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Relation of uric acid levels to aortic root dilatation in hypertensive patients with and without metabolic syndrome*

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Abstract: Objective: Uric acid (UA) is considered to be a powerful predictor of cardiovascular risk and hyperuricemia might be involved in the metabolic syndrome (MS). This study aims to investigate the relation between UA levels and aortic root dilatation. Methods: A total of 348 hypertensive patients [age (67.5±9.8) years] with or without MS were included in the study. The aortic root diameters at the aortic annulus, the sinuses of Valsalva, the sinotubular junction, and the proximal part of the ascending aorta were measured using a two-dimensional (2D) echocardiography. Serum UA levels were also measured for all patients. Results: A high UA level is independently associated with aortic root diameters at the sinuses of Valsalva (P=0.001) and the proximal ascending aorta (P<0.0001) in the hypertensive patients without MS. In contrast, aortic root diameters were not significantly related to UA levels in the hypertensive patients with MS. Furthermore, increased UA levels were associated with an increased risk for aortic root dilatation in the patients without MS (sex-adjusted hazard ratio 1.75, 95% confidence intervals (CI) 1.27–2.41), but not in those with MS. Conclusions: This study demonstrated an independent relationship between the aortic root dimensions and increased levels of serum UA in the hypertensive patients without MS. Further understanding of the mechanisms underlying these associations may allow a clearer interpretation of the potential value of specific urate-lowering treatment on cardiovascular disease.

Key words: Aortic root, Uric acid, Hypertension, Metabolic syndrome
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1 Introduction

Aortic root dilatation is frequently associated with aortic valve regurgitation, aneurysm, and dissection of the thoracic aorta (Roman *et al*., 1987; Eisenberg *et al*., 1993). A recent study showed that aortic root dimension was also predictive of incident congestive heart failure, stroke, cardiovascular disease mortality, and all-cause mortality (Gardin *et al*., 2006). Furthermore, aortic root dilatation has been observed more frequently in hypertensive than in normotensive individuals and was reported to be correlated with cardiac and extracardiac target organ damage in hypertensive patients (Kim *et al*., 1996; Cuspidi *et al*., 2006).

Uric acid (urate, UA), the final oxidation product of purine catabolism in humans, is considered to be a powerful predictor of cardiovascular risk and poor outcome, although the underlying machanisms remain unclear (Hjortnaes *et al*., 2007; Sui *et al*., 2008). Hypertensive patients with hyperuricemia have a

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3–5-fold increased risk of coronary or cerebrovascular disease compared to hypertensive patients with normal UA levels (Verdecchia *et al*., 2000). It has also been hypothesized that hyperuricemia might be involved in the metabolic syndrome (MS) (Hjortnaes *et al*., 2007).

To date, little information is available on the relationship between UA levels and aortic root dilatation. The purpose of this study was to determine the relationship between UA levels and aortic root dilatation in hypertensive patients. We also evaluated whether this relationship was dependent or not on the presence of the MS.

2 Patients and methods

2.1 Study population

The study population consisted of 348 consecutive hypertensive patients admitted for cardiovascular risk factor control or cardiovascular disease screening (Coats, 2009). The age of the enrolled subjects ranged from 43 to 97 years with a mean age of (67.5±9.80) years.

Diagnosis of MS was made according to the modified Asian criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) (Tan *et al*., 2004). Hyperuricemia was defined as serum UA concentration >7.0 mg/dl in men or >6.0 mg/dl in women (Sui *et al*., 2008). Exclusion criteria for study subjects included secondary causes of hypertension, connective tissue disease, cardiomyopathy, congestive heart failure, congenital heart disease, active cancer, infective endocarditis, syphilitic aortitis, rheumatic heart disease, and documented coronary artery disease. Subjects with significant abnormalities including aortic stenosis, bicuspid aortic valve, other valvular abnormality, and wall motion abnormality on echocardiographic evaluation were also excluded. Patients defined as smokers were those who had been smoking at least 10 cigarettes per day for at least five years. Heavy drinking was defined as average alcohol consumption ≥30 g/d.

