Original Research

Uric Acid Elevation in Atrial Fibrillation

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Introduction: Uric acid is a cardiovascular risk marker associated with oxidative stress and inflammation. Recently, atrial fibrillation (AF) has been associated with inflammation and oxidative stress. We therefore investigated the association between AF and uric acid levels.

Methods: Consecutive patients with AF and healthy control subjects were screened. Demographic, clinical, and echocardiographic characteristics were carefully recorded. In each participant, uric acid levels and conventional inflammatory markers were determined. The final study population consisted of 45 patients with paroxysmal AF, 41 patients with permanent AF, and 48 control subjects.

Results: A significant variance in uric acid levels was evident between patients with paroxysmal AF (5.7 ± 1.1 mg/dl), permanent AF (6.7 ± 1.4 mg/dl), and control subjects (5.1 ± 1.3 mg/dl) ($p<0.001$). After univariate analysis considering 2 groups (control, AF patients), the following variables were significantly associated with the presence of AF: age, hypertension, β-blocker use, low left ventricular ejection fraction (LVEF), increased left atrial diameter, uric acid levels, and C-reactive protein (CRP) levels. After multivariate logistic regression analysis, only CRP was an independent predictor for AF (odds ratio, OR: 2.172). In a subgroup analysis, CRP (OR: 1.434) and LVEF (OR: 0.361) were independent predictors of paroxysmal AF, while CRP (OR: 3.048), uric acid (OR: 2.172), and LVEF (OR: 0.34) were predictors of permanent AF.

Conclusions: There is an association between increased levels of uric acid and permanent AF. Also, uric acid elevation may be related to the burden of AF. Undoubtedly, larger studies should further examine this potential association.

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Atrial fibrillation (AF) is a rapidly evolving epidemic with different underlying substrates and serious health consequences.[1,2] Recently, AF has been associated with inflammation and oxidative stress and much of the current interest regarding pharmacologic therapy has shifted to non-channel blocking drugs with pleiotropic properties including anti-inflammatory and antioxidant.[3-10]

On the other hand, uric acid has emerged as a simple and independent marker of morbidity and mortality in a variety of cardiovascular disease states.[11] Regardless of the debate as to whether it is a predictor or a causative factor, uric acid has been clearly associated with oxidative stress and inflammation in several pathological conditions.[12-15] However, no study to date has examined the merit of uric acid determination in the AF setting. Thus, in this pilot observational study we sought to investigate the association between AF and uric acid levels, as well as the relative impact of other conventional inflammatory markers. Our aim was to examine this association in patients who had no significant comorbidities or associated cardiovascular conditions that markedly affect uric acid levels, and also had no marked underlying atrial structural remodeling.

Methods

Patients and study protocol

In this cross-sectional study, we recruited consecutive patients with AF, either paroxysmal or permanent, who were seen at the emergency department or at the outpatient cardiology clinic of our hospital. The arrhythmia diagnosis required an electrocardiographic documentation, whereas its classification was based on authoritative international consensus statements.[16] As the control group, we enrolled consecutive individuals with no history of arrhythmias who were undergoing a regular routine clinical examination for a health certificate. Exclusion criteria were thyroid dysfunction (including subclinical hyperthyroidism), history of coronary artery disease, valvular heart disease, congestive heart failure, left ventricular ejection fraction (LVEF) <50%, left atrial (LA) diameter >55 mm, recent infection, serum creatinine >1.2 mg/dl, malignancies or blood dyscrasias, autoimmune or inflammatory diseases, and administration of drugs or supplements with anti-inflammatory or antioxidant action, apart from statins. Patients receiving allopurinol, diuretics or other drugs interfering with uric acid metabolism were also excluded.

All baseline demographic and clinical characteristics were carefully recorded. A transthoracic echocardiographic examination was performed in each individual. In addition, laboratory examinations, including complete blood count and biochemical investigations, were performed in the fasting state. The white blood cell (WBC) count was determined using a Coulter counter. C-reactive protein (CRP) levels were assessed using a high sensitivity immunonephelometric assay (Beckman Coulter/Immage Immunochemistry Systems, Behring Diagnostics Inc., Somerville, NJ, USA). Plasma fibrinogen and uric acid levels were measured by standard analytical methods (Clauss technique and uricase enzymatic test, respectively; normal range of uric acid levels: 3.4-7 mg/dl for men, 2.4-6 mg/dl for women). All measurements were performed blindly with respect to the patients' characteristics and treatment. The participants consented to the study and the local research and ethics committee approved the protocol.

