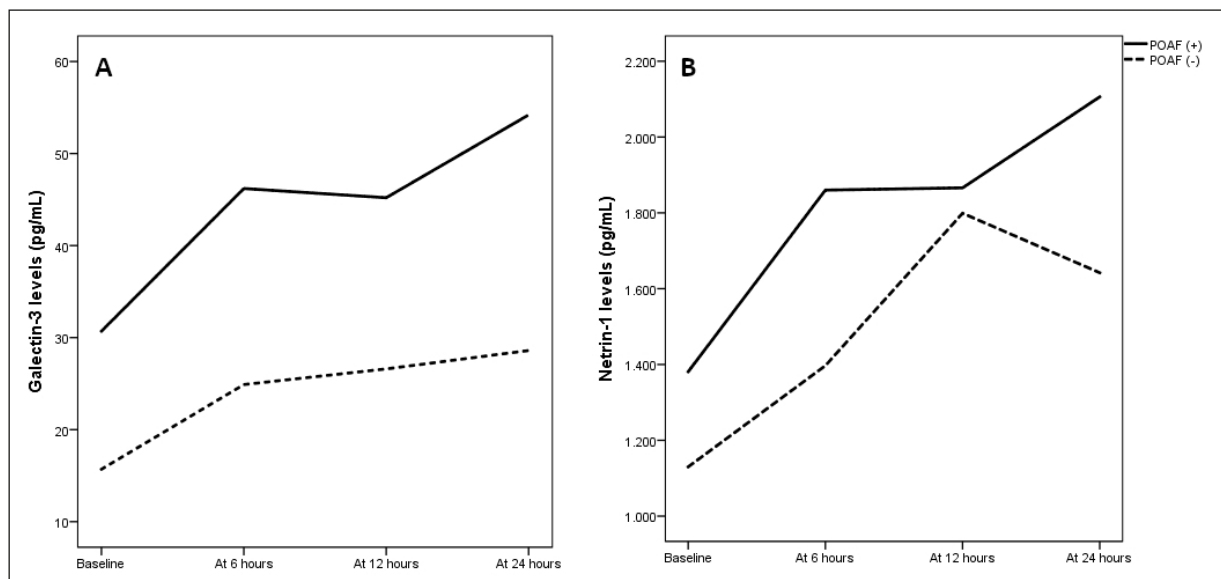
Figure 1. ROC curve analysis of the galectin-3 levels at baseline, 6, 12, and 24 h. (AUC 0.967, CI 0.908-1.000, *p*<0.0001; AUC 0.858, CI 0.721-0.996, *p*=0.002; AUC 0.689, CI 0.485-0.893, *p*=0.09; AUC 0.839, CI 0.687-0.991, *p*=0.003, respectively). AUC: Area under the curve; CI: confidence interval.

shown to predict the recurrence of AF following valve replacement surgery and AF ablation procedures[10,29]. In addition, two studies[10,22] reported conflicting results concerning the galectin-3 level and the occurrence of AF in CABG surgery patients. Bening et al[22], reported that the galectin-3 level did not differ between patients with and without POAF, which is in contrast to the present findings and might be partially due to the older population, different renal functions, and larger atrial chambers in their study. The present findings are consistent with those of Alexandre et al[10], which show that the galectin-3 level is higher in POAF (+) patients than in POAF (–) patients. Moreover, the present study also measured the galectin-3 level at 24 h post-CABG surgery and observed an increasing trend in both the POAF (+) and POAF (–) groups. Although these results indicate a correlation between an elevated preoperative galectin-3 level and POAF post-CABG surgery, we couldn't define a cutoff value for a high serum galectin-3 level in this patient cohort.

To the best of our knowledge, the present study is the first to evaluate the netrin-1 level's role in the development of POAF in patients undergoing CABG. Recently, the role of netrins in the cardiovascular system has become a popular research topic. In all, 4 netrins have been described in humans (netrin-1, -3, -4, and -5)[30]. To date, the only netrin that has been shown to be involved in the cardiovascular system is netrin-1. Recently, a high serum netrin-1 level was shown to have a significant association with a poor prognosis in female patients with acute coronary syndrome[14]. The present findings showed that there wasn't a significant difference in the baseline serum netrin-1 level or at 6, 12, and 24 h post-CABG surgery between the POAF (+) and POAF (–) groups, which indicates that the preoperative netrin-1 level cannot be considered a marker for predicting the development of POAF in patients undergoing CABG surgery.

Limitations

The present study has several limitations, including a small population, which may negatively affect the power of the present analysis. In addition, the extent of atrial fibrosis and activity of pulmonary veins in each patient was not known before surgery. Although complete medical histories and preoperative ECG data were collected, prior paroxysmal episodes of AF in these patients cannot be completely excluded. Moreover, the exclusion criteria were broad so as to minimize confounding factors. Lastly, the study did not include a healthy control group; therefore, it was not determined if there were any differences in the serum netrin-1 and galectin-3 levels between patients undergoing CABG and healthy individuals.

Conclusions

Based on the pre-and postoperative measurement of the galectin-3 and netrin-1 levels in patients undergoing CABG, an elevated galectin-3 level might be predictive of POAF; however, netrin-1 is not linked to POAF. Nonetheless, additional data from larger-scale clinical trials are required to determine the cutoff value for the serum galectin-3 level to be used as a biomarker for predicting POAF in patients undergoing CABG.

Conflict of Interest

The authors declare there are no conflicts of interest – financial or otherwise – related to the material presented herein.

Ethical Approval

Ethical approval was obtained from the Institutional Review Board of Selcuk University Faculty of Medicine (2019/141).

Informed Consent

Written informed consent was obtained from each patient before surgery.

Authors' Contribution

Conception and design: K. Erdem, E. Kurtoglu, T. F. Ilgenli and M. Oc; Acquisition of data: K. Erdem, T. F. Ilgenli, B. Oc and M. Oc; Analysis and interpretation of data: E. Kurtoglu and K. Erdem; Drafting the article: K. Erdem, M. Oc, B. Oc and E. Kurtoglu; Validation and final approval: All authors.

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