2.2 Ultrasound evaluation

All participants underwent two-dimensional (2D) mode and Doppler echocardiographies performed by an experienced research echocardiographer using a Vivid 7 digital ultrasound system (GE Vingmed Ultrasound, Horten, Norway). The dimensions of the aortic roots and ascending aorta were evaluated by 2D echocardiography. Aortic root dimension was assessed at end-diastole in the parasternal long axis view at the four levels using previously described techniques (Kim *et al*., 1996): (1) aortic annulus, (2) maximal diameter of the sinuses of Valsalva, (3) supra-aortic ridge (sinotubular junction), and (4) maximal diameter of the proximal ascending aorta. Measurements were taken on up to four separate cycles and averaged. The largest diameter of all measurements was accepted as the aortic root dilatation. The reproducibility of the aortic root dimension measurements was evaluated in 35 patients within two weeks of the first echocardiography examination. The correlation coefficient for aortic root diameters was 0.95–0.98. The aorta root was defined as dilated when its diameter was measured ≥ 38 mm (Karakaya *et al*., 2006).

2.3 Laboratory studies

At the time of enrolment, non-fasting plasma glucose concentrations were measured for all the participants of the study. Antecubital venous blood samples were collected from all subjects after fasting overnight. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), UA, creatinine, and fasting glucose concentrations were performed by commercially available standardized methods. Oral glucose tolerance tests were performed as described by the World Health Organization (WHO), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water (Tan *et al*., 2004).

2.4 Data analysis and statistical methods

An SPSS 11.5 software package was used for statistical analysis. Data were expressed as mean± standard deviation (SD) for continuous variables and as percentages for discrete variables. Differences between groups were assessed using analysis of variance (ANOVA) test for continuous variables and chi-square test for categorical variables. The strength of the relationship of each aortic root measurement with gender, age, body size, UA, and other clinical variables was evaluated by the Pearson's correlation coefficient and linear regression. Multiple linear

regression was used to evaluate the influence of UA on aortic root dimensions. Logistic regression was used to investigate potential independent risk factors for aortic root dilatation. $P<0.05$ was considered for statistical significance.

3 Results

3.1 Basic characteristics of the study population

Clinical characteristics of the 348 subjects are presented according to tertiles of serum UA levels in Table 1. There were 190 men [(64.2±10.1) years] and 158 women [(70.2±8.66) years]. Overall, 10.4% of the study population had aortic root dilatation. Although there was no significant difference in serum UA levels between MS patients [(5.20±1.78) mg/dl] and non-MS patients [(5.17±1.67) mg/dl], hyperuricemia was more prevalent (38 of 194, 19.6%) in subjects with MS than in those without MS (18/154, 11.7%) (P=0.046).

3.2 Correlation of uric acid and aortic root dimensions in patients with and without metabolic syndrome

Aortic root diameters at all levels were significantly related to sex and body surface area (BSA) ($P<0.05$, Table A1). As indicated in Table 2, no significant correlations between UA levels and aortic root diameters were found in the patients with MS. In contrast, bivariate correlation analysis showed that UA levels correlated significantly ($P<0.0001$) with the measured mean values at each site of the aortic root in the hypertensive patients without MS ($P<0.05$). The correlations of UA and the diameters at the sinuses of Valsalva and the ascending aorta still achieved statistical significance when adjusted for age, gender, and BSA ($P<0.01$). Age, gender, and BSA adjusted mean diameter according to UA tertiles was shown in Fig. 1.

After further analysis of the relationship between aortic root diameters and other variables (including blood pressure, lipid levels, creatinine, smoking, heavy drinking, antihypertensive therapy, and diabetes mellitus) in non-MS patients (Table A2), only diastolic blood pressure (DBP) was found to be significantly related with the diameter at the sinuses of Valsalva ($P<0.05$), and heavy drinking with the diameters at the supra-aortic ridge and ascending aorta ($P<0.05$). In multiple regression analysis with age, sex, BSA, DBP, and heavy drinking entered as variables, UA remains the independent predictor of the diameters at the sinuses of Valsalva (coefficient (β): 0.538, standard error (SE): 0.160, P=0.001) and

