Uric Acid and Left Ventricular Hypertrophy in Japanese Men

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Background: Experimental studies have reported that allopurinol protects hypertensive rats from left ventricular hypertrophy (LVH) with negligible effects on blood pressure (BP). Uric acid (UA) was thought to induce cardiomyocyte growth and interstitial fibrosis of the heart, partly via activation of the renin–angiotensin system. In the present study, the relationship between serum UA levels and electrocardiographically-diagnosed LVH (ECG-LVH) was examined in Japanese men not taking medication for hypertension (HTN), which could confound the association.

Methods and Results: A total of 3,305 male workers aged 35–66 years (mean age±SD, 48.0±7.1) were studied. LVH was defined as meeting the ECG criteria (ie, Sokolow-Lyon voltage and/or Cornell voltage QRS duration product). Subjects were divided into 3 groups by tertile of serum UA level. The highest tertile (UA range 0.39–0.65 mmol/L or 6.6–11.0 mg/dl) had a significantly increased prevalence of LVH compared with the lowest tertile independent of age, body mass index, serum creatinine level, HTN, diabetes and hyperlipidemia (odds ratio 1.58, 95% confidence interval 1.23–2.02, P<0.001). Similar results were obtained in both the normal and high BP subgroups.


Key Words: Electrocardiography; Epidemiology; Left ventricular hypertrophy; Uric acid

Uric acid (UA) is produced in the terminal stage of purine metabolism catalyzed by xanthine oxidase, and is a primary cause of gout. The relationship between serum UA and cardiovascular diseases has been, however, controversial. One recent experimental study demonstrated that allopurinol, a xanthine oxidase inhibitor, prevented cardiac hypertrophy in rats with negligible effects on blood pressure (BP). In humans, an elevated blood level of UA was reportedly associated with left ventricular hypertrophy (LVH) in hypertensive patients. However, the hypertensive state may have confounded or modified the association because it could be related to both LVH and the UA level. In addition, because some antihypertensive drugs are reported to reduce LVH or to affect the UA level, assessing the association only in those not on hypertension medication was warranted to clarify the role of UA as an independent risk factor for LVH.

The prevalence of LVH has been reported as approximately 20% in adult Japanese men. LVH diagnosed by electrocardiography (ECG-LVH), as well as that diagnosed by echocardiography, is known to increase the risk of cardiovascular morbidity and mortality. Although a major determinant of LVH is elevated BP, a previous report has indicated LVH in approximately 10% of the normotensive population. Thus, studies to find other risk factors are warranted.

In the present study, we investigated the association between UA and LVH in subjects not taking medication for hypertension (HTN). Moreover, we also investigated the association by stratifying subjects by BP, which might modify the association.

Methods

Study Population
This study used baseline data collected in 2002 for a workers’ cohort study on cardiovascular diseases in Aichi, Japan. The questionnaires were returned from 7,991 people, of whom 6,651 (83.2%) expressed their written consent to the use of the information. Consent for the use of data obtained during their annual health examination and to donate residual blood samples used for the examination was obtained from 5,596 (70.0%) and 4,213 (52.7%) people, respectively. In this analysis, we first restricted the subjects to men with available information on weight, height, BP, ECG, UA and other biomarker concentrations (3,773 men), because of the small number of women with...
LVH in this sample. We then excluded those who had been on medical treatment for HTN (n=274), hyperuricemia (n=130) or both (n=47). We further excluded subjects with ECG findings relevant to a history of myocardial infarction (n=4) and complete bundle branch block (n=13) under which a diagnosis of ECG-LVH is not reliable. Leaving 3,305 men aged 35–66 years who were eligible for the present analysis. The study protocol was approved by the Ethics Review Committee of the Nagoya University School of Medicine.