Statistical analysis

Continuous variables are presented as mean ± SD, and categorical variables as absolute and relative frequencies (percentages). Differences in quantitative characteristics between groups were evaluated using one-way analysis of variance (ANOVA) or Student's t-test, depending on the number of the groups compared. In order to evaluate differences in categorical variables between study groups Pearson's chi-square test was used. Correlations among study parameters were sought using Spearman's rho test. The association between AF and uric acid was assessed by means of logistic regression analysis (AF was the dependent variable) comparing AF and control subjects. Univariate and multivariate logistic regression analysis estimated the odds ratio of AF recurrence. Deviance residuals evaluated the models' goodness of fit. Candidate variables for entering the multivariate model were hypertension, β-blockers, calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blocking agents (ARB), LVEF, LA diameter, CRP, and fibrinogen. All models included age and gender, regardless of their statistical significance, in order to adjust for their potential confounding effects. All tests were two-sided at a significance level of 0.05. All data analysis was performed using STATA statistical software (Version 9.0, Stata Corporation, College Station, TX 77845, USA).

Results

The initial screened population consisted of 53 patients with paroxysmal AF, 64 patients with permanent AF, and 52 controls. However, after the implementation of the aforementioned exclusion criteria, the final study population consisted of 45 patients with paroxysmal AF, 41 patients with permanent AF and 48 controls. All subjects were free from symptoms and signs of heart failure and exhibited a preserved LVEF (>50%). The mean duration of the arrhythmia in permanent AF patients was 7.9 ± 4.2 months. With regard to the paroxysmal AF group, the number of the documented arrhythmia episodes was 4 ± 3.4, while the mean duration of the AF history was 24 ± 18 months.

The characteristics of the study participants are presented in Table 1. There were statistically significant differences between the 3 groups in the following parameters: age, hypertension, β-blocker use, CCB use, LVEF, LA diameter, uric acid levels, CRP levels, and fibrinogen levels. A significant variance in uric acid levels was evident between patients with paroxysmal (5.7 ± 1.1 mg/dl) AF, permanent AF (6.7 ± 1.4 mg/dl), and control subjects (5.1 ± 1.3 mg/dl) ($p<0.001$).

Table 1. Clinical, echocardiographic, and laboratory characteristics of the study population.

	Control (n=48)	Paroxysmal AF (n=45)	Permanent AF (n=41)	p
Age (yrs)	61.3 ± 14.7	67.4 ± 8.8	71.9 ± 9.9	<0.001
Men	27 (56%)	28 (62%)	26 (63%)	0.754
Hypertension	24 (50%)	32 (71%)	31 (76%)	0.023
Diabetes	4 (8%)	2 (4%)	6 (14%)	0.363
Hyperlipidemia	10 (21%)	8 (18%)	6 (15%)	0.749
Drugs:				
β-blockers	8 (17%)	23 (51%)	22 (54%)	<0.001
CCBs	2 (4%)	3 (7%)	8 (19%)	0.036
ACE-I/ARB	22 (46%)	18 (40%)	24 (59%)	0.216
statins	7 (15%)	7 (16%)	5 (12%)	0.889
LVEF (%)	61.2 ± 3.1	57.8 ± 5.3	55.9 ± 4.1	<0.001
LVEDD (mm)	47 ± 4	47 ± 5	49 ± 6	0.143
LA diameter (mm)	35 ± 6	37 ± 4	45 ± 5	<0.001
WBC count (per μL)	7155 ± 1877	7705 ± 2198	6971 ± 1909	0.217
Uric acid (mg/dl)	5.1 ± 1.3	5.7 ± 1.1	6.7 ± 1.4	<0.001
CRP (mg/dl)	0.22 ± 0.16	0.41 ± 0.37	0.51 ± 0.46	0.003
Fibrinogen (mg/dl)	360 ± 89	374 ± 103	412 ± 99	0.05

ACEI – angiotensin-converting enzyme inhibitors; AF – atrial fibrillation; ARB – angiotensin receptor blocking agents; CCBs – calcium channel blockers; CRP – C-reactive protein; LA – left atrial; LVEF – left ventricular ejection fraction; LVEDD – left ventricular end-diastolic diameter; WBC – white blood cells.

