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Serum uric acid level predicts new-onset atrial fibrillation after coronary artery bypass graft operation

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Abstract. – OBJECTIVE: To investigate the association between serum uric acid levels and the risk of incident atrial fibrillation in patients after coronary artery bypass graft (cABG) operation.

PATIENTS AND METHODS: A total of 174 patients undergoing nonemergency coronary artery bypass graft operation were included in the study. Patients with previous atrial arrhythmia or requiring concomitant valve surgery were excluded. We prospectively analyzed 174 patients (mean age: 59.8 years; 109 male and 65 female). The serum uric acid level was determined preoperatively.

RESULTS: After a coronary artery bypass graft operation operation, 35 (20%) patients developed atrial fibrillation. Preoperative uric acid levels were significantly higher in patients who developed atrial fibrillation than in those who did not (7.8 ± 1.1 vs 5 ± 0.9). Using a cutpoint of 6.55, the preoperative level correlated with the appearance of atrial fibrillation with a sensitivity of 91.4% and specificity of 84.2%.

CONCLUSIONS: Serum uric acid level can increase the sensitivity and specificity in predicting atrial fibrillation in patients after CABG operation.

Key Words:
Atrial fibrillation, Coronary artery bypass grafting, Uric acid.

Introduction

Atrial fibrillation (AF) is frequently seen in patients undergoing cardiac surgery: prevalence rates of 16-40% after coronary artery bypass graft operation (CABG)[1,2]. Development of postoperative AF leads to increased morbidity and prolonged intensive care unit (ICU) and hospital stays; it is associated with a need for prolonged inotropic support, higher ICU readmission rate, congestive heart failure, reintubation and shock[1]. Atrial fibrillation after cardiac surgery could predict in-hospital, as well as mid-term and long-term survival[3].

Serum uric acid (UA) is the endproduct of purine degradation in humans; it is produced via the action of xanthine oxidase, an enzyme that is implicated in oxidative processes[4].

Current evidence suggests that UA could be a marker of oxidative damage, a factor reported as a part of the mechanisms of AF[5].

However, the relationship between the UA level and postoperative AF has not been investigated. Thus, we aimed to investigate the relationship between the UA and postoperative AF in patients undergoing CABG surgery.

Patients and Methods

This prospective study was carried out from January 2013 to August 2013. The ethical implications regarding the study were approved by the local Ethics Committee and informed consent was obtained from each patient. All procedures were carried out in accordance with the Declaration of Helsinki.

The study population consisted of 174 patients undergoing their first CABG surgery.

Exclusion criteria were renal failure, chronic obstructive pulmonary disease (COPD), inflammatory and metabolic disorders including thyroid disorders, concomitant valve surgery, previous AF or flutter, 2nd or 3rd degree atrioventricular block and emergency operation.

In the postoperative period, heart rate and rhythm were continuously monitored for the first 48-72 hours and daily 12-lead electrocardiograms were performed from the first postopera-

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tive day until discharge. The study end point was any episode of documented (on 12-lead ECG) postoperative in-hospital AF, defined as an irregular rhythm with no identifiable P waves. Data including gender, age, hypertension, diabetes mellitus, smoking habitus, body mass index (BMI), history of stent implantation, preoperative left ventricular ejection fraction (EF), left atrial dimension with transthoracic echocardiographic assessment and patients' preoperative medication including beta receptor blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, aldosterone receptor antagonists, angiotensin receptor blockers, statins, and nonsteroidal anti-inflammatory drugs were recorded. The BMI was calculated as weight in kilograms divided by height in meters squared.

Patients' EuroSCORE (European System for Cardiac Operative Risk Evaluation) values were calculated[6].

We also recorded the distally bypass count including right coronary artery bypass, cardio-pulmonary bypass (CPB), cross clamp time, total bleeding (defined as the 24-hour postoperative chest tube output), number of transfusions of packed red cells perioperatively, and inotropic agent requirement postoperatively.

Blood Sampling

The blood samples were determined immediately before surgery. Fasting blood samples were drawn from a large antecubital vein of each patient for determination of biochemical and hemostatic parameters before operation. The tubes with EDTA were used for automatic blood count. The blood counts were measured on a Sysmex XT-1800i Hematology Analyzer (Sysmex Corporation, Kobe, Japan).

