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Peripheral arterial stiffness is associated with higher baseline plasma uric acid: A prospective cohort study

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Abstract This prospective cohort study aimed at identifying association between uric acid (UA) and peripheral arterial stiffness. A prospective cohort longitudinal study was performed according to an average of 4.8 years' follow-up. The demographic data, anthropometric parameters, peripheral arterial stiffness (carotid-radial pulse-wave velocity, cr-PWV) and biomarker variables including UA were examined at both baseline and follow-up. Pearson's correlations were used to identify the associations between UA and peripheral arterial stiffness. Further logistic regressions were employed to determine the associations between UA and arterial stiffness. At the end of follow-up, 1447 subjects were included in the analyses. At baseline, cr-PWV ($r = 0.200$, $p < 0.001$) was closely associated with UA. Furthermore, the follow-up cr-PWV ($r = 0.145$, $p < 0.001$) was also strongly correlated to baseline UA in Pearson's correlation analysis. Multiple regressions also indicated the association between follow-up cr-PWV ($\beta = 0.493$, $p = 0.013$) and baseline UA level. Logistic regressions revealed that higher baseline UA level was an independent predictor of arterial stiffness severity assessed by cr-PWV at follow-up cross-section. Peripheral arterial stiffness is closely associated with higher baseline UA level. Furthermore, a higher baseline UA level is an independent risk factor and predictor for peripheral arterial stiffness.

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1. Introduction

Hyperuricemia, a common clinical situation, has been demonstrated as an independent risk factor for cardiovascular diseases including arterial stiffening, atherosclerosis and hypertension (Chu et al., 2000; Iwashima et al., 2006; Katsiki et al., 2015). The abnormality of uric acid (UA) has also been

indicated to be associated with regional arterial stiffness in patients with chronic kidney disease and diabetes mellitus (DM) (Iwashima et al., 2006; Alderman, 2007; Santos, 2012; Zhao et al., 2013). The relationship between normal serum UA and arterial stiffness has also been well documented previously (Lin et al., 2012; Shin et al., 2012). Regarding the mechanism underlying arterial stiffness in which UA participates in, it is involved in thickening vessel wall (intima-media) *via* proliferation and differentiation of smooth muscle cells as well as dysfunction of endothelial cells (Bian et al., 2012; Elsurer and Afsar, 2014; Ishizaka et al., 2007; Zhang et al., 2014).

It is also demonstrated that arterial stiffness is a risk factor for or pre-pathophysiological processes of various cardiovascular and cerebra-vascular diseases (Sun, 2015). Presently, the pulse wave velocity (PWV) has been used as a reproducible and valid non-invasive gold standard indicator in the assessments of arterial stiffness (Covic and Siriopol, 2015; Laurent and Boutouyrie, 2007; Liu, 2013). Nevertheless, PWVs from different arteries usually represent stiffness in distinct regions in vasculature system (Jadhav and Kadam, 2005; Weber et al., 2015), such as carotid-radial PWV (cr-PWV) which is applied to assess stiffness in arterioles (Hughes et al., 2004).

Inconsistent results on associations between serum UA level and arterial stiffness have been reported before (Elsurer and Afsar, 2014; Mallamaci et al., 2015; Zhao et al., 2013). However, majority of them were performed primarily based on a basic disease such as DM, hypertension and chronic kidney disease (Elsurer and Afsar, 2014; Zhang et al., 2014) among various ethnic groups (Ishizaka et al., 2007; Liang et al., 2012; Lim et al., 2010; Kristina and Gooyers, 2016). However, there were few follow-up studies that have been performed to identify the roles of baseline level of UA in peripheral arterial stiffness. Thus, we postulated that the higher UA level may also play a critical role in increasing peripheral arterial stiffness and performed this follow-up observational study aiming at identifying the associations between UA level and peripheral stiffness evaluated by cr-PWV, to provide novel index for stratification and risk management of arterial stiffness.

