Increased Serum Uric Acid Levels Are Correlated with Decreased Left Atrial Appendage Peak Flow Velocity in Patients with Atrial Fibrillation

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Abstract

Objective: We aimed to examine the relationship between serum uric acid levels and left atrial appendage (LAA) peak flow velocity, an indicator of the mechanical functions of the LAA, and atrial fibrillation (AF). **Subjects and Methods:** Transesophageal echocardiography was performed before cardioversion in 153 patients with AF. The patients were categorized into 2 groups based on their LAA blood flow velocity. Group 1 included 87 patients with a low LAA flow velocity (<35 cm/s), and group 2 comprised 66 patients with a normal LAA flow velocity (≥35 cm/s). The χ^2 and Student's t tests were used to compare categorical and quantitative data between the groups. Linear regression analyses were performed to demonstrate the independent association between serum uric acid levels and LAA peak flow velocity. **Results:** The LAA blood flow velocity was 24.62 ± 5.90 cm/s in group 1 and 49.28 ± 13.72 cm/s in group 2, respectively (p < 0.001). The serum uric acid levels were 6.88 ± 1.85 mg/dl in group 1 and 5.97 ± 1.51 mg/dl in group 2, and the difference was statistically significant (p = 0.001). There was a negative correlation between serum uric acid levels and LAA blood flow velocity (r = −0.216, p = 0.007). Multivariate regression analysis showed that serum uric acid levels, age and gender differences were significant predictors of the LAA peak flow velocity. **Conclusions:** High serum uric acid levels were associated with a low contractile function of the LAA and could provide additional prognostic information on future thromboembolic events in patients with AF.

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Introduction

The risk of thromboembolism is affected by numerous factors and shows considerable variability among patients with atrial fibrillation (AF) [1]. Coexisting clinical, echocardiographic and biochemical factors, which increase the risk of thromboembolic events in patients with AF, have been identified [1, 2].

Serum uric acid is the end product of purine metabolism catalyzed by xanthine oxidoreductase (XO) [1]. Elevated serum uric acid levels have been reported as an independent risk factor of cardiovascular morbidity and mortality, especially in patients with heart failure and AF [2, 3]. The XO enzyme activity has been reported, and, hence, in the left atrium (LA), elevated uric acid levels may be a sign of oxidative damage and inflamma-

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tion, which may play a role in the pathogenesis of AF [4–6].

The left atrial appendage (LAA) is a blind-ended pouch, which is embryologically distinct from the main body of the LA. The contractile function of the LAA has been shown to provide a significant contribution to the overall compliance and reservoir function of the LA [7]. AF can lead to structural remodeling of the LA, causing reduced contractile function of the LA and/or the LAA. Most of the clinical interest in LAA peak flow velocity arises from its relationship with thromboembolism [5]. Both surgical and autopsy studies have shown that thromboembolic complications develop during AF and are mostly due to the emboli or thrombi formed during blood stasis in the LAA [7]. Thus, the contractile function of the LAA and the degree of blood stasis within the LAA have been regarded as substantial determinants of thromboembolic risk in patients with AF. Although much is known about the role of serum uric acid in atrial remodeling, less is known about the potential pathogenetic role of uric acid in maintaining the function of the LAA.

Therefore, in this study, the association between serum uric acid levels and LAA peak flow velocity was assessed using transesophageal echocardiography (TEE) in patients with AF, which may provide additional information about the pathogenesis of thromboembolic events in this patient group.

Subjects and Methods

Patient Selection

This was a retrospective study, and patients with AF, who were admitted to the Department of Cardiology and in whom TEE was performed before cardioversion, were retrospectively screened via the hospital's computerized patient database. Exclusion criteria were: thyroid dysfunction, end-stage heart failure, hepatic failure, recent acute myocardial infarction, malignancies, blood dyscrasias, autoimmune or inflammatory diseases and the use of drugs, which may potentially interfere with the uric acid metabolism, such as allopurinol, diuretics, anti-inflammatories and antioxidants.

A total of 231 patients were evaluated, and 56 patients were excluded from the study. Twenty-two patients who did not have serum uric acid levels on file were also excluded from the study. Hence, 153 patients were included in the study. After the assessment of baseline demographic and clinical characteristics, patients were divided into 2 subgroups according to their LAA peak flow velocity. Patients with a low LAA peak flow velocity (<35 cm/s) were identified as group 1, and patients with a normal LAA peak flow velocity (≥35 cm/s) were identified as group 2.

