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Uric Acid Levels and Atrial Fibrillation in Hypertensive Patients

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Abstract

Objective Uric acid (UA) is a cardiovascular risk marker associated with oxidative stress and inflammation. Recently, atrial fibrillation (AF) has been associated with inflammation and oxidative stress. The objective of this observational study was to investigate the association between UA levels and AF in hypertensive patients.

Methods Consecutive patients with hypertension were screened. We excluded subjects with coronary artery disease, congestive heart failure, diabetes, valvular heart disease, congenital heart disease, cardiomyopathy, renal failure, inflammatory conditions, thyroid dysfunction, respiratory diseases, and those who were taking drugs that affect UA metabolism (apart from diuretics). The final study population consisted of 451 patients. Fifty of them (11%) had AF (paroxysmal: 38; persistent: 8; permanent: 4). Demographic, clinical, laboratory, and echocardiographic characteristics were carefully recorded.

Results After univariate analysis, age, duration of hypertension, serum creatinine, serum UA, left atrial diameter (LAD), interventricular septum thickness, and left ventricular posterior wall thickness were significantly increased in patients with AF compared with non-AF patients, while the estimated glomerular filtration (eGFR) level was much lower in patients with AF than in those without AF. After multivariate logistic regression analysis, the independent predictors of AF were UA (OR: 1.008; 95% CI: 1.003-1.013, p=0.002) and LAD (OR: 1.160; 95% CI: 1.068-1.260; p<0.001).

Conclusion We demonstrated an independent association between increased serum UA levels and AF in hypertensive patients. Undoubtedly, larger studies in different populations should further examine this potential association as well as the underlying pathophysiological mechanisms.

Key words: uric acid, atrial fibrillation, hypertension, inflammation, oxidative stress

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Introduction

Atrial fibrillation (AF) is a rapidly evolving epidemic representing a multifactorial, dynamic disorder with different underlying substrates and serious health consequences (1). Hypertension is a well-known risk factor for AF and due to its high prevalence in the general population it increases the AF burden more than any other factor (1). 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 properties (2-7). Inflammation and oxidative stress have also been implicated in the pathophysiology of hypertension (8, 9).

On the other hand, uric acid (UA) has emerged as a simple and independent marker of morbidity and mortality in a variety of cardiovascular disease states (10, 11). Regardless of the debate whether it is a predictor or a causative factor, UA has been clearly associated with oxidative stress and inflammation in several pathological conditions (12-16). Thus,

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in this pilot observational study we sought to investigate the association between AF and UA levels in patients with essential hypertension as well as the relative impact of other conventional risk markers. Our aim was to examine this association in hypertensive patients without significant comorbidities and associated cardiovascular conditions that markedly affect UA levels and also, without marked underlying atrial structural remodeling.

Patients and Methods

Study population

In this cross-sectional study we recruited consecutive patients with essential hypertension with or without a history of AF seen in the Department of Cardiology of our hospital between January 2005 and December 2007. Hypertension was diagnosed as blood pressure levels ≥140/90 mmHg (mean of 3 measurements) in the supine position or the use of antihypertensive medications. The arrhythmia diagnosis required documentation from an official medical record, a 12-lead ECG, or a 24-hour Holter recording and its classification was based on authoritative international consensus statements (17). Exclusion criteria were history of coronary artery disease, valvular heart disease, congenital heart disease, cardiomyopathy, left ventricular systolic dysfunction, left atrial (LA) diameter >55 mm, previous cardiac surgery, diabetes, thyroid disease, serum creatinine >110 μmol/L, recent infection, autoimmune or inflammatory diseases, respiratory diseases, administration of drugs that affect UA metabolism (apart from diuretics), and consumption of alcoholic beverages. The study was approved by the ethics committee of the Second Hospital of Tianjin Medical University and written informed consent was obtained from all patients.