2. Material and methods

### 2.1. Participants and procedures

A total of 1680 health check participants were recruited between September 2007 and January 2009 from Pingguoyuan area, the Shijingshan district in this community-based follow-up cohort study according to the inclusion and exclusion criteria. The exclusion criteria were listed as following: endocrine and metabolic diseases (except DM), infection, neoplastic or severe liver or renal diseases. The inclusion criteria were as follows: residents who received a routine health examination in the community.

2.2. Follow-up and outcome assessment

Our study was reviewed and approved by the ethics committee at People's Liberation Army General Hospital. The study was thoroughly explained to all of the subjects who agreed to par-

ticipate, and all of the subjects signed informed consent forms before their examinations.

The participants were followed up for cardiovascular diseases mortality, all-cause mortality, and the development of DM from the initial screening to September 30, 2013. After a median of 4.8 years' follow-up for 1680 subjects, 181 participants were lost for follow-up and excluded from analysis. Therefore, 1499 subjects (follow-up rate 89.2%) finished the follow-up and fifty-two of which were excluded because of death. In the final data analysis, 1447 participants were included.
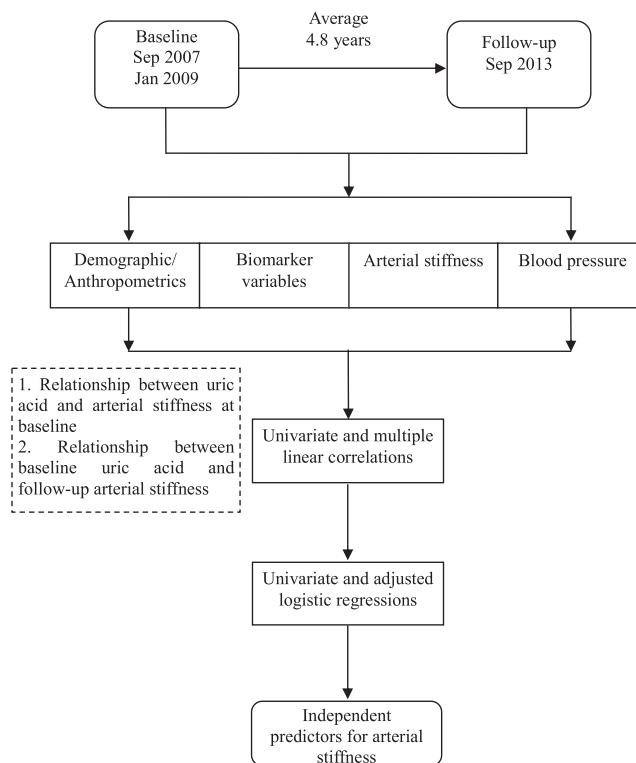
2.3. Clinical data collection

The lifestyle factors, prevalent diseases, demographic information, anthropometrics, family history and medication use were recorded using a standardized self-reported questionnaire in our following-up study. Smoking status and alcohol use was categorized as current, former, or never drinking/smoking, respectively. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were also examined on the right arm in a sitting position after a rest of five minutes.

2.4. Biomarker variable determination

Between 8 am and 10 am after an overnight fast (at least 12 h), the venous blood samples were obtained from all participants. Plasma aliquots were obtained and stored at −80 °C for further study. Concentrations of plasma UA, total cholesterol (TC), triglyceride (TG), fasting blood glucose (FBG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) concentrations were

measured from venous blood samples using commercially available ELISA kits by Roche enzymatic assays (Roche Diagnostics GmbH, Mannheim, Germany). Concentration of plasma creatinine (Cr) was also measured by enzymatic assay (Roche Diagnostics GmbH) on a Hitachi 7600 autoanalyzer (Hitachi, Tokyo, Japan).

The biochemical variables were measured from the blood specimens in the Departments of Clinical Laboratory, Chinese PLA General Hospital, following the criteria of the World Health Organization Lipid Reference Laboratories.