Transesophageal Echocardiography

All the patients included in the study had undergone TEE examination for left atrial thrombus investigation. The TEE record-

ings were re-examined offline irrespective of the previous results by 2 echocardiography specialists (M.C. and Y.G.) who were blinded to the data of the patients. The TEE examinations were performed after an overnight fasting period in the left lateral decubitus position with the application of 10% lidocaine spray to the hypopharynx (Philips iE 33 6.0 ultrasound system and Live 3D TEE probe X7-2t; Philips Medical Systems, Andover, Mass., USA). LAA blood flow velocity was measured by placing the pulsed-wave Doppler sample volume at the orifice of the LAA, and the peak outflow velocity signals were averaged over a minimum of six cardiac cycles. The presence of a thrombus and spontaneous echocardiographic contrast (SEC) was also evaluated. All TEE findings and the transthoracic echocardiography findings that have been made before the TEE procedure were compared between the 2 groups.

Laboratory Measurements

Blood samples for standard biochemical tests were obtained in the early morning hours 1 or 2 days prior to TEE examination. In all patients, the serum uric acid level, fasting plasma glucose, serum urea, serum creatinine, total serum cholesterol, triglyceride, high-density lipoprotein and low-density lipoprotein cholesterol were measured with an Olympus AU2700 autoanalyzer using its own kits (Olympus Diagnostics, Hamburg, Germany) in the central laboratory of our institute. The estimated glomerular filtration rate (eGFR) was measured using the 4-variable modifications of diet in renal disease equation.

Statistical Analysis

Continuous variables were expressed as the mean ± standard deviation and categorical variables as percentages. Continuous variables were also checked for the normal distribution assumption using the Kolmogorov-Smirnov statistics. The χ^2 and Student's t tests were used to compare categorical and quantitative data between the 2 groups, respectively. Pearson's and Spearman's coefficients were used to perform an analysis of correlation. A univariate linear regression analysis was performed to demonstrate the independent association between serum uric acid levels and LAA peak flow velocity. To determine the independent influence of serum uric acid levels on LAA blood flow velocity, multivariate linear regression analysis was performed, using the backward method based on various independent variables, which likely affect the LAA peak flow velocity. A p value <0.05 was considered statistically significant. All statistical analyses and calculations were conducted using the SPSS 20.0 Statistical Package Program for Windows (SPSS, Chicago, Ill., USA).

The Institutional Ethics Committee approved this study protocol, and the study was conducted according to the regulations of the Declaration of Helsinki.

Results

Of the 153 patients, 91 were men (59.5%) and 62 were women (40.5%), with a mean age of 65.92 ± 12.92 years. Group 1 consisted of 87 patients [43 men (49.4%) and 44 women (50.6%), with a mean age of 68.3 ± 9.9 years], and group 2 consisted of 66 patients [48 men (72.7%) and 18 women (27.3%), with a mean age of 62.8 ± 15.5 years].

Table 1. Demographics, clinical and biochemical data of AF patients categorized according to LAA blood flow velocity

	Group 1 (n = 87)	Group 2 (n = 66)	p
Age, years	68.3±9.9	62.8±15.5	0.010
Females	44 (50.6)	18 (27.3)	0.003
Coronary artery disease	31 (35.6)	18 (27.3)	0.178
Hypertension	46 (52.9)	31 (47.0)	0.288
Hyperlipidemia	18 (20.7)	10 (15.2)	0.254
Diabetes mellitus	20 (23.0)	14 (21.2)	0.476
Fasting glucose, mg/dl	110.6±35.1	119.5±50.3	0.202
GFR, ml/min/1.73 m^2	63.5±16.1	72.9±18.8	0.001
Serum uric acid, mg/dl	6.9±1.8	5.9±1.5	0.001
High-density lipoprotein cholesterol, mg/dl	43±13	46±12	0.307
Low-density lipoprotein cholesterol, mg/dl	107±33	114±33	0.235
Triglyceride, mg/dl	133±84	143±84	0.450
Total serum cholesterol, mg/dl	176±43	189±44	0.070
White blood cell, $10^3/\mu l$	7.73±2.73	7.63±2.47	0.554
Neutrophil/lymphocyte ratio	3.32±2.54	3.24±2.66	0.861
Hemoglobin, g/dl	13.2±1.6	13.6±1.8	0.088
Hematocrit, %	40±4	41±7	0.104
Red cell distribution width, %	15.2±2.3	15.1±3.5	0.786
Platelet count, $10^3/\mu l$	241±75	244±76	0.818
Mean platelet volume, fl	8.9±1.1	8.7±0.9	0.249

Figures in parentheses are percentages.