**ECG**

Standard 12-lead ECGs were recorded at a paper speed of 25 mm/s and 1 mV/cm standardization. Every ECG was read independently by 2 experienced investigators blinded to the information of the health checkup according to a slightly modified 1982 revision of the Minnesota Code. QRS duration and voltage of R waves in leads aVL, V5 (RV5) and V6 (RV6), and S waves in leads V1 (SV1) and V3 (SV3) were measured manually by a third cardiologist. LVH in this study was defined using a combination of the Cornell product and the Sokolow-Lyon voltage. The Cornell product and the Sokolow-Lyon voltage were obtained by the formulae: Cornell voltage (RaVL + SV1) and the Sokolow-Lyon voltage. The Cornell product was defined using a combination of CoVL and RV5. The Sokolow-Lyon voltage was defined using a combination of SV1 + RV5.

**UA Concentration**

Participants underwent an annual health checkup including blood testing at several quality-assured institutes. Venous blood samples were withdrawn from each subject after 8-hour or overnight fast. Serum UA concentrations were determined either at the institute immediately by uricase peroxidase system or centrally at a commercial laboratory using samples stored at ~80°C by the enzyme assay (EA) system. The latter, which comprised 59% of the present dataset, was used for UA level determination in subjects whose UA concentrations had not been obtained during the health check up. The UA level, as well as the interassay coefficient of variation (CV) of the stored samples, did not differ systematically from those measured during the health check-up (UA level: both 0.36 mmol/L (6.0 mg/dl), P=0.78; CV%: 0.39% vs 0.55%, respectively).

**Clinical Features and Other Laboratory Measurements**

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters, both of which were obtained in the standing position during the annual health checkup. Overweight was defined as BMI ≥25 kg/m². Otherwise subjects were regarded as normal weight. BP measurements were obtained while seated, after at least five min of rest, by auscultation with an appropriate arm cuff and a mercury column manometer in 34% of the subjects analyzed, and automatic sphygmomanometer (BP-103N II; Omron-Colin Co, Tokyo, Japan) in 66% of the subjects. HTN was defined as systolic BP (SBP) ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg. The following items were determined: creatinine (Creat) (EA system 74%, Jaffe’s method 26%), total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C) (Lipids: EA system) and fasting blood glucose (FBG) (EA system 5%, hexokinase ultraviolet absorption spectrophotometry system 95%). Diabetes mellitus (DM) was defined as either TG ≥3.9 mmol/L (150 mg/dl),

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**Table 1. Baseline Characteristics of the Study Sample According to UA Tertile**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Lowest (n=1,109)</th>
<th>Middle (n=1,123)</th>
<th>Highest (n=1,073)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>UA range (mmol/L)a</td>
<td>0.03–0.32</td>
<td>0.33–0.38</td>
<td>0.39–0.65</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>48.8 (48.3–49.2)</td>
<td>47.9 (47.5–48.3)</td>
<td>47.4 (47.0–47.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.5 (22.3–22.7)</td>
<td>23.1 (22.9–23.2)</td>
<td>23.9 (23.8–24.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>124.7 (123.9–125.5)</td>
<td>126.4 (125.6–127.2)</td>
<td>128.3 (127.4–129.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>76.9 (76.5–77.5)</td>
<td>78.5 (77.9–79.2)</td>
<td>80.4 (79.7–81.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UA, mmol/La</td>
<td>0.281 (0.279–0.283)</td>
<td>0.360 (0.359–0.361)</td>
<td>0.440 (0.436–0.441)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creat, μmol/L</td>
<td>78.2 (77.5–79.1)</td>
<td>82.0 (81.2–82.9)</td>
<td>85.0 (84.1–85.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>5.27 (5.22–5.32)</td>
<td>5.42 (5.37–5.47)</td>
<td>5.56 (5.51–5.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG, mmol/Lb</td>
<td>2.63 (2.55–2.71)</td>
<td>2.86 (2.78–2.95)</td>
<td>3.53 (3.41–3.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C, mmol/Lb</td>
<td>1.42 (1.40–1.44)</td>
<td>1.39 (1.37–1.41)</td>
<td>1.31 (1.29–1.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FBG, mmol/L</td>
<td>5.40 (5.33–5.46)</td>
<td>5.27 (5.22–5.32)</td>
<td>5.32 (5.28–5.36)</td>
<td>0.003</td>
</tr>
<tr>
<td>HTN, n (%)</td>
<td>182 (16.4)</td>
<td>221 (19.7)</td>
<td>250 (23.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>97 (8.7)</td>
<td>58 (5.2)</td>
<td>51 (4.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HL, n (%)</td>
<td>312 (28.1)</td>
<td>376 (33.5)</td>
<td>516 (48.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVH, n (%)</td>
<td>155 (14.0)</td>
<td>188 (16.7)</td>
<td>211 (19.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All means (age, BMI, SBP, DBP and TC) and geometric means (UA, Creat, TG, HDL-C and FBG) are expressed with 95% CI. HTN, DM, HL and LVH are expressed as n, %.