2.5. Assessments of arterial stiffness

Caffeine, smoking and alcohol were avoided before the assessment for at least 12 h. Arterial stiffness was assessed by automatic cr-PWV measurements using a Complior SP device (Createch Industrie, France) after a 5–10 min rest in supine position in the morning, in a quiet environment, and at a stable temperature. PWV along the artery was measured with two strain-gauge transducers in the noninvasive procedure using the TY-306 Fukuda pressure-sensitive transducer (Fukuda Denshi Co, Japan) that is fixed transcutaneously over the course of a pair of arteries separated by a known distance on the carotid and radial arteries (both on the right side). Two transducers were used: one positioned at the base of the neck over the common carotid artery and the other over the radial artery. Cr-PWV were obtained simultaneously. The measurement was repeated over 10 different cardiac cycles. PWV was calculated from the measurement of the pulse transit time and the distance traveled by the pulse between the two recording sites: PWV (m/s) = distance (m)/transit time (s) (O'Rourke et al., 2002).

2.6. Definition of variables

Smoking status was defined as smoking 1 or more cigarettes per day for at least 1 year. Body mass index (BMI) was defined as weight (kilograms) divided by square of height (meters). DM was defined as a fasting glucose $\geqslant 7.0$ mmol/L, glucose $\geqslant 11.1$ mmol/L at two hours after an oral 75 g glucose challenge, or both, or use of antihyperglycemic medication. Alcohol users were defined as drinking once a week (white spirit or beer or red wine).

2.7. Statistical analysis

Normally distributed baseline continuous variables are expressed as mean ± standard deviation (SD) and analyzed with Student's t-tests while the baseline dichotomous variables are presented as numbers (percentages) and compared using chi-square test. Non-normally distributed variables such as UA levels and other biomarkers were normalized by natural logarithm transformation as necessary.

A Pearson's regression analysis, a stepwise multivariate linear regression analysis and a multicollinearity analysis were performed to evaluate the associations between UA (natural logarithm transformed) level and arterial stiffness (cr-PWV) and other parameters at both the baseline and the end of the 4.8-year follow-up. Plasma UA levels at baseline were categorized as Quartile 1 ($\leqslant 238.95$ mmol/L, n = 370), Quartile 2

(239–284.60 mmol/L, n = 352), Quartile 3 (284.61–341.85 mmol/L, n = 372), and Quartile 4 ($\geqslant 341.90$ mmol/L, n = 353).

Further analysis by a stepwise multivariate logistic regression analysis was performed to identify the risk of UA (baseline) on the follow-up arterial stiffness (cr-PWV $\geqslant 8.76$ m/s vs. cr-PWV < 8.76 m/s) (Lin et al., 2012). Regression models were adjusted for age and sex as the independent variable (Model 1) and additionally adjusted for alcohol use (g/day), smoking, DM, LDL-C, TG, SBP, TC, DBP, HDL-C and Cr as the independent variables (Model 2).

All analyses were performed using SPSS 19.0 for Windows (SPSS, Chicago, IL, USA). P values < 0.05 were considered as statistically significant. Statisticians from the People's Liberation Army General Hospital were consulted for all of the statistical methods and results.

3. Results

3.1. Baseline clinical characteristics

The mean age of the subjects was 61.40 ± 11.4 years and 59.98% were women. The baseline clinical characteristics were categorized into four groups by quartiles of UA. The cr-PWV were significantly higher in Quartiles 2, 3 and 4 than in Quartile 1 at baseline (all $p < 0.05$, Table 1).

3.2. Associations between peripheral arterial stiffness and UA level at baseline

At the baseline, peripheral artery stiffness index, cr-PWV was strongly related to UA level ($r = 0.200$, $p < 0.001$) in the Pearson's analysis. In addition, cr-PWV was also closely correlated with DBP, SBP, Cr and TG in univariate linear analysis, while it negatively associated with HDL-C (Table 2).

However, in multivariate analysis, cr-PWV was uncorrelated to UA level ($\beta = 0.284$, $p = 0.107$) which may be adjusted by other variates such as age, DBP, Cr and TG in multivariate linear analysis (Table 2).

3.3. Follow-up cr-PWV was tightly associated with baseline UA level

Pearson's correlation analyses were employed to identify the association between follow-up peripheral arterial stiffness and baseline UA. As shown in Table 3, both univariate and multivariate linear regression analyses revealed statistically significant association between cr-PWV and UA ($r = 0.145$, $p < 0.001$ and $\beta = 0.493$, $p = 0.013$). Furthermore, the significant associations between follow-up cr-PWV and baseline parameters such as age, blood pressure, HDL-C ($r = -0.061$, $p = 0.028$), Cr ($r = 0.132$, $p < 0.001$) and TG ($r = 0.085$, $p = 0.002$) were also present in univariate analysis.

