The association between hyperuricemia and left atrial enlargement in healthy adults

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Background: Although hyperuricemia (HU) has been reported to be related to atrial fibrillation (AF), the relationship between HU and left atrial (LA) enlargement is unclear. The aim of this study was to investigate the interaction between HU and LA enlargement in healthy adults in China.

Methods: This study retrospectively surveyed 5,392 people (3,336 males and 2,056 females) who underwent health checks. Basic data were obtained from all participants, including baseline characteristics and general health status through laboratory tests, echocardiography, and interviews. Multinomial logistic regression was used to analyze the experimental data and determine the association between HU and LA enlargement. In addition, the relationship between HU and LA enlargement in different gender groups was analyzed.

Results: The prevalence of HU in this study was 20.3%. Compared with the normal LA group, the prevalence of HU in the LA enlargement group was significantly higher [31.5% vs. 18.1%; P<0.001; odds ratio (OR) =2.09, 95% confidence interval (CI): 1.78–2.45]. After adjustment for confounding variables, the interrelation of HU on LA enlargement was found to be independent in the total participants (OR =1.25, 95% CI: 1.04–1.51; P=0.017), especially in women (OR =1.73; 95% CI: 1.10–2.74; P=0.019) but not in men (P=0.195).

Conclusions: HU is independently associated with LA enlargement in healthy adults, especially in women.

Keywords: Hyperuricemia (HU); uric acid; left atrium; atrial remodeling

Submitted Apr 30, 2021. Accepted for publication Jul 15, 2021.
doi: 10.21037/atm-21-3402
View this article at: https://dx.doi.org/10.21037/atm-21-3402

Introduction

One of the most common clinical types of arrhythmia is atrial fibrillation (AF). Patients with AF are 5 times more likely to have a stroke, and AF approximately doubles the risk of death (1) and can also cause heart failure. In addition, patients with hyperuricemia (HU) are more likely to develop paroxysmal or persistent AF and have an increased risk of AF after cardiovascular surgery. The reason for this phenomenon may be based on the inflammation or oxidative stress of the disease (2). The most important aspects in the process of AF are electrical remodeling and structural remodeling, with inflammation and oxidative stress also being significant factors (3-6). However, structural remodeling may aggravate the extent of left atrial (LA) enlargement, which is critical in the progression of AF (7). Meanwhile, several researchers have reported high serum uric acid (SUA) level to be significantly correlated with enlarged LA size and HU to be associated with a larger LA diameter (8,9).

In order to examine the development of HU and AF, it
is essential to explore the atrial remodeling caused by HU. However, previous experimental studies have not confirmed the connection between HU and LA enlargement in large sample size. Thus, this study aimed to understand the interaction between HU and LA enlargement in a relatively large healthy adults in China and analyze any potential sex differences.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-3402).

**Methods**

**Study population**

All subjects underwent routine examinations and echocardiography in the First Affiliated Hospital of Wenzhou Medical University from January 2015 to December 2017. The patients’ general physical condition, height, weight and body mass index (BMI), blood pressure (BP), past history, and drug use history were recorded. According to expert consensus and standard on weight management for overweight or obese status in China, a BMI greater or equal to 24 kg/m$^2$ and less than 28 kg/m$^2$ is considered overweight, while a BMI greater or equal to 28 kg/m$^2$ is considered obese. A total of 6,909 participants were screened, with 1,517 being excluded based on the following exclusion criteria: (I) cardiovascular disease type, including congestive heart failure, congenital heart diseases, cardiomyopathy, coronary heart disease, and AF; (II) anemia; (III) thyroid dysfunction; (IV) history of malignant tumor; (V) history of rheumatic immune system disease; and (VI) ingestion of diuretics or other drugs that can increase SUA. Finally, 5,392 subjects in this experiment (3,336 males and 2,056 females) were included. The participants in this study were divided into an LA enlargement group and a normal LA group. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board (IRB) of the first affiliated hospital of Wenzhou Medical University (No. 2020107). Individual consent for this retrospective analysis was waived.