Table 1 Characteristics of the study population (n=348) according to uric acid tertiles

Variables	Tertiles of serum uric acid*			P
	T1 (n=114)	T2 (n=119)	T3 (n=115)	
Uric acid range/median (mg/dl)	1.50–4.42/3.45	4.46–5.78/5.06	5.80–12.10/6.76	
Average age (year)	65.6±9.5	66.0±9.9	70.9±9.2	0.284
Males	40 (35.1%)	69 (58.0%)	81 (70.4%)	<0.0001
Body mass index (kg/m^2)	22.7±2.75	24.0±3.06	24.0±3.58	0.363
Body surface area (m^2)	1.67±0.13	1.78±0.14	1.77±0.15	0.001
Systolic blood pressure (mmHg)	152.0±24.0	148.0±22.6	147.0±22.5	0.151
Diastolic blood pressure (mmHg)	87.9±12.4	85.8±11.3	84.2±15.8	0.089
Pulse pressure (mmHg)	62.4±18.6	60.1±16.4	58.9±17.2	0.718
Triglycerides (mg/dl)	1.61±0.99	1.91±1.05	1.74±0.82	0.015
Total cholesterol (mg/dl)	4.87±1.25	4.73±0.84	4.80±1.01	0.505
HDL-cholesterol (mg/dl)	1.06±0.31	1.01±0.22	1.04±0.26	0.017
LDL-cholesterol (mg/dl)	3.09±1.00	2.89±0.70	3.02±0.99	0.112
Creatinine (μmol/L)	76.8±9.2	90.1±14.6	100.8±16.8	<0.0001
Uric acid (mg/dl)	3.44±0.74	5.05±0.37	7.05±1.36	<0.0001
Dyslipidemia	82 (71.9%)	88 (74.0%)	78 (67.8%)	0.570
Anti-hypertensive therapy	49 (43.0%)	52 (43.7%)	56 (48.7%)	0.637
Diuretics therapy	8 (7.0%)	4 (3.4%)	3 (2.6%)	0.213
Diabetes mellitus	24 (21.1%)	32 (26.9%)	22 (19.1%)	0.334
Smoking (current or past)	8 (7.0%)	25 (21.0%)	33 (28.7%)	<0.0001
Heavy drinking (current or past)	10 (8.8%)	11 (9.2%)	23 (20.0%)	0.017
Metabolic syndrome	62 (54.4%)	70 (58.8%)	62 (53.9%)	0.709

* Values are expressed as mean±SD or n (%). HDL: high-density lipoprotein; LDL: low-density lipoprotein; T1: Tertile 1

Table 2 Correlations between serum uric acid levels and aortic root dimension

Population	Aortic annulus		Sinuses of Valsalva		Supra-aortic ridge		Ascending aorta	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Entire population (*n*=348)								
Univariate unadjusted analyses	0.047	0.383	0.058	0.281	0.108	0.045	0.174	0.001
Univariate adjusted analyses[#]	−0.091	0.092	−0.140	0.009	−0.073	0.179	0.058	0.283
Hypertensive patients with MS (*n*=194)								
Univariate unadjusted analyses	0.022	0.765	−0.037	0.609	0.060	0.406	0.079	0.272
Univariate adjusted analyses[#*]	−0.109	0.134	−0.304	0.100	−0.214	0.210	−0.105	0.150
Hypertensive patients without MS (*n*=154)								
Univariate unadjusted analyses	0.182	0.024	0.304	0.000	0.225	0.005	0.355	0.000
Univariate adjusted analyses[#]	0.077	0.349	0.222	0.006	0.135	0.099	0.289	0.000

[#] Adjusted for age, gender, and BSA; [*] $P>0.05$ for every level of aortic root when adjusted for age, gender, and height