Surgical Procedure

All operations were performed on cardiopulmonary bypass with the use of an intermittant global ischemia with the allowable systemic temperature between 32-34°C. Anesthetic medication and surgical techniques were applied using the same procedures.

Statistical Analysis

Statistical analyses were assessed with SPSS statistical package for Windows 15.0 (SPSS Inc, Chicago, IL, USA). Descriptive statistics are given as median, minimum, maximum, frequency, and percentage values. All continuous variables were compared by the Mann-Whitney U test. Categorical data were compared by the Pearson Chi-squared test. Odds Ratios were given to determine the risk of AF occuring. Receiver-operating characteristic (ROC) curves were obtained for SUA (serum uric acid) to explore the sensitivity and specificity. ROC curve analysis was used to determine the optimum cutoff levels of serum UA level to predict the occurrence of AF. In addition, multivariate logistic regression models were created to identify independent predictors of postoperative AF. All tests were two-sided at a significance level of $p < 0.05$.

Results

After CABG surgery, 35 (20%) patients developed AF and 139 (80%) patients did not. Comparison of the basal characteristics as well as preoperative echocardiographic and laboratory parameters among patients with or without postoperative AF was examined in Table I. Univariate analysis for differences between patients with and without AF is shown in Table II.

Accordingly, female patients with AF (62.9%) was more than male patients (30.9%; $p < 0.001$) with the risk of AF 3.78 times greater in females than males.

In patients with AF, the prevalence of hypertension (71.4%) was higher than those without (51.1%; $p = 0.03$). Risk of AF in patients with hypertension is 2.39 times higher than in patients without hypertension. The risk of AF in patients not using beta blockers (BBs) is 4.1 (1/0, 244) times higher than patients taking BBs, and 2.89 (1/0, 346) times higher in patients not taking statins. The median age of patients who developed AF (median: 67) were higher the patients without AF (median: 58; $p < 0.001$). The preoperative UA and RDW (Red cell Distribution Width) values were significantly higher in patients with AF and the value of EF was lower (p p <0.001). Creatinine ($p = 0.004$), EuroSCORE ($p < 0.001$), and total bleeding values ($p = 0.028$) were significantly higher in patients who developed AF (Table II).

Analyses of independent risk factors for development of atrial fibrillation are shown in Table III. Beta receptor-blocker use, EF, and UA were found to be predictive factors for AF development ($p < 0.05$).

Receiver-operating characteristic (ROC) analysis (Figure 1) was performed with the value of uric acid which is the most significant inde-

Table I. Comparison of the basal characteristics, preoperative echocardiographic and laboratory parameters among patients with or without postoperative AF.

		AF – n = 139	AF + n = 35	p
Diabetes mellitus	(-)	91 (65.5)	22 (62.9)	0.772
	(+)	48 (34.5)	13 (37.1)	
Dyslipidemia	(-)	89 (64.0)	19 (54.3)	0.288
	(+)	50 (36.0)	16 (45.7)	
Smoking	(-)	71 (51.1)	21 (60.0)	0.345
	(+)	68 (48.9)	14 (40.0)	
Stent	(-)	111 (79.9)	30 (85.7)	0.429
	(+)	28 (20.1)	5 (14.3)	
Calcium channel blockers	(-)	100 (71.9)	26 (74.3)	0.782
	(+)	39 (28.1)	9 (25.7)	
Angiotensin converting enzyme inhibitors	(-)	116 (83.5)	27 (77.1)	0.383
	(+)	23 (16.5)	8 (22.9)	
Aldosterone receptor antagonists	(-)	129 (92.8)	32 (91.4)	0.727
	(+)	10 (7.2)	3 (8.6)	
Angiotensin receptor blockers	(-)	124 (89.2)	30 (85.7)	0.559
	(+)	15 (10.8)	5 (14.5)	
NSAID	(-)	16 (11.5)	4 (11.4)	1.00
	(+)	123 (88.5)	31 (88.6)	
RCA bypass	(-)	29 (20.9)	6 (17.1)	0.624
	(+)	110 (79.1)	29 (82.9)	
Inotropic agent requirement	(-)	117 (84.2)	26 (74.3)	0.172
	(+)	22 (15.8)	9 (25.7)	
Postoperative creatinine (mg/dl)		1.0 (0.1-2.3)	1.1 (0.7-2.3)	0.420
Number PRC		1 (0-5)	1 (0-6)	0.054
LA diameter (mm)		38 (25-57)	40 (30-57)	0.066
BMI		28 (20-36)	29 (19-35)	0.420
Preop WBC ($\times 10^9$/L)		7.5 (2.7-15.4)	7.2 (2.7-15.4)	0.238
Preop MPV (fl)		8.6 (5-13)	9.2 (6-14)	0.058
Preoperative Lymphocyte ($\times 10^9$/L)		2.0 (0.1-23)	1.9 (0.1-4.2)	0.795