**Data collection and diagnostic definition**

After patients fasted for 8 hours, blood samples were collected from the median cubital vein and analyzed. An automatic biochemical analyzer (Beckman Coulter AU5800, USA) was then used to analyze biochemical indicators such as SUA, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG) and serum creatinine (Scr). Definition of HU: in a normal purine diet, fasting SUA level is higher than 420 μmol/L in men and higher than 360 μmol/L in women, or taking xanthine oxidase inhibitors (10). BP measurements were taken according to Hypertension Canada’s 2016 guidelines (11). BP was measured by a trained medical staff using auscultatory or automatic electronic sphygmomanometers (HEM-705CP, Omron, Kyoto, Japan). An ultrasound system (Vivid E95, GE Healthcare, Amersham, UK) was used for echocardiography. Degree of LA enlargement and left ventricular ejection fraction were determined from M-mode images following a standardized imaging protocol. LA enlargement was considered to be LA diameter >40 mm, and normal LA was considered to be LA diameter ≤40 mm (12).

**Statistical analysis**

SPSS 19.0 software (IBM Corporation, Armonk, NY, USA) was used for data analysis. Measurement data are expressed as mean ± standard deviation and were compared with t test or one-way analysis of variance (ANOVA). If the variable was normally distributed, a $\chi^2$ test or Fisher’s exact test was used; otherwise, the Mann-Whitney U test was performed. The associations between HU and LA enlargement were analyzed through multiple logistic regression. The results are reported with odds ratios (ORs) and 95% confidence intervals (CIs). A P value <0.05 indicated that the difference in component data was statistically significant.

**Results**

**Participant characteristics**

Table 1 contains the general demographic and clinical information of the participants. Table 2 shows the comparison of demographic and clinical information between men and women. Out of the 5,392 subjects, 891 (16.5%) were diagnosed with LA enlargement. There were significant differences between the LA enlargement group and normal LA group in age, prevalence of HU, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), SUA, TG, HDL-C, FPG, Scr, and history of
hypertension and diabetes (P<0.001). However, there were no differences in the TC and LDL-C between the control group and the study group.

**HU was related to the incidence of LA enlargement**

In this study, patients with HU accounted for 20.3% of the total sample size, and the prevalence of HU in LA enlargement group was significantly higher than in normal LA group (31.5% vs. 18.1%; P<0.001; Table 1). In univariate analysis, the experimental results showed that subjects with HU had an increased incidence of LA enlargement (OR =2.09, 95% CI: 1.78–2.45; P<0.001) compared with subjects without HU (Table 3). Other risk factors, such as age, BMI, SBP, DBP, TG, HDL-C, FPG, and SCr were significantly associated with LA enlargement (P<0.001). No correlation was found between TC, LDL-C and LA expansion. After adjustments for the above clinical and biochemical covariates were made, correlation was still found between HU and LA enlargement in the total sample size (OR =1.25, 95% CI: 1.04–1.51; P=0.017; Table 3).

**The association between HU and LA enlargement in gender subgroup analysis**

Table 4 and Table 5 show the association between HU and LA enlargement in the gender subgroup analysis. In the univariate analysis, HU was significantly related to LA enlargement in women (OR =3.53, 95% CI: 2.35–5.26; P<0.001) and in men (OR =1.48, 95% CI: 1.24–1.77; P<0.001), respectively. Other risk factors, such as age, BMI, SBP, DBP, TG, HDL-C and FPG, were significantly associated with LA enlargement in both men and women (P<0.05). LDL-C was associated with LA enlargement in women (P=0.027). After adjustment for the above confounding factors, HU and LA expansion still remained independent in women (OR =1.73, 95% CI: 1.10–2.74; P=0.019), but this relationship was not found in men (OR =1.14, 95% CI: 0.93–1.40; P=0.195).

**Discussion**

Our findings suggest that HU is independently associated
Table 2 Demographic and clinical characteristics of the LA enlargement group and the normal LA group by gender