Study protocol

All baseline demographic and clinical characteristics were carefully recorded. A transthoracic echocardiographic examination was performed in all patients using the Vivid-7 system equipped with a 2.4 MHz transducer (GE Medical Systems, Milwaukee, WI, USA). Parasternal long- and short-axis, apical four chamber, and two chamber views were obtained. LA diameter (LAD), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT) and left ventricular end-diastolic diameter (LVEDD) were assessed. Left ventricular ejection fraction (LVEF) was determined from apical four-chamber and two-chamber views using Simpson's biplane formula. All echocardiographic data were analyzed by the same investigator who was blind to the clinical status of the participants. Moreover, laboratory examinations including complete blood count and blood chemistries were performed at the fasting state. In patients with paroxysmal AF, a blood sample was drawn for examination when the patient was in sinus rhythm for at least one week. The white blood cell (WBC) count was determined using a Coulter counter. As a measure of renal function, the baseline glomerular filtration was estimated (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) Study Equation (18): eGFR (mL/min/1.73 m^2 of body surface area) =186× (serum creatinine in mg/dL)$^{-1.154}$× (age in years)$^{-0.203}$×0.742 in female subjects. UA levels were measured by uricase enzymatic test (Toshiba TBA 120FR chemistry analyzer, Toshiba Medical Systems, Otawara-shi Tochigi, Japan). Normal range of uric acid levels: 208-420 μmol/L for men, 155-357 μmol/L for women. All measurements were performed blindly to the patients' characteristics and treatment.

Statistical analysis

Continuous variables are presented as mean ± SD and categorical variables as percentages. The normality of the distribution of each variable was tested by the Kolmogorov-Smirnov test. Statistical analysis was performed using the Student's t-test for continuous variables while the Chi-square test was used to compare categorical variables. The relationship between variables was analyzed with Pearson correlation coefficients. Multivariable logistic regression analysis was used to examine the association between the candidate risk factors and AF. Variables which were significantly associated with AF on univariate analysis were inserted into a stepwise multiple logistic regression analysis. A p value of <0.05 was considered statistically significant. All data were analyzed using SPSS 11.5 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA).

Results

Four hundred fifty-one patients were finally included in the analysis while 50/451 (11.1%) had AF (paroxysmal AF: 38; persistent AF: 8; permanent AF: 4). The characteristics of the study population according to the presence or absence of AF are presented in Table 1. There were no significant differences between the two groups regarding sex (males 54% vs 49%), hypertension classification, systolic and diastolic blood pressure, WBC Count, hyperlipidemia, fasting blood glucose, potassium level, LVEDD, and LVEF. There were also no statistical differences between the two groups in terms of the medical drug therapies such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), diuretics, β-blockers, statins, and calcium channel blockers. Compared with the patients without AF, patients with AF were older (61.8±9.2 vs 54.9±12.1 years, $p<0.001$), had a longer duration of hypertension (11.7±9.6 vs 6.6±8.3 years, $p<0.001$), higher serum Cr levels (88.9±26.6 vs 77.0±22.5 μmol/L, $p=0.001$), decreased eGFR levels (112.69±33.4 vs 138.6±65.0 mL/min/1.73 m^2, $p<0.001$), higher UA levels (368.9±100.7 vs 314.6±92.9 μmol/L, $p<0.001$), increased LAD (41.2±7.6 vs 33.7±5.6 mm, $p<0.001$), IVST (12.2±3.9 vs 10.0±2.5 mm, $p<0.001$), and LVPWT ($p=0.004$). In univariate analysis, age, duration of hypertension, serum Cr, serum UA levels, LAD, IVST, and LVPWT were significantly elevated in patients with AF

Table 1. Baseline Clinical and Echocardiographic Characteristics of Study Population