The between group comparisons regarding uric acid levels showed the following results: control vs. paroxysmal AF, p=0.051; control vs. permanent AF, p<0.001; paroxysmal AF vs. permanent AF, p=0.001. Uric acid levels were correlated with age (p=0.09), LVEF (p<0.001), LA diameter (p<0.001), and CRP levels (p<0.003). After univariate analysis considering 2 groups (control, AF patients as a whole), the following variables were significantly associated with the presence of AF: age (odds ratio, OR: 1.043, 95% confidence interval, CI: 1.014-1.073, p=0.004), hypertension (OR: 2.333, 95%CI: 1.132-4.810, p=0.022), β-blocker use (OR: 6.658, 95%CI: 2.718-16.312, p<0.001), low LVEF (OR: 0.780, 95%CI: 0.696-0.875, p<0.001), increased LA diameter (OR: 4.925, 95% CI: 2.431-9.978, p<0.001), uric acid levels (OR: 1.644, 95% CI: 1.226-2.204, p=0.001), and CRP levels (OR: 1.092, 95% CI: 1.011-1.179, p=0.003).

The association between uric acid and AF was assessed by multivariate logistic regression modeling after adjusting for age, gender and statin use. The adjusted OR for AF as a whole (paroxysmal and permanent) was 2.172 (95%CI: 1.327-3.555, p=0.002) for CRP. No other variable was independently associated with AF after multivariate analysis. Subsequently, we performed a separate multivariate logistic regression analysis using paroxysmal and permanent AF as dependent variables (subgroup analysis), again adjusting for age, gender and statin use. The adjusted OR for paroxysmal AF was 0.361 (95%CI: 0.137-0.949, p=0.039) for LVEF, and 1.434 (95%CI: 1.028-2.001, p=0.034) for CRP. For permanent AF the adjusted OR was 2.172 (95%CI: 1.327-3.555, p=0.002) for uric acid, 0.34 (95%CI: 0.137-0.949, p=0.039) for LVEF, and 3.048 (95%CI: 1.331-6.983, p=0.008) for CRP. The use of statins was not associated with paroxysmal or persistent AF in the multivariate analysis (OR: 0.884, 95%CI: 0.621-1.257, p=0.494, OR: 0.974, 95%CI: 0.885-1.072, p=0.595, respectively).

In order to evaluate any potential correlation between uric acid levels and AF burden (duration of AF in the permanent AF group and number of AF episodes in the paroxysmal AF group), bivariate correlation analysis was performed. An indicatory (0.05< p<0.1) significant correlation between AF duration and uric acid levels (Spearman's rho: 0.344, p=0.077) was found in the permanent AF group, possibly implying a trend. In the paroxysmal AF group no significant association between the number of AF episodes and uric acid levels was observed (Spearman's rho: 0.451, p=0.543).

Discussion

In the present study we report an independent association between increased levels of uric acid and permanent AF. Uric acid levels were also increased in paroxysmal AF patients compared to control subjects,

but this association was not significant after multivariate analysis. However, we should acknowledge that the small patient sample does not allow safe conclusions.

A large body of evidence indicates that, apart from the triggers, AF development and perpetuation depend on the electrophysiologic and structural remodeling of the atria.[17] Recent studies have demonstrated the implication of inflammation and oxidative stress in the pathophysiology of AF, although it is not clear yet whether these processes are a cause or consequence. In particular, inflammatory indexes, mainly CRP, have been related to future AF development, AF persistence, recurrence after cardioversion, LA enlargement, as well as to the associated prothrombotic state.[3-7] Also, CRP seems to be related to AF burden, since its elevation is more pronounced in patients with persistent AF than in those with the paroxysmal form.[18] Additionally, studies in animals and humans have directly demonstrated that AF is associated with increased oxidative stress.[6] Very recently, Neuman et al demonstrated by means of multivariate analysis an independent association between persistent or permanent AF and markers of oxidative stress, whereas this was not the case with respect to the inflammatory markers.[19]