| Variables       | Men (n=3,336) | Women (n=2,056) | P value | Men (n=3,336) | Women (n=2,056) | P value |
|-----------------|---------------|-----------------|---------|---------------|-----------------|---------|
|                 | LA enlargement (n=714) | Normal LA (n=2,622) |         | LA enlargement (n=177) | Normal LA (n=1,879) |         |
| Hyperuricemia, n (%) | 243(34.0) | 677(25.8) | <0.001 | 38(21.5) | 136(7.2) | <0.001 |
| Age (years)     | 52.58±10.79 | 46.40±11.05 | <0.001 | 58.70±10.77 | 47.70±10.97 | <0.001 |
| BMI (kg/m²)     | 26.90±2.76 | 23.94±2.95 | <0.001 | 26.18±2.88 | 22.60±2.94 | <0.001 |
| SBP (mmHg)      | 135.70±17.83 | 127.28±17.07 | <0.001 | 140.66±19.01 | 121.19±19.49 | <0.001 |
| DBP (mmHg)      | 80.71±12.19 | 76.53±12.03 | <0.001 | 75.78±12.07 | 69.54±12.03 | <0.001 |
| SUA (μmol/L)    | 392.12±80.06 | 376.57±79.95 | <0.001 | 304.62±70.19 | 272.52±60.37 | <0.001 |
| TC (mmol/L)     | 5.33±1.03 | 5.37±1.14 | 0.398 | 5.35±1.05 | 5.23±1.07 | 0.180 |
| TG (mmol/L)     | 2.34±1.88 | 2.09±1.92 | 0.002 | 1.70±0.76 | 1.34±0.92 | <0.001 |
| HDL-C (mmol/L)  | 1.15±0.24 | 1.23±0.28 | <0.001 | 1.30±0.29 | 1.47±0.33 | <0.001 |
| LDL-C (mmol/L)  | 3.17±0.83 | 3.22±0.85 | 0.195 | 3.22±0.86 | 3.07±0.87 | 0.027 |
| FPG (mmol/L)    | 5.28±1.47 | 4.96±1.36 | <0.001 | 5.50±1.63 | 4.84±1.04 | <0.001 |
| Creatinine (μmol/L) | 73.04±11.97 | 73.32±11.80 | 0.528 | 55.13±18.66 | 53.70±18.14 | 0.316 |

LA, left atrium; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose.

Table 3 Univariate and multivariate analyses for LA enlargement in all participants

| Variables                          | Univariate analysis | Multivariate analysis |
|------------------------------------|---------------------|-----------------------|
|                                    | Crude OR (95% CI)   | P value               |
|                                    | Adjusted OR (95% CI)| P value               |
| Gender, male vs. female            | 0.34 (0.29–0.41)    | <0.001                |
|                                    | 0.48 (0.39–0.59)    | <0.001                |
| Hyperuricemia, yes vs. no          | 2.09 (1.78–2.45)    | <0.001                |
|                                    | 1.25 (1.04–1.51)    | 0.017                 |
| Age (years), ≥50 vs. <50           | 2.63 (2.27–3.05)    | <0.001                |
|                                    | 2.59 (2.18–3.07)    | <0.001                |
| BMI (kg/m²), ≥24 vs. <24           | 4.18 (3.73–4.69)    | <0.001                |
|                                    | 3.56 (3.14–4.04)    | <0.001                |
| SBP (mmHg), ≥140 vs. <140          | 2.62 (2.24–3.05)    | <0.001                |
|                                    | 1.59 (1.33–1.89)    | <0.001                |
| DBP (mmHg), ≥90 vs. <90            | 2.09 (1.73–2.52)    | <0.001                |
|                                    | 0.99 (0.78–1.26)    | 0.942                 |
| TC (mmol/L)                        | 1.02 (0.95–1.09)    | 0.612                 |
|                                    | –                   | –                     |
| TG (mmol/L)                        | 1.14 (1.09–1.18)    | <0.001                |
|                                    | 0.94 (0.89–0.99)    | 0.020                 |
| HDL-C (mmol/L)                     | 0.18 (0.14–0.24)    | <0.001                |
|                                    | 0.49 (0.35–0.67)    | <0.001                |
| LDL-C (mmol/L)                     | 1.04 (0.95–1.13)    | 0.401                 |
|                                    | –                   | –                     |
| FPG (mmol/L)                       | 1.22 (1.17–1.28)    | <0.001                |
|                                    | 1.07 (1.02–1.14)    | 0.013                 |
| Creatinine (μmol/L)                | 1.019 (1.015–1.024) | <0.001                |
|                                    | 1.00 (0.99–1.00)    | 0.411                 |