The baseline demographic characteristics of the study population are shown in table 1. We found that AF patients with a low peak flow velocity were older (p = 0.010) and female (p = 0.003). We also found that patients with an LAA peak flow velocity <35 cm/s have a decreased eGFR compared with those with an LAA peak flow velocity ≥35 cm/s (63.5 ± 16.1 vs. 72.9 ± 18.8 ml/min/1.73 m²; p = 0.001). There were no significant differences with regard to other demographic and clinical features or the laboratory findings between the groups.

The LAA peak flow velocity was lower (24.62 ± 5.90 cm/s) in group 1 compared with group 2 (49.28 ± 13.72 cm/s), and the difference was statistically significant (p = 0.001). Additionally, the presence of LAA thrombi and SEC was significantly higher in group 1 than in group 2 (p = 0.027 and p < 0.001, respectively; table 2). Serum acid levels were 6.9 ± 1.8 mg/dl for group 1 and 5.9 ± 1.5 mg/dl for group 2, and the difference was statistically significant (p = 0.001). Serum uric acid levels were negatively correlated with the LAA blood flow velocity (r = –0.216, p = 0.007).

Multivariate regression showed that the serum uric acid level (β = –0.196, p = 0.010), age (β = –0.201, p = 0.009) and gender differences (β = –0.289, p < 0.001) were statistically significant predictors of LAA peak flow velocity (table 3). Although univariate correlation analysis showed diastolic blood pressure, LAA peak flow velocity, SEC, LAA thrombus, left atrial size, left ventricular ejection fraction and GFR were correlated with serum uric acid, and only diastolic blood pressure (β = –0.305, p = 0.016) and GFR (β = –0.498, p < 0.001) were independent predictors of serum uric acid in multivariate regression analysis, using the backward method.

Discussion

The major finding of this study was that serum uric acid levels were higher in patients with AF and a lower LAA peak flow velocity than in those with AF and a normal LAA peak flow velocity; and, there was an independent association between increased levels of serum uric acid and decreased LAA function in patients with AF. Hence, elevated serum uric acid levels could be considered as a predictor of decreased contractile function of the LAA contributing to the prothrombotic state of patients with AF.

Table 2. TEE findings of study patients

	Group 1 (n = 87)	Group 2 (n = 66)	p values
LAA peak flow velocity, cm/s	24.62±5.90	49.28±13.72	<0.001
LAA thrombus	19 (21.8)	6 (9.1)	0.027
SEC			<0.001
0	28 (32.2)	51 (77.3)	
1+	11 (12.6)	6 (9.1)	
2+	19 (21.8)	3 (4.5)	
3+	29 (33.3)	6 (9.1)	

Figures in parentheses are percentages.

Table 3. Multivariate regression analysis based on independent variables likely to affect the LAA peak flow velocity

Independent variables	95% CI	β	p[1]
Serum uric acid	−3.082 to −0.425	−0.196	0.010
Age	−0.428 to −0.063	−0.201	0.009
Male gender	−14.024 to −4.558	−0.289	<0.001
Hypertension	−5.910 to 4.088	−0.029	0.719
eGFR	−0.157 to 0.199	0.024	0.815
LDL-C	−0.014 to 0.128	0.119	0.115
N/L ratio	−0.771 to 1.170	0.033	0.685
RDW	−1.207 to 0.453	−0.068	0.371
MPV	−3.154 to 1.300	−0.062	0.412

CI = Confidence interval; LDL-C = low-density lipoprotein cholesterol; N/L ratio = neutrophil/lymphocyte ratio; RDW = red cell distribution width; MPV = mean platelet volume.
[1] p value at the last step, adjusted for the independent variables.

Serum uric acid is the end product of purine metabolism and is produced by the conversion of hypoxanthine to xanthine and then xanthine to uric acid, and both reactions are catalyzed by the XO enzyme [1]. Serum uric acid is a well-established endothelium-injuring factor. Bo et al. [8] showed that elevated serum uric acid levels cause a detrimental effect on endothelial function. However, Ames et al. [9] suggested that serum uric acid has anti-oxidant effects and may be a powerful scavenger of oxygen and free radicals at physiological concentration levels. These contradictory findings suggest a concentration-dependent dual effect of serum uric acid that exerts beneficial antioxidant properties while within normal limits, whereas harmful pro-oxidant effects could be seen above normal serum concentrations.

Numerous studies have demonstrated that serum uric acid is clearly associated with oxidative stress and inflammation in several pathological conditions. Elevated serum uric acid levels have been suggested as a simple and independent predictor of morbidity and mortality in patients with congestive heart failure [10]. Elevated serum uric acid levels were also found as an independent predictor of cardiovascular events and mortality in patients with coronary artery disease, ST-elevation myocardial infarction [11], hypertension [12], stroke [13], diabetes mellitus [14], metabolic syndrome [15], insulin resistance [14], obesity [16] and renal failure [17]. These findings pointed out that serum uric acid is not only an indicator of the catabolic phase of purine nucleotides but also a manifestation of systemic inflammation in many cardiovascular diseases.