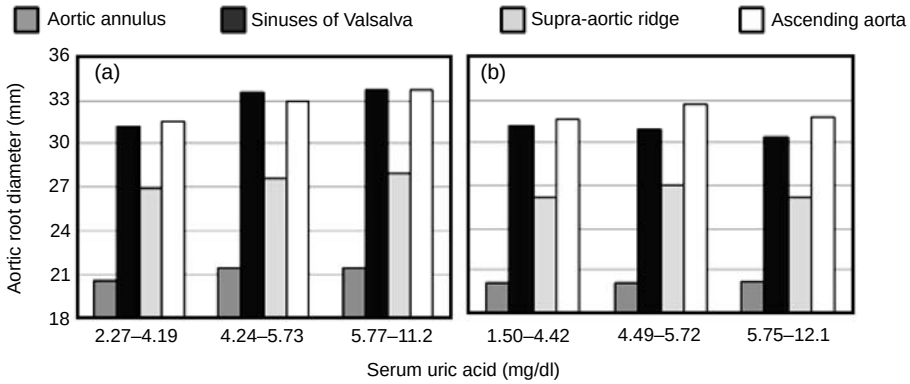

Fig. 1 Age, gender, and BSA adjusted mean diameters in patients without (a) and with (b) MS according to uric acid tertiles

ascending aorta (coefficient (β): 0.556, SE: 0.154, $P<0.0001$). In patients with MS (Table A3), aortic root diameters were associated with blood pressure at each level except for the diameter of the aortic annulus. Furthermore, the dimension of the ascending aorta was negatively associated with TC and LDL-C, and positively associated with heavy drinking, independent of age, sex, and height (the anthropometric variable resulting in the best model) ($P<0.05$).

3.3 Frequency of aortic root dilatation in the study population

Aortic root dilatation was more prevalent in the patients without MS (24 of 154, 15.6%) than in the patients with MS (12 of 194, 6.2%) ($P=0.004$). Increased UA concentrations were associated with the risk for aortic root dilatation in patients without the MS (sex-adjusted hazard ratio 1.75, 95% confidence intervals (CI) 1.27–2.41). In contrast, there was no significant association between UA levels and aortic root dilatation in the patients with the MS ($P=0.996$).

Although hyperuricemia was more prevalent in the patients with MS than in the patients without MS, among these hyperuricemia subjects, the aortic root was more frequently enlarged in non-MS patients (8 of 18, 44.5%) than in MS patients (2 of 38, 5.26%) ($P<0.0001$).

4 Discussion

In the present study, we show that a high UA level is independently associated with aortic root diameters at the sinuses of Valsalva and the proximal ascending aorta in hypertensive subjects without MS. In contrast, aortic root diameters at all levels were not significantly related with UA levels in those with MS. Furthermore, increased UA concentrations were associated with an increased risk for aortic root dilatation in hypertensive patients without MS, but not in those with MS.

It has been shown that modest elevations of

serum UA can produce subtle glomerulotubular damage that, in turn, activates the renin-angiotensin system (RAS), which could be reversed by removal of the hyperuricemic stimulus. Hyperuricemia has also been shown to produce renovascular constriction and to correlate with activity of the RAS (Saito *et al*., 1978; Sanchez-Lozada *et al*., 2002; Johnson *et al*., 2003). On the other hand, there is increasing evidence from in vitro studies that local production of angiotension II may contribute to the development of aortic aneurysm pathologies. Results obtained from pharmaceutical intervention in humans and animals of these systems strongly support this hypothesis (Habashi *et al*., 2006; Lu *et al*., 2008). Therefore, the activation of the RAS by the elevation of serum UA could be a possible mechanism through which UA might be responsible for aortic root enlargement. Further study of the role of UA in aortic root dilatation development is needed.