3.4. Logistic regressions for UA and arterial stiffness

Logistic regression using univariate UA for peripheral artery stiffness measured as cr-PWV indicated only Quartile 4 were risk for peripheral artery stiffening (OR: 1.260; 95%CI: 1.000–1.588; $p = 0.050$). In the Model 2 for cr-PWV, Quartile 3 UA range revealed significantly risk for peripheral artery

Table 1 Characteristics of the subjects categorized by Uric acid levels at baseline.

Variable	Overall	Quartile 1 ⩽238.95	Quartile 2 239–284.60	Quartile 3 284.61–341.85	Quartile 4 ⩾341.90
No. of subjects	1447	370	352	372	353
Age (years)	61.40 ± 11.4	57.13 ± 10.87	61.64 ± 11.59*	61.68 ± 9.69*	66.16 ± 8.73*
Women [n (%)]	868(59.98)	310(83.78)	252(71.59)*	223(59.94) *	83(23.51) *
Current smoking [n (%)]	380(26.26)	81(21.89)	55(15.62) **	96(25.80)	148(42.92) *
Current alcohol use [n (%)]	274(18.93)	63(17.02)	49(13.92)	75(20.16)	87(24.64) **
BMI(kg/m^2)	25.41 ± 3.32	24.72 ± 3.52	26.41 ± 3.31*	25.68 ± 2.93*	25.37 ± 3.43*
TG (mmol/l)	1.90 ± 1.24	1.53 ± 0.93	2.23 ± 1.58*	1.87 ± 1.17*	1.88 ± 1.07
TC (mmol/l)	5.03 ± 0.93	4.88 ± 0.93	4.94 ± 0.96	5.06 ± 0.88**	4.91 ± 0.99
HDL-C (mmol/l)	1.38 ± 0.36	1.51 ± 0.42	1.25 ± 0.33*	1.34 ± 0.31*	1.36 ± 0.41
LDL-C (mmol/l)	2.91 ± 0.71	2.83 ± 0.69	2.89 ± 0.74	3.02 ± 0.69*	2.89 ± 0.72
SBP (mmHg)	128.74 ± 17.71	125.93 ± 17.32	133.17 ± 18.86*	129.58 ± 16.34**	136.79 ± 19.65*
DBP (mmHg)	76.92 ± 10.23	75.37 ± 9.93	78.80 ± 10.51*	76.89 ± 9.98	76.93 ± 11.34
FBG (mmol/L)	5.39 ± 1.65	5.69 ± 2.13	5.38 ± 1.29	5.18 ± 1.09*	5.73 ± 1.79**
Cr (μmoI/L)	66.14 ± 18.16	57.24 ± 13.22	76.57 ± 16.69*	67.49 ± 14.94*	71.16 ± 19.70*
cr-PWV (m/s)	9.38 ± 1.47	9.11 ± 1.41	9.71 ± 1.57*	9.40 ± 1.44**	9.72 ± 1.61*

Notes: Characteristics are reported as percentages for categorical variables and means (±SD) or medians (with interquartile range) for continuous variables. The study participants were divided into four groups based on the baseline levels of the quartile of Uric acid (⩽238.95, 239–284.60, 284.61–341.85, ⩾341.90 mmol/L). Categorical variables are presented as counts (percentages). The values outside the parentheses are the number of subjects, and the values inside the parentheses are prevalence. The quartile 1 level of Uric acid was used as the reference and quartiles 2, 3, 4 evaluated vs. quartile 1.
 * <0.05 vs. Quartile 1,
 ** <0.01 vs. Quartile 1.

Table 2 Univariate and stepwise multiple linear regression analyses at baseline.