RCA bypass: Right coronary artery bypass; Number PRC; number of transfusion of packed red cells; LA diameter: Left atrial diameter; BMI: Body mass index; Preop WBC: Preoperative blood white cell; Preop MPV: Preoperative mean platelet volume.

Table II. Univariate analysis for differences between patients with and without atrial fibrillation (AF).

		AF – n = 139	AF + n = 35	p	Odds Ratio 95% CI
Gender	Male	96 (69.1%)	13 (37.1%)	< 0.001	3.778
	Female	43 (30.9%)	22 (62.9%)		1.742-8.195
Hypertension	(-)	68 (48.9%)	10 (28.6%)	0.03	2.394
	(+)	71 (51.1%)	25 (71.4%)		1.07-5.357
Beta Blockers	(-)	26 (18.7)	17 (48.6)	< 0.001	0.244
	(+)	113 (81.3)	18 (51.4)		0.111-0.536
Statins	(-)	87 (62.6)	29 (82.9)	0.023	0.346
	(+)	52 (37.4)	6 (17.1)		0.135-0.89
Age		58 (36-80)	67 (44-80)	< 0.001	
Preop EF		50 (30-65)	45 (35-60)	< 0.001	
Preop UA		5 (1.0-9.8)	7.8 (5.0-11.0)	< 0.001	
Preop RDW		13.5 (9.0-20.6)	14.5 (11.5-20.6)	< 0.001	
Creatinine		1.0 (0.4-2.3)	1.2 (0.6-2.8)	0.004	
Euroscore		2.0 (0-6)	3.0 (1-6)	< 0.001	
Total bleeding (ml)		140 (25-1500)	175 (50-550)	0.028	

Preop EF: Preoperative Ejection Fraction; Preop UA: Preoperative Uric Acid; Preop RDW: Preoperative Red Cell Distribution Width.

Table III. Multivariate logistic regression analysis for the detection of independent risk factors for atrial fibrillation (AF).

	Wald	df	p	Odds Ratio	95% CI lower limit	95% CI upper limit
Gender	1.211	1	0.271	0.505	0.149	1.705
Age	0.342	1	0.559	0.978	0.907	1.054
Hypertension	2.665	1	0.103	0.345	0.096	1.238
Statins	0.147	1	0.701	0.758	0.184	3.120
Beta Blockers	4.696	1	0.030	4.432	1.153	17.037
Preoperative EF	7.613	1	0.006	0.888	0.816	0.966
Preoperative UA (mg/dl)	18.869	1	< 0.001	3.137	1.873	5.256

Model Ki-Kare: 92.755; -2LL = 81.938; sd: 7; n = 174; $p < 0.001$; Success rate = 88.5%; Cox & Snell $R^2 = 0.413$; Nagelkerke $R^2 = 0.652$; EF: Ejection Fraction; UA: Uric Acid.

pendent risk factor for evaluating AF resulting from logistic regression. The performance of UA as a diagnostic test in AF development was evaluated. The sensitivity of UA according to cut value of 6.55 was 91.4%, selectivity was 84.2%, and the area under the curve (AUC) was 0.922 (standard error: 0.022; 95% CI from 0.880 to 0.964). In addition, positive predictive value (PPV) was found to be 59.3%, and negative predictive value (NPV) was 97.5%.