UA has been demonstrated to be a strong and independent predictor of incident MS (Verdecchia *et al*., 2000; Hjortnaes *et al*., 2007). Our study documents that increased levels of UA are associated with aortic root dilatation risk in non-MS patients, in contrast to patients with MS in whom elevated UA is not associated with an increased risk for aortic root enlargement. Among those hyperuricemia subjects, the aortic root was more frequently enlarged in non-MS patients than in MS patients. Interestingly, it was recently reported by Hjortnaes *et al*. (2007) that elevated serum UA levels are not an independent risk factor for vascular disease in patients with the MS. In patients with the MS, elevated serum UA levels were associated with increased risk for vascular disease including abdominal aortic aneurysm. Similarly, Ishizaka *et al*. (2005) also showed UA levels are associated with carotid plaque independently of other atherogenic risk factors in men without MS or in women in general. These findings might be explained by UA being a vascular risk factor already accounted for by the presence of other risk factors clustering in the MS. Although hyperuricemia is well recognized as a risk factor for cardiovascular diseases such as coronary artery disease and stroke, the independence of this association from other confounding factors remains controversial (Verdecchia *et al*., 2000; Hjortnaes *et al*., 2007; Sui *et al*., 2008).

Our results should be interpreted in light of the limitation that the study population consisted exclusively of Chinese subjects; as a result, it is uncertain whether these findings are generalizable in other ethnic groups. On the other hand, there is no common definition for aortic root dilatation (Roman *et al*., 1989; Cuspidi *et al*., 2007). Therefore, the cutoff point (≥38 mm) in the present study might be arbitrary. Yet, the statistical results for the association of UA levels and aortic root dilatation of our study did not change when the other standards for aortic root enlargement were used.

In conclusion, this is the first study in hypertensive patients without MS that has demonstrated an independent relationship between the aortic root dimensions and increased levels of serum UA. The lack of association between serum UA and aortic root dimensions in patients with MS could indicate that the observed association between UA and aortic root dimensions may be attributed to MS-dependent and -independent mechanisms. Further understanding of the mechanisms underlying these associations may allow a clearer interpretation of the potential value of specific urate-lowering treatment on cardiovascular disease.

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Appendixes

Table A1 Correlations between age, gender, body habitus, and aortic root dimension

Variables	Aortic annulus		Sinuses of Valsalva		Supra-aortic ridge		Ascending aorta	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Entire population (*n*=348)								
Age	0.023	0.674	0.205	0.000	0.149	0.005	0.162	0.000
Male	0.399	0.000	0.504	0.000	0.497	0.000	0.321	0.000
Height*	0.253	0.000	0.180	0.001	0.220	0.000	0.148	0.006
Weight*	0.087	0.107	0.116	0.032	0.133	0.013	0.139	0.010
Body mass index*	0.004	0.941	0.068	0.204	0.074	0.171	0.107	0.047
Body surface area*	0.129	0.016	0.140	0.009	0.164	0.002	0.154	0.004
Hypertensive patients with MS (*n*=194)								
Age	−0.007	0.926	0.246	0.001	0.254	0.000	0.291	0.000
Male	0.323	0.000	0.463	0.000	0.516	0.000	0.315	0.000
Height*	0.282	0.000	0.282	0.000	0.389	0.000	0.310	0.000
Weight*	0.161	0.026	0.135	0.062	0.156	0.030	0.069	0.340
Body mass index*	0.070	0.333	0.047	0.515	0.028	0.696	−0.046	0.523
Body surface area*	0.202	0.005	0.179	0.013	0.220	0.002	0.125	0.083
Hypertensive patients without MS (*n*=154)								
Age	−0.049	0.546	0.079	0.332	−0.017	0.838	−0.013	0.874
Male	0.413	0.000	0.494	0.000	0.445	0.000	0.310	0.000
Height*	0.248	0.000	0.081	0.032	0.075	0.359	−0.016	0.850
Weight*	0.119	0.144	0.174	0.032	0.046	0.150	0.256	0.001
Body mass index*	0.032	0.697	0.176	0.030	0.172	0.034	0.332	0.000
Body surface area*	0.160	0.049	0.169	0.037	0.157	0.053	0.218	0.007

*Adjusted by age and gender

Table A2 Correlations between risk factors and aortic root dimension in hypertensive patients without MS*