	Pearson correlation		Multiple linear correlation		
	r	P	β	95%CI	P
cr-PWV					
UA[#]	0.200	<0.001**	0.284	−0.061–0.629	0.107
Age	−0.027	0.337	0.049	0.037–0.062	<0.001**
SBP	0.178	<0.001**	0.003	0.003–0.009	0.271
DBP	0.241	<0.001**	0.020	0.010–0.031	<0.001**
LDL-C	0.002	0.942	0.003	−0.234–0.241	0.980
HDL-C	−0.091	0.001**	0.207	−0.091–0.505	0.173
Cr	0.201	<0.001**	0.058	0.048–0.068	<0.001**
TC	0.028	0.321	0.022	−0.175–0.220	0.824
TG	0.102	<0.001**	0.201	0.010–0.393	0.039*

 [#] Natural logarithm transformed.
 * <0.05;
 ** <0.01.

stiffening (OR: 1.781; 95%CI: 1.156–2.744; *p* = 0.009) (Table 4). Furthermore, the UA level in the Quartile 4 showed significant risk for peripheral artery stiffening (OR: 1.259; 95% CI: 0.942–1.681; *p* = 0.019).

3.5. Subgroups analyses in MetS and non-MetS

We performed the subgroup analyses to identify the affection of MetS on arterial stiffness. However, cr-PWV showed no correlation with UA in the MetS subgroup (all *p* > 0.05). Interestingly, in the non-MetS group, UA was associated with cr-PWV in both linear analyses (*r* = 0.190, *p* < 0.001 and β = 0.561, *p* = 0.017). Association's analyses for subgroups are displayed in Table 5.

Regarding the prediction roles of UA in MetS group, logistic regressions revealed no predictive values for arterial stiffening. Importantly, in the non-MetS subgroup, UA (Quartile 4 vs. Quartile 1) was an independent risk factor or predictor for arterial stiffening reflected by cr-PWV in Model 2 which was adjusted by age, gender, hypertension, DM, current smoking, DBP, SBP and levels of serum TC, TG, HDL-C, LDL-C and Cr (Table 6).

4. Discussion

In the current 4.8 years of follow-up study, we found that UA level was associated with cr-PWV. However, only Quartile 3 and 4 levels of baseline UA were independent predictors for follow-up peripheral arterial stiffness. Furthermore, UA predicts arterial stiffness in a MetS independent way.

Table 3 Univariate and multiple linear regression analysis of baseline parameters and follow-up cr-PWV.

	Pearson correlation		Multiple linear correlation		
	r	P	β	95%CI	P
cr-PWV					
UA[#]	0.145	<0.001[**]	0.493	0.106–0.880	0.013[*]
Age	0.163	<0.001[**]	0.000	−0.014–0.014	0.968
SBP	0.108	<0.001[**]	0.005	−0.002–0.012	0.136
DBP	0.205	<0.001[**]	0.016	0.004–0.027	0.009[**]
LDL-C	0.028	0.314	0.083	−0.183–0.349	0.541
HDL-C	−0.061	0.028	0.390	0.056–0.724	0.022[*]
Cr	0.132	<0.001[**]	0.031	0.020–0.042	<0.001[**]
TC	−0.036	0.202	−0.197	−0.419–0.024	0.081
TG	0.085	0.002[**]	0.312	0.097–0.527	0.004[**]

[#] Natural logarithm transformed.
[*] <0.05;
[**] <0.01.

Table 4 Logistic regression analysis for baseline levels of uric acid and follow-up cf-PWV.

	Quartile 2 vs. Quartile 1 239–284.60 vs ≤238.95		Quartile 3 vs. Quartile 1 284.61–341.85 vs ≤238.95		Quartile 4 vs. Quartile 1 ≥341.9 vs. ≤238.95	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
cr-PWV						
Unadjusted	0.645(0.264–1.579)	0.337	1.390(0.980–1.970)	0.065	1.260(1.000–1.588)	0.050[*]
Model 1	0.534(0.207–1.379)	0.195	1.515(1.058–2.171)	0.023[*]	1.322(1.045–1.672)	0.020[*]
Model 2	0.453(0.005–1.241)	0.123	1.781(1.156–2.744)	0.009[**]	1.259(0.942–1.681)	0.019[*]

Notes: Data were presented as ORs (per SD increase in uric acid level) and corresponding 95% CIs. In the logistic regression model, cr-PWV (PWV ≥ 8.76m/s vs. PWV < 8.76 m/s) were treated as the dependent variable.
Model 1: adjusted for age, gender; Model 2: adjusted for age, gender, DM, current smoking, MetS, DBP, SBP and levels of TC, TG, HDL-C, LDL-C and Cr.
[*] : *p* < 0.05.