OR, odds ratio; CI, confidence interval; LA, left atrium; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose.
### Table 4: Univariate and multivariate analyses for LA enlargement in women

| Variables                      | Univariate analysis | Multivariate analysis |
|--------------------------------|---------------------|-----------------------|
|                                | Crude OR (95% CI)   | P value               | Adjusted OR (95% CI) | P value |
| Hyperuricemia, yes vs. no      | 3.53 (2.35–5.26)    | <0.001                | 1.73 (1.10–2.74)     | 0.019   |
| Age (years), ≥50 vs. <50       | 4.57 (3.20–6.52)    | <0.001                | 2.59 (1.74–3.87)     | <0.001  |
| BMI (kg/m²), ≥24 vs. <24       | 4.15 (3.31–5.19)    | <0.001                | 3.16 (2.47–4.04)     | <0.001  |
| SBP (mmHg), ≥140 vs. <140      | 3.92 (2.85–3.58)    | <0.001                | 1.83 (1.27–2.64)     | 0.001   |
| DBP (mmHg), ≥90 vs. <90        | 2.24 (1.39–3.61)    | 0.001                 | 1.28 (0.72–2.27)     | 0.398   |
| TC (mmol/L)                    | 1.10 (0.96–1.27)    | 0.180                 | –                     | –       |
| TG (mmol/L)                    | 1.33 (1.18–1.51)    | <0.001                | 0.83 (0.68–1.00)     | 0.065   |
| HDL-C (mmol/L)                 | 0.17 (0.10–0.29)    | <0.001                | 0.28 (0.14–0.53)     | <0.001  |
| LDL-C (mmol/L)                 | 1.21 (1.02–1.43)    | 0.027                 | 0.90 (0.73–1.11)     | 0.316   |
| FPG (mmol/L)                   | 1.38 (1.25–1.52)    | <0.001                | 1.23 (1.10–1.37)     | <0.001  |
| Creatinine (μmol/L)            | 1.01 (1.00–1.03)    | 0.064                 | –                     | –       |

OR, odds ratio; CI, confidence interval; LA, left atrium; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose.

### Table 5: Univariate and multivariate analyses for LA enlargement in men

| Variables                      | Univariate analysis | Multivariate analysis |
|--------------------------------|---------------------|-----------------------|
|                                | Crude OR (95% CI)   | P value               | Adjusted OR (95% CI) | P value |
| Hyperuricemia, yes vs. no      | 1.48 (1.24–1.77)    | <0.001                | 1.14 (0.93–1.40)     | 0.195   |
| Age (years), ≥50 vs. <50       | 2.50 (2.12–2.97)    | <0.001                | 2.65 (2.19–3.20)     | <0.001  |
| BMI (kg/m²), ≥24 vs. <24       | 3.81 (3.33–4.37)    | <0.001                | 3.77 (3.26–4.36)     | <0.001  |
| SBP (mmHg), ≥140 vs. <140      | 2.25 (1.89–2.69)    | <0.001                | 1.49 (1.22–1.82)     | <0.001  |
| DBP (mmHg), ≥90 vs. <90        | 1.71 (1.39–2.10)    | <0.001                | 0.95 (0.73–1.24)     | 0.713   |
| TC (mmol/L)                    | 0.97 (0.90–1.04)    | 0.398                 | –                     | –       |
| TG (mmol/L)                    | 1.06 (1.02–1.10)    | 0.003                 | 0.97 (0.92–1.02)     | 0.212   |
| HDL-C (mmol/L)                 | 0.33 (0.24–0.47)    | <0.001                | 0.66 (0.45–0.95)     | 0.025   |
| LDL-C (mmol/L)                 | 0.94 (0.85–1.03)    | 0.195                 | –                     | –       |
| FPG (mmol/L)                   | 1.16 (1.10–1.22)    | <0.001                | 1.03 (0.96–1.10)     | 0.402   |
| Creatinine (μmol/L)            | 1.00 (0.99–1.01)    | 0.525                 | –                     | –       |

OR, odds ratio; CI, confidence interval; LA, left atrium; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose.
with LA enlargement in healthy adults, and after adjustments were made for various clinical and biochemical characteristics, HU was found to greatly increase the risk of LA enlargement in women. The link between HU and LA has not been demonstrated in studies that use gender as an independent variable before. Thus our study aimed to further investigate the relationship between HU and LA enlargement in different gender in a relatively large cohort.

Recent studies have reported the connection between SUA and LA size. Letsas et al. (8) conducted a study consisting of 86 AF and 48 non-AF patients, and demonstrated that SUA level was significantly related to LA diameter and SUA elevation was a predictor of permanent AF. However, the sample size was very small and was not from a healthy population. Moreover, AF itself may promote atrial remodeling (13), which may interfere with the measurement of the LA diameter. Chao et al. (9) demonstrated that SUA was positively correlated with LA size and HU was associated with a larger LA diameter. Consistent with these results, our study found a significant correlation between HU and LA enlargement in healthy adult participants even after adjusting for various clinical and biochemical characteristics. Therefore, HU is a significant risk factor for the prevalence of LA enlargement. Structural modeling can lead to LA enlargement, which plays a vital role in the management of AF (7). Thus, our results revealed atrial remodeling caused by HU might partially explain the reason why HU is independently associated with the occurrence of paroxysmal or persistent AF (8,9,14-16).