Variables	*P* value							
	Aortic annulus		Sinuses of Valsalva		Supra-aortic ridge		Ascending aorta	
	UA	A	UA	A**	UA	A**	UA	A**
Uric acid	0.024	0.349	0.000	0.006 (0.222)	0.005	0.099	0.000	0.000 (0.289)
Systolic blood pressure	0.553	0.340	0.201	0.842	0.416	0.512	0.367	0.976
Diastolic blood pressure	0.905	0.869	0.050	0.011 (0.207)	0.262	0.169	0.159	0.184
Pulse pressure	0.384	0.239	0.003	0.647	0.060	0.654	0.027	0.788
Triglycerides	0.020	0.101	0.069	0.165	0.154	0.268	0.089	0.217
Total cholesterol	0.056	0.995	0.965	0.093	0.633	0.061	0.890	0.212
HDL-cholesterol	0.019	0.146	0.034	0.212	0.238	0.759	0.245	0.525
LDL-cholesterol	0.123	0.689	0.972	0.080	0.515	0.136	0.830	0.462
Creatinine	0.032	0.500	0.000	0.365	0.018	0.974	0.128	0.629
Fast glucose concentration	0.398	0.652	0.798	0.438	0.968	0.616	0.760	0.915
Smoking	0.087	0.554	0.074	0.995	0.017	0.219	0.040	0.208
Heavy drinking	0.082	0.188	0.456	0.620	0.002	0.014 (0.199)	0.006	0.019 (0.191)
Antihypertensive therapy	0.388	0.430	0.887	0.450	0.470	0.312	0.697	0.743
Diuretics therapy	0.292	0.436	0.331	0.729	0.463	0.543	0.287	0.191
Diabetes mellitus	0.316	0.165	0.684	0.541	0.623	0.468	0.346	0.543
Dyslipidemia	0.356	0.658	0.584	0.298	0.630	0.958	0.589	0.829

* n=154. Univariate analyses: adjusted for age, gender, and BSA (the anthropometric variable resulting in the best model); ** The values in the parentheses are r. UA: unadjusted; A: adjusted; HDL: high-density lipoprotein; LDL: low-density lipoprotein

Table A3 Correlations between risk factors and aortic root dimension in hypertensive patients with MS*

Variables	*P* value							
	Aortic annulus		Sinuses of Valsalva		Supra-aortic ridge		Ascending aorta	
	UA	A**	UA	A**	UA	A**	UA	A**
Uric acid	0.765		0.609		0.406		0.272	
Systolic blood pressure	0.453	0.633	0.002	0.000 (0.265)	0.003	0.000 (0.269)	0.008	0.000 (0.255)
Diastolic blood pressure	0.423	0.631	0.108	0.061	0.003	0.000 (0.396)	0.027	0.000 (0.324)
Pulse pressure	0.091	0.297	0.003	0.032 (0.157)	0.104	0.558	0.086	0.259
Triglycerides	0.159	0.202	0.052	0.264	0.122	0.486	0.118	0.592
Total cholesterol	0.155	0.201	0.989	0.093	0.572	0.878	0.042	0.008 (−0.192)
HDL-cholesterol	0.002	0.025 (0.164)	0.117	0.754	0.251	0.649	0.154	0.401
LDL-cholesterol	0.185	0.681	0.962	0.228	0.210	0.826	0.007	0.004 (−0.210)
Creatinine	0.037	0.830	0.002	0.564	0.000	0.186	0.000	0.066
Fast glucose concentration	0.479	0.066	0.545	0.438	0.199	0.560	0.055	0.546
Smoking	0.023	0.905	0.050	0.306	0.006	0.679	0.040	0.459
Heavy drinking	0.174	0.806	0.007	0.472	0.011	0.766	0.003	0.052
Antihypertensive therapy	0.504	0.667	0.139	0.213	0.200	0.321	0.190	0.135
Diuretics therapy	0.220	0.912	0.130	0.456	0.145	0.236	0.251	0.126
Diabetes mellitus	0.163	0.746	0.225	0.806	0.046	0.181	0.134	0.320
Dyslipidemia	0.139	0.431	0.451	0.217	0.691	0.243	0.291	0.198

* n=194. Univariate analyses: adjusted for age, gender, and height (the anthropometric variable resulting in the best model); ** The values in the parentheses are r. UA: unadjusted; A: adjusted; HDL: high-density lipoprotein; LDL: low-density lipoprotein