Characteristics	AF (n=50)	non-AF (n=401)	p value
Clinical features			
Age(years)	61.8±9.2	54.9±12.1	**<0.001**
Male/Female(n)	27/23	196/205	0.495
Classification of Hypertension*			
Grade1/Grade2/Grade3(n)	5/14/31	67/116/218	0.420
Duation of Hypertension (Years)	11.7±9.6	6.6±8.3	**<0.001**
SBP(mmHg)	143.0±20.1	150.5±28.2	0.071
DBP(mmHg)	85.9±13.9	89.6±16.5	0.139
Current smoking(n,%)	11(22.0%)	102(25.4%)	0.597
Laboratory examinations			
WBC Count(10*9/L)	6.5±1.9	7.2±2.2	0.052
Cr(μmol/L)	88.9±26.6	77.0±22.5	**0.001**
eGFR(mL/min/1.73 m^2)	112.6±34.4	138.6±65.0	**<0.001**
UA(μmol/L)	368.9±100.7	314.6±92.9	**<0.001**
Potassium (mmol/L)	4.2 ±0.4	4.1 ±0.5	0.531
Albumin (g/L)	40.1±3.5	41.9±18.6	0.506
Globulin (g/L)	26.0±4.8	26.9±15.7	0.712
Total cholesterol (mmol/L)	4.7±1.1	5.1±2.7	0.293
HDL-c(mmol/L)	1.2±0.3	1.2±0.3	0.225
LDL-c(mmol/L)	3.0±1.0	3.1±0.9	0.441
Triglycerides(mmol/L)	1.6±0.7	1.98±1.9	0.145
Fasting glucose(mmol/L)	5.3±0.8	5.3±0.7	0.762
Echocardiogram variables			
IVST(mm)	12.2±3.9	10.0±2.5	**<0.001**
LVPWT(mm)	12.1±4.4	10.27±3.7	**0.004**
LAD(mm)	41.2±7.6	33.7±5.6	**<0.001**
LVEDD(mm)	47.4±5.1	46.4±5.1	0.261
LVEF(%)	60.2±8.4	61.1±8.1	0.535
Drug therapy			
ACEIs/ARBs(n,%)	37(74.0%)	277(69.1%)	0.475
Diuretics(n,%)	9(18.0%)	47(11.7%)	0.204
Statins(n,%)	31(62.0%)	242(60.3%)	0.822
Beta-blockers(n,%)	18(36.0%)	198(49.4%)	0.074
CCBs (n,%)	20(40.0%)	221(55.1%)	0.043

*Classification of Hypertension is according to the 2007 Guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

AF=atrial fibrillation; SBP= Systolic blood pressure; DBP = diastolic blood pressure; WBC=white blood cells; Cr=creatinine; eGFR=estimated glomerular filtration rate, UA= Uric Acid; HDL-c=high-density lipoprotein; LDL-c=low-density lipoprotein; IVST= interventricular septum thickness; LVPWT=left ventricular posterior wall thickness; LAD= left atrial diameter; LVEDD=left ventricular end-diastolic diameter; LVEF=left ventricular ejection fraction; ACEIs=angiotensin-converting enzyme inhibitors; ARBs=angiotensin receptor blocking agents; CCBs=calcium channel blockers.

compared to non-AF patients, while eGFR level was much lower in patients with AF than in those without AF. Pearson's correlation analysis showed that there were positive correlations between LAD and IVST (r=0.59, p<0.001), LAD and LVPWT (r=0.40, p<0.05).

The association between UA and AF was further assessed by multivariate logistic regression analysis after adjusting for age, hypertension duration, Cr, eGFR, IVST, and LVPWT. This analysis showed independent associations between AF and UA (OR: 1.008; 95% CI: 1.003-1.013, p= 0.002), and LAD (OR: 1.160; 95% CI: 1.068-1.260; p< 0.001) (Table 2).

Discussion

In the present study we demonstrated an independent association between UA levels and AF in hypertensive patients. More specifically, the presence of AF in hypertensive patients was associated with an increased LA size and elevated serum levels of UA. Increased LA size is a well-known factor that facilitates the initiation and perpetuation of AF and is related to atrial remodeling (1, 19-21).

A large body of evidence indicates that, apart from the triggers, AF development and perpetuation depends on the electrophysiological and structural remodeling of the atria (22). Recent studies have demonstrated the implication of inflammation and oxidative stress in the pathophysiology

Table 2. Multivariate Logistic Regression Analysis on Predictors of Atrial Fibrillation

	B	SE	Wald	p	OR	95% CI
Age (years)	-0.037	0.046	0.659	0.417	0.964	0.881-1.054
HBP duration (years)	0.037	0.020	3.582	0.580	1.038	0.999-1.079
Cr (μmol/L)	0.002	0.011	0.220	0.882	1.002	0.981-1.023
eGFR (mL/min/1.73 m^2)	-0.023	0.012	3.356	0.067	0.978	0.954-1.002
UA (μmol/L)	0.008	0.003	9.780	0.002	1.008	1.003-1.013
LAD (mm)	0.148	0.042	12.307	0.000	1.160	1.068-1.260
IVST (mm)	0.080	0.079	1.020	0.313	1.083	0.928-1.265
LVPWT (mm)	0.014	0.054	0.070	0.792	1.014	0.913-1.127