*Differences in mean values were tested by 1-way analysis of variance and differences in the proportions were tested by chi-square test.

a UA, uric acid; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Creat, creatinine; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; FBG, fasting blood glucose; HTN, hypertension; DM, diabetes mellitus; HL, hyperlipidemia; LVH, left ventricular hypertrophy; CI, confidence intervals.
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Table 2. Association Between UA Tertile and Prevalence of LVH by Multivariate Logistic Regression Analysis (n=3,305)

<table>
<thead>
<tr>
<th>UA tertile</th>
<th>Crude OR (95%CI)</th>
<th>P value</th>
<th>Model 1* OR (95%CI)</th>
<th>P value</th>
<th>Model 2† OR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest</td>
<td>1 (reference)</td>
<td>1.00</td>
<td>1 (reference)</td>
<td>1.00</td>
<td>1 (reference)</td>
<td>1.00</td>
</tr>
<tr>
<td>Middle</td>
<td>1.24 (0.98–1.56)</td>
<td>0.071</td>
<td>1.29 (1.02–1.64)</td>
<td>0.035</td>
<td>1.28 (1.01–1.63)</td>
<td>0.043</td>
</tr>
<tr>
<td>Highest</td>
<td>1.51 (1.20–1.89)</td>
<td>&lt;0.001</td>
<td>1.61 (1.26–2.06)</td>
<td>&lt;0.001</td>
<td>1.58 (1.23–2.02)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for institute, age, BMI, HTN and log-transformed Creat.
†Adjusted for institute, age, BMI, HTN, DM, HL and log-transformed Creat.

Table 3. Association Between UA Tertile and the Prevalence of LVH in the Sample Stratified by Presence of HTN (n=3,305)

<table>
<thead>
<tr>
<th>UA tertile</th>
<th>No. of LVH (%)</th>
<th>Crude OR (95%CI)</th>
<th>P value</th>
<th>Trend P</th>
<th>Model 1* OR (95%CI)</th>
<th>P value</th>
<th>Model 2† OR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest</td>
<td>155/1,109 (14.0)</td>
<td>1 (reference)</td>
<td>1.51 (1.20–1.89)</td>
<td>&lt;0.001</td>
<td>1.61 (1.26–2.06)</td>
<td>&lt;0.001</td>
<td>1.58 (1.23–2.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Middle</td>
<td>188/1,123 (16.7)</td>
<td>1.24 (0.98–1.56)</td>
<td>0.071</td>
<td>1.29 (1.02–1.64)</td>
<td>0.035</td>
<td>1.28 (1.01–1.63)</td>
<td>0.043</td>
<td></td>
</tr>
<tr>
<td>Highest</td>
<td>211/1,073 (19.7)</td>
<td>1.51 (1.20–1.89)</td>
<td>&lt;0.001</td>
<td>1.61 (1.26–2.06)</td>
<td>&lt;0.001</td>
<td>1.58 (1.23–2.02)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