Electrical remodeling is known as the main operative mechanism in paroxysmal AF, whereas atrial structural remodeling holds the principal role in permanent AF [18]. The consequences of inflammation and oxidative stress can lead to cardiac remodeling and atrial fibrosis as well as increase the susceptibility of AF. However, it is unclear whether serum uric acid participates actively in atrial remodeling or simply represents a marker of the oxidative and inflammatory processes.

Since there is a relationship between serum uric acid levels and markers of inflammation and oxidative stress, the elevated serum uric acid level appears to be an emerging prognostic risk factor of AF. Suzuki et al. [19] reported that the serum uric acid levels were significantly higher in 1,131 AF patients compared with non-AF patients. In another recently published study, Kuwabara et al. [20] showed that serum uric acid levels ≥8 mg/dl might be accepted as an independent predictor of the future development of AF. The association between serum uric acid and AF is largely explained by oxidative stress, which may be responsible for atrial remodeling in patients with AF [21]. XO-induced increased oxidative stress may cause cellular damage and impair the myofibrillar energetics which causes atrial contractile dysfunction [22]. The LA has been found to be more sensitive to oxidative stress [23], and the XO enzyme found in the LA seems to contribute to the increased atrial oxidative stress in patients with AF [21]. Hoeper et al. [2] demonstrated that elevated serum uric acid levels are related to increased right and left atrial filling pressures, which leads to structural and electrophysiological abnormalities that expedite the initiation and continuation of AF. Additionally, Letsas et al. [5] showed a correlation between elevated serum uric acid levels and increased LA diameter as a re-

Celik et al.

sult of the effects of serum uric acid on atrial structural remodeling.

The LAA is a blind-ended pouch, which is embryologically distinct from the main body of the LA. The contractile function of the LAA has been shown to provide a significant contribution to the overall compliance and reservoir function of the LA [7]. Most of the clinical interest in LAA peak flow velocity arises from its relationship with thromboembolism. The contractile function of the LAA and the degree of blood stasis within the LAA have been regarded as substantial determinants of thromboembolic risk in patients with AF. Although much is known about the role of serum uric acid in atrial remodeling, less is known about the potential pathogenetic role of uric acid in maintaining the function of the LAA. In an experimental porcine model of rapid atrial pacing, Dudley et al. [24] demonstrated that increased XO activity was more apparent in the LAA. However, it is unclear whether uric acid participates actively in the mechanical dysfunction of the LAA or simply represents a marker of the oxidative and inflammatory processes.

In the present study, we aimed to investigate the association between LAA function and serum uric acid levels in patients with AF and observed that uric acid levels were significantly higher in patients with AF and a lower LAA peak flow velocity than in those with AF and a normal LAA peak flow velocity. Consequently, we suggested that the LAA might be more susceptible to the direct toxic effect of increased serum levels of uric acid, and elevated levels might further impair the myofibrillar energetics of the LAA compared to the other left atrial myocardium.

Additionally, we observed that patients with decreased LAA peak flow velocities were females and older and had a decreased eGFR compared with patients with normal LAA peak flow velocities. It is obvious that atrial fibrosis and susceptibility to AF is increased with aging. It is a matter of controversy in the literature whether there is a gender difference in the incidence of AF. Nevertheless, Michelena et al. [25] stated that morbidity and mortality are greater in women with AF than in men with AF. In accordance, we also found that male AF patients generally have normal LAA peak flow velocities compared with females. In multivariate regression analysis, the eGFR did not remain an independent predictor of LAA peak flow velocity.

This study had several limitations. Firstly, the limited number of patients and the retrospective design of the paper create a difficulty for the definite cause-effect relation between serum uric acid and LAA peak flow velocity. Considering that the study was conducted with a special cohort, further studies with larger cohorts are required to improve the generalizability of the results. Secondly, patients were pooled and analyzed irrespective of the duration and type of AF rhythm or a history of heart failure, which could affect the function of the LAA and the level of serum uric acid. Also, we did not evaluate the use of diuretics and statins, which may have a potential effect on the elevated serum uric acid level. Lastly, we did not examine the relative influence of other conventional inflammatory markers.

Conclusions

In the present study, there was an independent association between high serum uric acid levels and low LAA peak flow velocity. This finding could indicate that a high serum uric acid level seemed to be a predictor of low LAA peak flow velocity in patients with AF. However, further large-scale studies are needed to elucidate the exact pathophysiologic and prognostic role of serum uric acid.

Disclosure Statement

There are no conflicts of interest.

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