HBP=hypertension; Cr=creatinine; eGFR=estimated glomerular filtration rate; UA=Uric Acid; HDL-c=high-density lipoprotein; LDL-c=low-density lipoprotein; LAD=left atrial diameter; IVST=interventricular septum thickness; LVPWT=left ventricular posterior wall thickness.

of AF although it is not clear yet whether these processes are a cause or consequence (2-7). In particular, inflammatory indexes, mainly CRP, have been related to future AF development, AF persistence, recurrence after cardioversion, LA enlargement, and the associated prothrombotic state (2-7). Additionally, studies in animals and humans have directly demonstrated that AF is associated with increased oxidative stress (4). Recently, Neuman et al by means of multivariate analysis demonstrated an independent association between persistent or permanent AF and markers of oxidative stress while this was not the case with respect to the inflammatory markers (23).

Current epidemiological evidence suggests that serum UA 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. UA is a metabolic product of purine metabolism produced via the action of xanthine oxidase, an enzyme that is implicated in oxidative processes (10, 13). Thus, UA represents a marker of oxidative stress and inflammation but, depending on the cellular environment, it may exert antioxidant or pro-oxidant effects (12-14).

Data regarding the association between AF and UA are scarce. One very recent small observational study demonstrated an independent association between UA and permanent AF (24). UA levels were also increased in paroxysmal AF patients compared to control subjects, but this association was not significant after multivariate analysis (24). Although persistent AF patients were not included in the analysis it could be speculated that UA elevation is related to the AF burden (24). Interestingly, a large epidemiological study (ARIC study) very recently showed that serum UA is an independent predictor of incident AF in middle-aged individuals (25). Importantly, there was an interaction between race and UA in the development of AF since the hazard ratio of AF for black subjects was 1.56 [95%CI 1.28-1.90] compared to 1.05 [95%CI 0.95-1.11] for whites (25).

In the present study, we included patients with essential hypertension. Hypertension is a well-established risk factor for AF and is often accompanied by other metabolic abnormalities associated with AF such as diabetes, obesity, metabolic syndrome. We excluded patients with diabetes or other cardiovascular disorders in order to avoid potential effects of these abnormalities on the levels of UA or on atrial remodeling. Although a cause-effect relationship has not been firmly established, accumulating evidence links UA elevation with hypertension (26). More specifically, epidemiological data indicates that elevated UA consistently predicts the development of hypertension, while elevated UA levels are observed in 25-60% of patients with untreated essential hypertension (26). Moreover, reducing UA levels with xanthine oxidase inhibitors lowers blood pressure in adolescents with recent-onset hypertension (26). It should also be noted that the relation between UA and cardiovascular risk is observed not only with pathologic hyperuricemia but with UA levels in the high normal range as well (26). Also, we have to acknowledge that the present study patients with AF had higher levels of eGFR. Therefore, a deficient excretion of UA in these subjects may have contributed to the increased UA levels.

It is unclear whether UA participates actively in the atrial remodeling or it 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 before, UA 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 (27). Consequently, the increased oxidative stress may aggravate cellular damage promoting the remodeling process (4). On the other hand, given that UA exhibits antioxidant activity both in vitro and in vivo, its elevation could represent a compensatory protective mechanism against oxidative damage (12).

Study Limitations

In the present study there are several potential limitations.

First, we did not exclude the patients who were taking diuretics, drugs that affect uric acid metabolism. However, the number of patients taking diuretics was small and also there was no significant difference between the two groups. *Secondly*, most of the AF patients had paroxysmal AF (76%) and therefore we could not perform a separate analysis for the different types of AF. *Thirdly*, specific inflammatory and oxidative stress markers were not assessed. *Fourthly*, the observational design of the study identifies only an association and not causality. Moreover, due to the observational design only a single UA measurement was available. Although LA size seems to reflect left ventricular diastolic dysfunction, we do not have data on other specific indexes of ventricular diastolic function. Furthermore, we do not provide data on the body mass index (BMI) which is related to LA size. *Finally*, there are no data on the exact AF burden (number of episodes, duration).

Conclusion

In conclusion, we showed that UA levels are associated with AF in hypertensive patients. 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 hypertension to reduce the AF burden constitutes a subject for future research.

The authors state that they have no Conflict of Interest (COI).

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The first 2 authors contributed equally to this study.

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