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ORIGINAL

Relationship between carotid-femoral pulse wave velocity and uric acid in subjects with hypertension and hyperuricemia

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Abstract. Increasing of arterial stiffness is the pathophysiological characteristic of hypertension. Carotid-femoral pulse wave velocity (CF-PWV) is an index of arterial stiffness. Serum uric acid has been found to be involved the development of hypertension. We investigated the relationship between CF-PWV and serum uric acid in subjects with hypertension and hyperuricemia. 651 subjects (M/F 271/380) were divided into four groups, group 1: subjects without hypertension and hyperuricemia; group 2: hypertension subjects without hyperuricemia; group 3: hyperuricemia subjects without hypertension; group 4: subjects with hypertension and hyperuricemia. CF-PWV was measured by Complior apparatus. Results showed that levels of CF-PWV (10.75 ± 2.03 *vs.* 10.06 ± 1.98 m/s, $p < 0.001$) and serum uric acid (319.33 ± 80.12 *vs.* 298.78 ± 74.88 umol/L, $p = 0.001$) were significantly higher in hypertensive (groups 2 + 4) group than in normotensive (groups 1 + 3) group. CF-PWV was significantly higher in group 4 than group 1, group 2 and group 3 (ANOVA analysis: F = 13.348, $p < 0.001$; 11.78 ± 2.10 *vs.* 9.98 ± 1.98, 10.52 ± 1.93, 10.56 ± 1.99 m/s, all $p < 0.05$, respectively). There was positive correlation between CF-PWV and serum uric acid in entire study group ($r = 0.187$, $p < 0.001$), even after adjusting for gender, body mass index, systolic blood pressure (SBP) and diastolic blood pressure ($r = 0.100$, $p = 0.015$). Multiple linear regressions showed that SBP, age, benzbromarone, statin and serum uric acid were independent associating factors of CFPWV in all subjects ($\beta = 0.310$, $p < 0.001$; $\beta = 0.330$, $p < 0.001$; $\beta = 0.172$, $p = 0.002$; $\beta = -0.143$, $p = 0.006$; $\beta = 0.126$, $p = 0.027$; respectively). In conclusions, CF-PWV was significantly higher in hypertension subjects with hyperuricemia compared to hypertension without hyperuricemia subjects, and serum uric acid was an independent associating factor of CF-PWV.

Key words: Carotid-femoral pulse wave velocity, Hypertension, Uric acid, Arterial stiffness, Hyperuricemia

HYPERTENSION is one of the most common vascular diseases in the world, and the prevalence of hypertension in Chinese population was 30.09% in males and 24.79% in females, respectively [1]. Hypertension is one of the most important factors of coronary artery disease, stroke, and renal disease. Arteriosclerosis which could be evaluated by arterial stiffness is the basic pathophysiological change during the development of hypertension. An increase of arterial stiffness is a strong predictor of future cardiovascular events and all-cause mortality [2]. Arterial stiffness could be measured by pulse wave velocity (PWV), which is considered as the gold standard method suggested by European Society of Hypertension/ European Society of Cardiology guidelines [3]. Our previous studies showed that carotid-femoral PWV (CF-PWV) was positively correlated with pulse pressure and it was increased in hypertension patients with left ventricular hypertrophy [4, 5]. Our recent study showed that CF-PWV was significantly higher in healthy subjects with hypertension family history [6].

There are many mechanisms involving the development of hypertension, such as salt intake, insulin resistance and oxidative stress. Some biomarkers such as homocysteine and serum uric acid (UA) had been found to be involved the development of hypertension. Serum uric acid is the final metabolite of purines in human and increasing serum UA levels are known to be associated with incident hypertension [7]. An observational study showed that hyperuricemia was significantly associated with the risk of hypertension in both male and female patients, with odds ratios of 2.152 and 2.133, respec-

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tively [8]. Recent study showed that high serum uric acid level was associated with future hypertension in young and middle-aged Japanese males [9].

However, there were few studies on the relationship between CF-PWV and serum uric acid in hypertension subjects with hyperuricemia simultaneously. The aim of the present study was to investigate the relationship between CF-PWV and serum uric acid in subjects with hypertension and hyperuricemia.