GM-C ≥4.1 mmol/L (160 mg/dl), and/or medical treatment for HL.20

Statistical Analysis

Because the distributions of UA, TG, Creat and HDL-C were skewed, a natural log-transformed value was used for the subsequent analyses to approximately normalize the distributions. These log-transformed continuous variables were expressed as geometric means with 95% confidence intervals (CI). Other continuous variables were expressed as simple means with the 95% CI. Subjects were divided into 3 categories by the tertile of their serum UA level. Comparisons of continuous variables among the 3 categories were performed by 1-way analysis of variance, and categorical variables by the χ² test. The odds ratios (OR) and their 95% CI of LVH according to UA level were calculated by multivariate logistic regression analysis adjusting for known confounding factors such as age, BMI21 Creat22 and HTN in addition to the institute (model 1), and by potential confounding factors such as HL23,24 and DM (model 2)25,26. We conducted the model-2 analysis using samples stratified by BP. We added SBP as an adjustment factor in this analysis. Test for trend in which each UA tertile (lowest, middle and highest) was regarded as continoul variable (1, 2 and 3), was also conducted to examine the linear association between the UA tertiles and ECG-LVH. In addition, the same analyses were conducted with different criteria of ECG-LVH. A P-value <0.05 was considered statistically significant. All analyses and calculations were performed using the statistical package SPSS 12.0 J for Windows (Chicago, IL, USA).

Results

The mean age of the present sample was 48.0±6.1 years (range 35–65). BMI ranged from 15.1 to 35.8 kg/m² (mean 22.3 kg/m²); SBP ranged from 84 to 191 mmHg (mean 127.6 mmHg); serum UA levels ranged from 0.03–0.65 mmol/L (0.5–11.0 mg/dl); mean 0.35 mmol/L (6.0 mg/dl)). The intertertile range was 0.33–0.38 mmol/L (5.6–6.5 mg/dl).

Baseline characteristics of the study sample according to serum UA tertile are shown in Table 1. Significant differences among the 3 tertiles were found in age, BMI, SBP, DBP, Creat, TC, TG, HDL-C, FBG, and the prevalence of HTN, DM and HL. The prevalence of ECG-LVH was 16.9%; in the lowest, middle, and the highest UA tertiles it was 14.0%, 16.8%, and 19.7%, respectively (P<0.001, 2 test).

In model 1, the OR of ECG-LVH in the highest tertile relative to the lowest tertile was 1.61 (95% CI 1.26–2.06, P<0.001) (Table 2). Adjustment for the other potential confounding factors (model 2) did not materially alter the association (OR of the highest tertile =1.58, 95% CI 1.23–2.02, P<0.001, OR of the middle tertile: 1.28, 95% CI 1.01–1.63, P=0.042). The associations between ECG-LVH and DM or HL were not significant (DM: OR=0.76, P=0.18, HL: OR=1.09, P=0.43), whereas there was a strong association with HTN (OR=2.40, P<0.001). The ORs of LVH in the highest tertiles compared to the lowest tertiles were 1.43 (95% CI 1.06–1.92, P=0.020) in the normal BP group (n=2,652) and 1.68 (1.07–2.64, P=0.025) in the high BP group (n=653) in the model 2 analysis (Table 3). Significant linear associations between the UA tertiles and ECG-LVH were also observed in each group (trend P=0.022 and 0.021, respectively). In addition, including subjects on HTN medication in the hypertensive group and subjects on hyperuricemia medication in the highest UA tertile did not materially alter the findings; that is, the OR of the highest UA tertile, which included subjects on UA medication in the normotensive group was 1.45 (P=0.012), and that in the hypertensive group, which also included subjects on UA medication, was 1.75 (P=0.012).

The same analyses without including subjects on HTN or UA medications were also conducted by dividing the sample into normal and overweight groups. The OR of ECG-LVH in the highest tertile was 1.69 (95% CI 1.27–2.25, P=0.001) in the normal weight group (n=2,530), but was not statistically significant in the overweight group (n=775) (OR: 1.21, 95% CI 0.73–1.99, P=0.46).

The change in the definition of ECG-LVH (Table 4) did not materially alter the findings; that is, the OR of the highest UA tertile (UA medication) was 1.58 (95% CI 1.23–2.02, P=0.001) (Table 2).
not substantially influence the present findings; that is, Minnesota code (OR: 1.40, 95% CI 1.11–1.76, P=0.004), the Sokolow Lyon voltage (OR: 1.50, 95% CI 1.12–2.01, P=0.006), QRS duration (OR: 1.58, 95% CI 1.02–2.47, P=0.044) or Cornell product (OR: 1.48, 95% CI 1.02–2.14, P=0.039).