Table 5 Subgroups analyses by linear regressions in baseline parameters and follow-up arterial stiffness.

	MetS					Non-MetS				
	Pearson correlation		Multiple linear correlation			Pearson correlation		Multiple linear correlation		
	r	P	β	95%CI	P	r	P	β	95%CI	P
cr-PWV										
UA[#]	0.059	0.274	0.271	−0.394–0.935	0.424	0.190	<0.001[**]	0.561	0.099–1.024	0.017[*]
Age	−0.215	<0.001[**]	0.002	−0.025–0.029	0.869	−0.150	<0.001[**]	0.002	−0.014–0.018	0.772
SBP	0.112	0.025[*]	0.007	−0.003–0.017	0.170	0.110	0.001[**]	0.007	−0.002–0.016	0.133
DBP	0.238	<0.001[**]	0.016	−0.002–0.034	0.074	0.208	<0.001[**]	0.015	0.000–0.030	0.045
LDL-C	−0.060	0.237	0.478	0.009–0.947	0.046[*]	−0.067	0.040[*]	−0.095	−0.421–0.232	0.570
HDL-C	0.027	0.591	1.160	0.418–1.901	0.002[**]	−0.049	0.128	0.227	−0.147–0.600	0.235
Cr	0.057	0.261	0.029	0.009–0.049	0.005[**]	0.157	<0.001[**]	0.032	0.019–0.046	<0.001[**]
TC	−0.058	0.249	−0.590	−1.005 to −0.174	0.006[**]	−0.027	0.409	−0.071	−0.336–0.195	0.601
TG	0.055	0.277	0.581	0.134–1.027	0.011[*]	0.114	<0.001[**]	0.369	0.108–0.629	<0.001[*]

[#] Natural logarithm transformed.
[*] <0.05;
[**] <0.01.

4.1. UA and its distribution in the health check up population

UA as the end-product of purine nucleotide metabolism participates in many pathophysiological processes in vascular diseases (Sabio et al., 2010). Over the past decades, hyperuricemia has been indicated to be a risk factor for cardiovascular and cerebrovascular diseases such as atherosclerosis and hypertension (Katsiki et al., 2015; Sabio et al., 2010). However, the role of UA in its normal physiological range, such as upper level, was remained elusive.

Table 6 Logistic regressions for cr-PWV in the subgroups.

| | MetS | | Non-MetS | |
| | Quartile 4 vs. Quartile 1 | | Quartile 4 vs. Quartile 1 | |
	OR (95%CI)	p	OR (95%CI)	p
cr-PWV				
Unadjusted	1.441(0.637–3.259)	0.380	0.909(0.633–1.305)	0.604
Model1	1.370(0.491–3.828)	0.548	1.117(0.775–1.653)	0.581
Model2	1.252(0.469–3.345)	0.654	1.034(0.661–1.619)	0.043

In the logistic regression model, cr-PWV (PWV $\geq$ 8.76 m/s vs. PWV $<$ 8.76 m/s) were treated as the dependent variable.
Model 1: adjusted for age, gender; Model 2: adjusted for age, gender, DM, current smoking, DBP, SBP and levels of TC, TG, HDL-C, LDL-C and Cr.
*: <0.05; **: <0.01.

In our present study, we did observe that the higher UA levels were accompanied with higher cr-PWV, indicating that higher range of UA may contribute to peripheral arterial stiffening. This result was partly in consistent with previous studies (Hsu et al., 2013). Furthermore, individuals with higher levels (such as Quartiles 3 and 4) of UA account for almost half of the health check up population. Thus, the higher normal UA levels should be given proper attention with critical importance. Additionally, our observations that both SBP and DBP were lower in the lowest normal UA level interval (Quartile 1), combining with the results on arterial stiffness mentioned-above may provide clue for further stratifications and managements of cardiovascular diseases risk.