Materials and Methods

Subjects

This was a retrospective cross-sectional study, and according to our present study, the enrolled standards were as follows: subjects with hypertension were enrolled, and subjects with coronary artery diseases, diabetes mellitus, heart failure, stroke, renal function impairment, liver function impairment, systemic inflammatory diseases, infectious disease or cancer were excluded. Finally, 651 subjects (M/F 271/380) from Department of Vascular Medicine for health examination from January 2012 to December 2016 were enrolled into our study. Hypertension was defined as blood pressure measurement ≥140/90 mmHg in three occasions at rest or subjects with known cases of diagnosed hypertension before and taking antihypertensive drugs at present. Hyperuricemia was defined as serum uric acid >420 μmol/L for men and >360 μmol/L for women. And these 651 subjects were divided into four groups, group 1: subjects without hypertension and hyperuricemia; group 2: hypertension subjects without hyperuricemia; group 3: hyperuricemia subjects without hypertension; group 4: subjects with hypertension and hyperuricemia.

This study was approved by the ethics committee of Peking University Shougang Hospital (No IRBK-2017-022-01, May, 2, 2017).

Pulse wave velocity measurement

Arterial stiffness was evaluated by measuring automatic PWV using the Complior apparatus which was used for the measurement of PWV widely around the world with great accuracy and reproducibility [10]. The basic principle of PWV assessment is that pressure pulse generated by ventricular ejection is propagated along the arterial system at a speed determined by elasticity of the arterial wall. Knowing the distance and pulse transit time, the velocity can be calculated. Patients were placed in supine position and, after a 10-minute rest, underwent PWV measurement and carotid-femoral PWV (CF-PWV) was obtained automatically. Estimation of the distance travelled by the pulse is based on measuring the distance between the common carotid artery and the right femoral artery according to the latest guideline [11].

Laboratory measurements

Blood samples were drawn from an antecubital vein in the morning after overnight fasting and collected into vacuum tubes containing EDTA for the measurement of plasma lipid and lipoprotein levels. Fasting plasma glucose (FPG), Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG), homocysteine, creatinine, serum uric acid levels were analyzed by colorimetric enzymatic assays with the use of an autoanalyzer (HITACHI-7170, Hitachi, Tokyo, Japan) at the central chemistry laboratory of the Peking University Shougang Hospital. Low-density lipoprotein cholesterol (LDL-C) levels were calculated.

Statistical analysis

The differences between groups were analyzed by *t*-test, one-way ANOVA and least-significant difference (LSD). Proportions were analyzed by χ^2 -test. Correlation coefficient was done to find linear relation between different variables using Pearson correlation analysis. Multiple linear regressions were used to estimate the coefficients of the linear equation, involving independent variables that affected the value of the dependent variables. Values were shown as mean ± SD unless stand otherwise. $p < 0.05$ (2-tailed) was considered statistically significant.

Results

Clinical characteristics of the study participants

First, these subjects were divided into two groups: non-hypertension group ($n = 325$), hypertension group ($n = 326$). The clinical characteristics of study participants are shown in Table 1. Our results showed that the levels of age, body mass index (BMI), CFPWV, SBP, DBP, creatinine, serum uric acid were significantly higher in hypertension group than in non-hypertension group. HDL-C was significantly lower in hypertension group than in non-hypertension group. There was no significant difference about FPG, TC, TG, and LDL-C between these two groups. There was no significant difference in composition of gender between these two groups.

Next, the entire study was divided into four groups according to hypertension and hyperuricemia. As shown in Table 2, the level of CFPWV was significantly higher in group 4 than in group 1, group 2 and group 3 (ANOVA analysis: $F = 13.348$, $p < 0.001$; 11.78 ± 2.10 *vs.* 9.98 ± 1.98, 10.52 ± 1.93, 10.56 ± 1.99 m/s, all $p < 0.05$, respectively). Levels of TG and homocysteine were higher in group 4, with lower level of HDL-C. There was significant difference in composition of gender between