Discussion

The present study revealed a significant and positive relationship between high serum UA and ECG-LVH in apparently healthy Japanese men. Overall, the association was independent of age, degree of obesity, renal function, HTN and other potential confounding factors, including DM and HL. This finding is consistent with the results of an experimental study that have reported allopurinol-treated rats developing significantly less cardiac hypertrophy with negligible effects on BP, and is also in agreement with the current understanding of the association as observed in small samples of hypertensive patients. We have demonstrated the association in more detail in a large sample of apparently healthy individuals not taking medication for HTN, and have also revealed a significant independent association in normotensive as well as hypertensive subjects.

We excluded subjects under medical treatment for HTN, and analyzed the association using a normal-BP and a high-BP sample in an attempt to minimize the confounding effects of BP and medication for HTN. The significant association between UA and LVH revealed in subjects with normal BP is thought to suggest that a higher UA level may be causally associated with the development of LVH. Incidentally, inclusion of subjects on HTN or UA medication did not materially change the association between UA tertile and ECG-LVH (OR of the highest UA tertile to the lowest: 1.49, 95% CI 1.20–1.87, P<0.001).

In addition, other evidence may support this causal relationship. UA is reported to inhibit the generation of nitric oxide, thus inducing endothelial dysfunction and smooth muscle cell proliferation by activating inflammatory mediators such as tumor necrosis factor-alpha and mitogen-activated protein kinases. UA is also capable of activating the renin–angiotensin system, which is thought to mediate the development of LVH through the following mechanisms. Angiotensin II induces hypertrophy and hyperplasia of myocytes and vascular smooth muscle cells, and may also regulate collagen synthesis. Excess production of angiotensin II influences the expression of fibrogenic cytokine, and may induce perivascular and interstitial fibrosis. Aldosterone stimulates extracellular collagen deposition, and may promote myocardial fibrosis.

In the present study, we could not find a significant association between UA and ECG-LVH in subjects with a high BMI. One possible reason may be the lower sensitivity of the ECG for detecting LVH in subjects with high BMI, which would have distorted the association toward null. Although we used a combination of criteria that are known to have the highest sensitivity at a given high specificity as 95% CI 2.94–5.81, P<0.001) compared with the group exhibiting neither of them, after adjusting for age, BMI, Creat, DM and HL. Considering the result that the group with HTN, but not hyperuricemia, had only a 2.2-fold higher prevalence of ECG-LVH and that there is a significant interaction between the 2 conditions (P=0.048), an improvement in the control of either BP or UA level might be clinically effective for the prevention of LVH.

We also confirmed the association in a multivariate-adjusted model using the log-transformed estimated glomerular filtration ratio instead of log-transformed Creat (model 2), because both the UA level and LVH have been reported to have an association with renal function (OR: 1.57, 95% CI 1.22–2.00, P<0.001). Moreover, because other factors such as insulin resistance smoking habit...
and exercise? in this study, we repeated the analyses adding HOMA-IR, smoking status or exercise to the adjustment factors in a sub-sample with the information (n=1,925) (OR; 1.50, 95%CI 1.08–2.07, P=0.016).

The LVH prevalence in each UA tertile adjusted for age, BMI, log-transformed Creat, HTN, HL, and DM by logistic regression analysis was 14.0, 17.1 and 20.1%, respectively. From the point of view of public health, supposing the causality between high UA and LVH, (20.1–14.0)/20.1=30.3% of the LVH in the highest tertile, was attributable to the high UA concentration, it could thus be prevented if the UA level was as low as in the lowest tertile.

**Study Limitations**

Certain methodological issues must be addressed. First, serum UA levels were not obtained in a single laboratory at the same time; however, there were no systematic differences in the mean UA level or the inter-assay CV% among them. We have also confirmed the finding by stratifying the analyses by the test conditions, as well by analysis with statistical adjustment for the test institute. Second, although the present study revealed a significant positive association of ECG-LVH with the serum UA level, this findings should be confirmed by a prospective cohort study using echocardiography, or among females and other ethnic groups.

In conclusion, the serum UA level was positively, independently and significantly associated with ECG-LVH in both normotensive and hypertensive male Japanese subjects. Future studies to confirm the causality are warranted and our findings would justify a study of whether interventions to decrease the UA level in LVH patients may alleviate LVH.

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**References**


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