4.2. Peripheral stiffness were associated with UA levels

It has been demonstrated that arterial stiffness occurs in both aortic and peripheral arteries, and the latter one is prior to the former one (Lee and Oh, 2010; Sun, 2015). There are also a number of studies that have indicated that UA was related to arterial stiffening that assessed by brachial-ankle PWV or heart-femoral PWV (Ishizaka et al., 2007; Lim et al., 2010). In our current study, we evaluated peripheral arterial stiffness using cr-PWV. We also found that cr-PWV was associated with baseline UA which is partly similar to the previous results (Liang et al., 2012).

In accordance with many others' reports, the current study showed that UA was correlated with peripheral stiffening at baseline (Shin et al., 2012; Bian et al., 2012); Homma et al., 2015). These results suggested that the subclinical arterial stiffening may exist in normal healthy persons. Particularly, the association between baseline UA and follow up peripheral arterial stiffness suggests that UA may be used to predict the incident of arterial stiffness which will be discussed in the next section.

Up to date, though various studies have focused on the association between UA and arterial stiffness (Lin et al., 2012; Shin et al., 2012; Hsu et al., 2013; Bae et al., 2013; Cicero et al., 2014), the mechanisms underlying the pathogenesis that UA participates in arterial stiffening have not been clearly uncovered. However, several basic investigations demonstrated prominent roles of UA in arterial stiffness (Iwashima et al., 2006; Bobik and Grassi, 2012; Kanellis et al., 2003; Kang et al., 2005; Luft, 2012).

First of all, UA has been indicated to thick vascular wall *via* promoting proliferation and differentiation of smooth muscle cells. The biological behaviors of smooth muscle cells mentioned above were triggered by the activated renin-angiotensin system and reactive oxygen species (Bobik and Grassi, 2012; Jae et al., 2012; Jain et al., 2014; Park and Lakatta, 2012). Those results subsequently lead to the reduction in elasticity of artery wall promoting the arterial stiffness. Secondly, numerous studies also conclude that the essential roles of UA in arterial stiffness prior to hypertension process may be attributed to the inflammatory activation (increased levels of C-reactive protein and other pro-inflammatory factors) (Kang et al., 2005). Thirdly, UA has also implicated in endothelial cell dysfunction which plays crucial roles in arterial stiffening (Bellien et al., 2010). It is elucidated that UA participates in arterial stiffness maybe also *via* the nitric oxide pathway dysfunction, oxidative stress, insulin resistance which result endothelial cell dysfunction (Bellien et al., 2010). Endothelial cell dysfunction further increases proliferation and migration of smooth muscle cells and the rearrangement of artery wall components. Those changes decrease the complaisance and stiffen arteries functionally and structurally. Lastly, it has also been addressed that UA injures arteries chronically through up-regulating the expression of platelet-derived growth factor and monocyte chemotactic protein-1 (Kanellis et al., 2003). In a word, though UA participates in arterial stiffness primarily through the four mechanisms mentioned above, other potential mechanisms still warrant further study.

4.3. Higher baseline UA level was an independent predictor for peripheral arterial stiffness

Further analyses by logistic regressions indicated that higher baseline UA level was an independent risk factor and predictor for central stiffness and peripheral stiffness. In both adjusted models, higher UA levels exhibited risk for arterial stiffness measured by cr-PWV indicating that higher UA level was an independent predictor for peripheral arterial stiffening. In addition, baseline UA level in Quartiles 3 and 4 were still an independent predictor for peripheral arterial stiffening (cr-PWV).

Though others' cross sectional studies have indicated the risk for arterial stiffness ubiquitously (Lin et al., 2012; Bae et al., 2013), the predictive value of UA for arterial stiffness has not been confirmed in a long time longitudinal study. Thus, we performed this follow up survey and demonstrated that higher normal UA levels were risk factors and predictors for arterial stiffness. Particularly, the UA level ≥ 341.90 mmol/

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