Current epidemiological evidence suggests that serum uric acid is an independent predictor of cardiovascular events and mortality in patients with hypertension, diabetes, congestive heart failure, coronary artery disease, as well as in stroke survivors.[13,15] However, in healthy populations the evidence is weak and less consistent. Uric acid is a metabolic product of purine metabolism produced via the action of xanthine oxidase, an enzyme that is implicated in oxidative processes.[11,13] Thus, uric acid represents a marker of oxidative stress and inflammation but, depending on the cellular environment, it may exert antioxidant or pro-oxidant effects.[12-14]

To the best of our knowledge no study to date has examined the role of uric acid in the AF setting. Elevated inflammatory indexes, such as CRP and interleukin-6, are related to higher uric acid levels.[14,20] Although uric acid elevation may be attributed to various pathological conditions associated with AF, we demonstrated an independent association between permanent AF and uric acid levels. It is noteworthy that this association was independent of CRP. A potential explanation could be that uric acid levels reflect more selectively the increased atrial oxidative stress, despite the fact that oxidative stress and inflammation are usually interrelated. In line with this assumption, Dudley et al, in an experimental model of atrial tachy-pacing, demonstrated increased xanthine oxidase activity in left atrial appendages, as well as reduced superoxide production after administration of oxypurinol (a xanthine oxidase inhibitor).[21]

The observed differences in uric acid levels between the 2 AF groups could be attributed to different underlying pathophysiologic mechanisms. It is well known that in paroxysmal AF the main operative mechanisms are the triggers and the atrial electrical remodeling, whereas in permanent AF the atrial structural remodeling has the principal role.[17] Although inflammation and oxidative stress have been related to both forms of remodeling, it seems that the structural remodeling has a stronger association.[3,4,6]

It is unclear whether uric acid participates actively in atrial remodeling or simply represents a marker of the oxidative and inflammatory processes. Since our study was observational, only speculations on this issue can be made. As mentioned above, uric acid derives from the conversion of hypoxanthine to xanthine and of xanthine to uric acid, both reactions being catalyzed by the enzyme xanthine oxidase, which is inhibited by allopurinol.[13] This enzyme uses molecular oxygen and leads to the formation of the free radical superoxide anion, thereby promoting oxidative stress.[12] In a recent experimental study, the enzymatic activity of xanthine oxidase in left atrial appendages was 4.4 times greater in the AF group compared to the control group.[21] Thus, the increased oxidative stress may aggravate cellular damage, promoting the remodeling process.[6] On the other hand, given that uric acid exhibits antioxidant activity both *in vitro* and *in vivo*, its elevation could represent a compensatory protective mechanism against oxidative damage.[12]

We also demonstrated an association between AF, either paroxysmal or permanent, and LVEF, LVEF being significantly lower in AF patients. Despite being within normal limits, the LV performance may play a role in AF. Thamilarasan et al have demonstrated a significant increase in LA dimensions, LV diastolic dysfunction, and a significant decrease in LVEF in patients with lone paroxysmal AF.[22] However, the reversibility of LV dysfunction in patients with isolated AF following the restoration of sinus rhythm suggests that this dysfunction may be attributed in part to AF.[23] It should also be borne in mind that LV and LA remodeling are interrelated processes, and uric acid metabolism may be implicated in common pathophysiologic pathways.

Limitations

In our study there are some potential limitations. First, the number of participants was relative small. Second, patients with persistent AF were not included. Third, oxidative stress markers were not assessed. Fourth, the observational design of the study identifies only an association and not causality. Moreover, due to the observational design, only a single uric acid measurement was available. Finally, we have to acknowledge that paroxysmal AF patients are a quite heterogeneous group in terms of symptoms and arrhythmia burden, thus the relative impact on uric acid levels may be different. However, many episodes of paroxysmal AF are brief and/or asymptomatic and therefore the exact burden cannot be assessed.

Conclusions

Uric acid may represent a simple, easily determined marker of inflammation and oxidative stress in AF. Further studies are needed to elucidate its exact pathophysiologic and prognostic role in this setting. Finally, the role of uric acid-lowering agents, such as allopurinol, as an upstream therapy in AF constitutes a subject for future research.

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