Discussion

Higher UA level has been the most important risk factor for postoperative AF in this study with sensitivity of 91.4%, selectivity of 84.2%, positive predictive value (PPV) of 59.3%, and negative predictive value (NPV) of 97.5% according to the cut value of 6.55 mg/dl of UA level. Our findings showed that the risk of new-onset AF in patients after CABG surgery is significantly associated with UA levels of more than 6.55 mg/dL.

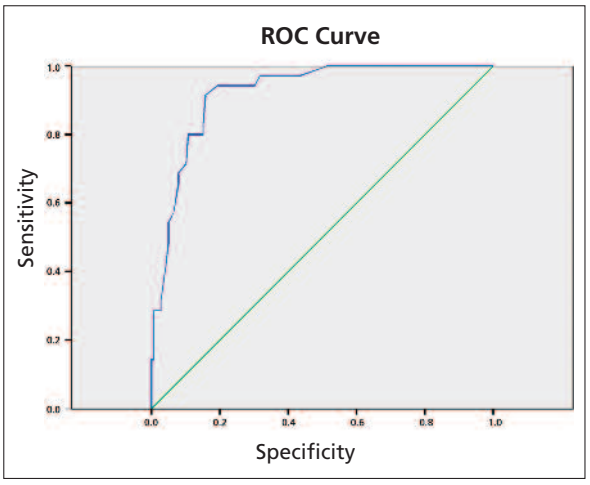

Figure 1. Receiver-operating characteristic (ROC) curve analysis for prediction of atrial fibrillation (AF) by uric acid (UA) level.

Atrial fibrillation worsens hemodynamic status and increases the risk of thrombo-embolism and longer ICU stays (1). Stroke is a major complication seen in 2% of CABG patients, 37% of whom had preceding AF. Apart from a higher risk of stroke, postoperative AF after CABG was associated with greater in-hospital mortality and worse survival (74% vs. 87%) at long-term follow-up (4-5 years; 7). The exact mechanism underlying the initiation and maintenance of postoperative AF is still being investigated.

Numerous trials have investigated several risk factors for post-operative AF after cardiac surgery. Older age, female gender, hypertension, low EF, and high RDW levels have been reported as risk factors for AF[1,11-14]; all of which were confirmed by the results of our study. Prolonged mechanical ventilation, atrial ischemia, hypokalemia[15], hypomagnesemia have also been reported as associated with postoperative AF[16]. There is conflicting data as to whether increased aortic cross-clamp and cardiopulmonary bypass increase postoperative AF time[17].

Pretreatment with beta receptor blockers and statins has been studied most extensively and has been shown to be effective for prevention of AF after cardiac surgery[18]. Pretreatment or early treatment with beta receptor blockers or amiodarone reduced the risk as well[19,2]). In concordance with those reports, our work indicated that preoperative beta receptor blocker and statin therapy seemed to reduce new-onset AF development postoperatively. Finally, we found an independent association of postoperative AF with the amount of total bleeding after CABG surgery at first 24 hours.

It has been revealed that some markers predict the potential risk for postoperative AF. Inflammatory markers such as C-reactive protein, complement, neutrophil/lymphocyte ratio, white blood cell count, interleukin-6, TNF-α, and RCDW have been associated with an increased appearance of postoperative AF[8-11].

Elevated serum UA levels are associated with an increased occurrence of AF in patients with type 2 diabetes mellitus[22] and ischemic heart failure[23]. A recent study reported that hyperuricemia is associated with a larger left atrial size and may be a novel risk factor for the development of AF[24]. However, there is a great deal of debate about whether the relationship is one of cause and effect and about the potential mechanism by which elevated serum UA may predispose patients to AF[25].

In the light of these findings, we suggest that high uric acid levels might be correlated with postoperative AF, but it is as yet unclear whether uric acid is a culprit, a risk factor, or just a surrogate of the disease. Prospective studies with a larger number of patients are needed to evaluate the role of UA in postoperative AF. To the best of our knowledge, this is the first study describing the association with UA and postoperative AF in coronary artery disease patients.

Conclusions

Serum UA levels can increase the sensitivity and specificity in predicting AF. We suggest that UA might be an obtainable biomarker that might predict a patient's predilection to develop AF after CABG surgery.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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