The association between HU and AF may possibly be explained by their relationship with inflammation or oxidative stress (2). It is understood that the increased risk of AF may be related to the behavior of inflammation regulating atrial electrophysiology and structural substrates (17). Inflammation promotes LA enlargement and atrial fibrosis, which can cause AF through atrial conduction disturbance (18). Other studies have reported that the process by which HU causes inflammation is actually through inducing protein expression in cells and activating uric acid transporter (UAT) (19-21). It has been reported that renin-angiotensin-aldosterone system (RAAS) may induce atrial inflammation (22). Some experimental evidence has indicated that SUA may stimulate the circulating and local RAAS in the cardiovascular system (23,24). Xanthine oxidoreductase (XOR) has also been investigated in a number of studies in relation to its critical role in the pathogenesis of AF. A canine model studying left ventricular dysfunction found that xanthine oxidase inhibitors can prevent AF (25). Another study in mice indicated that an increase of SUA can lead to cardiomyocyte hypertrophy and the weakening of myocardial relaxation tension, mainly as a result of an increase in xanthine oxidase activity in heart tissue. These conditions were improved with allopurinol treatment (26). These results may offer an explanation for the relationship between HU and cardiac structure remodeling. In short, the accumulation of uric acid in cardiomyocytes may lead to ion and structural remodeling of the atria, and UATs can mediate atrial remodeling by regulating the concentration of uric acid in the cells.

The Atherosclerosis Risk in Communities (ARIC) study (27) demonstrated a link between race and gender differences with HU and AF, with LA enlargement being more obvious among those of Black race or female sex. After adjusting for other covariates, Suzuki et al. (28) found that the level of SUA only affects AF in women; however, the authors could not determine the underlying mechanisms. In this study, the association between HU and LA enlargement remained independent in women after considering confounding variables, but not in men, suggesting that HU is specifically associated with an increased risk of LA enlargement in women. Another study found HU was independently associated with endothelial dysfunction in post-menopausal, but not pre-menopausal women (29). Consistent with the findings of the above study, our results indicated that HU is independently associated with LA enlargement in women age 50 years or older. This suggests that HU could be an independent risk factor for LA enlargement, particularly in post-menopausal women. Therefore, our results may explain the gender differences in the association of elevated SUA with AF risk. Further study is warranted to explain this connection and explore the potential mechanisms.

Our results showed that in addition to HU, independent variables such as age, BMI, BP, TG, HDL-C, FPG and SCr were related to LA enlargement in total sample size (Table 3). Therefore, in patients age 50 years or older, especially with metabolic syndrome such as obesity, hypertension, hypertriglyceridemia, low HDL-C, and DM, we recommend monitoring and maintaining SUA levels below the upper limit of normal. Specific diets, keep healthy weight and increase physical activity, and uricosuric anti-hypertensive drugs (losartan) can be used as first choice therapy in these patients; diuretics should be avoided.

Some limitations to our study should be addressed.
First, due to the cross-sectional design employed, follow-up research is needed to evaluate the relationships we identified more accurately. Second, this study was single center in nature, and the selection of samples could have been biased towards the Chinese population. Therefore, more prospective clinical trials are needed to verify the influence between HU and LA enlargement in different regions and races. Finally, further prospective studies are needed to determine whether the treatment of HU can improve atrial remodeling and then reduce the occurrence and development of AF.

**Conclusions**

Our research shows that HU is independently connected to LA enlargement in healthy adults and specifically associated with an increased risk of LA enlargement in women.

**Acknowledgments**

**Funding:** This study was supported by grants from the Wenzhou Municipal Sci-Tech Bureau’s program (No. Y2020315).

**Footnote**

**Reporting Checklist:** The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-3402

**Data Sharing Statement:** Available at https://dx.doi.org/10.21037/atm-21-3402

**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-3402). The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Institutional Review Board (IRB) of the first affiliated hospital of Wenzhou Medical University approved the research protocol (No. 2020107) and individual consent for this retrospective analysis was waived.

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(English Language Editors: G. Stone and J. Gray)