Table 1 Clinical characteristics in different groups

Characterisitics	Non-hypertension (N = 325)	Hypertension (N = 326)	p
Age (year)	57.51 ± 8.52	59.30 ± 9.16	0.010
Male/Famale	140/185	131/195	0.454
BMI (Kg/M^2)	24.12 ± 3.50	25.73 ± 3.11	<0.001
CFPWV (m/s)	10.06 ± 1.98	10.75 ± 2.03	<0.001
SBP (mmHg)	127.40 ± 15.84	142.17 ± 20.28	<0.001
DBP (mmHg)	79.86 ± 8.87	87.47 ± 11.02	<0.001
Creatinine (umol/L)	63.47 ± 12.68	66.36 ± 21.32	0.042
FPG (mmol/L)	5.41 ± 0.84	5.53 ± 0.92	0.094
UA (umol/L)	298.78 ± 74.88	319.33 ± 80.12	0.001
TC (mmol/L)	5.06 ± 1.16	4.94 ± 1.10	0.191
HDL-C (mmol/L)	1.30 ± 0.35	1.24 ± 0.30	0.014
LDL-C (mmol/L)	3.20 ± 0.86	3.12 ± 0.83	0.203
TG (mmol/L)	1.74 ± 1.51	1.85 ± 1.53	0.372
HCY (umol/L)	12.75 ± 6.66	13.65 ± 7.68	0.127
Smoking usage (No.)	95	87	0.470
Alcohol usage (No.)	76	85	0.427

Note: BMI, body mass index; CFPWV, carotid-femoral pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; UA, uric acid; TC, cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; HCY, homocysteine.

these four groups. The medication drugs such as diuretic, angiotensin converting anzyme inhibitior (ACEI), angiotensin II receptor antagonist (ARB), calcium channel blocker (CCB), beta blockers, allopurinol, benzbromarone and statin used in these subjects were also shown in Table 2.

Pearson correlation between CFPWV and metabolic markers

Next, we investigated the Pearson correlation between CFPWV and metabolic markers and other variables in the entire group. As shown in Table 3, our results showed that CFPWV was positively correlated with age, SBP, DBP, creatinine, FBG, serum uric acid, and TG in the entire study group (r = 0.419, p < 0.001; r = 0.414, p < 0.001; r = 0.232, p < 0.001; r = 0.168, p < 0.001; r = 0.134, p = 0.001; r = 0.187, p < 0.001; r = 0.096, p = 0.019; respectively).

As shown in Table 2, there was significant difference about gender composition, BMI, SBP, DBP between these two groups. Our further results showed that there was positive correlation between CFPWV and serum uric acid in the entire study group after adjusting for gender, BMI, SBP and DBP (r = 0.100, p = 0.015).

Multiple linear regression analysis

Multiple linear regressions were used to estimate the coefficients of the linear equation, involving independent variables including age, gender, BMI, SBP, DBP, creatinine, FPG, serum uric acid, TC, TG, HDL-C, LDL-C, homocysteine, medication drugs such as diuretic, angiotensin converting anzyme inhibitior (ACEI), angiotensin II receptor antagonist (ARB), calcium channel blocker (CCB), beta blockers, allopurinol, benzbromarone and statin that might affect the value of CFPWV. As shown in Table 4, our results showed that SBP, age, benzbromarone, statin and serum uric acid were independent associating factors of CFPWV in all subjects (β = 0.310, p < 0.001; β = 0.330, p < 0.001; β = 0.172, p = 0.002; β = –0.143, p = 0.006; β = 0.126, p = 0.027; respectively).

Discussion

Our present study has shown that CF-PWV was significantly higher in hypertension subjects with hyperuricemia compared to hypertension without hyperuricemia subjects, and serum uric acid was an independent associating factor of CF-PWV.

Arterial stiffness is one of the earliest detectable manifestations of adverse structural and functional changes within the vessel wall during the development of arteriosclerosis caused by hypertension [12]. Pulse wave velocity (PWV) could reflect the severity of arteriosclerosis. Many studies have shown the role of PWV in the predic-

Table 2 Clinical characteristics in different groups

Characterisitics	Group 1 ($N = 282$)	Group 2 ($N = 268$)	Group 3 ($N = 43$)	Group 4 ($N = 58$)	F value	p
Age (year)	57.33 ± 8.26	59.23 ± 8.85	58.72 ± 10.05	59.60 ± 10.56	2.547	0.055
Male/Famale	114/168	94/174	26/17	37/21	—	<0.001
BMI (Kg/M^2)	24.01 ± 3.48	25.66 ± 3.07*	24.82 ± 3.63	26.06 ± 3.32*	13.126	<0.001
CFPWV (m/s)	9.98 ± 1.98	10.52 ± 1.93*	10.56 ± 1.99	11.78 ± 2.10*$^{\#\$}$	13.348	<0.001
SBP (mmHg)	127.11 ± 16.10	140.28 ± 20.13*	129.33 ± 14.05$^{\#}$	150.89 ± 18.83*$^{\#\$}$	40.006	<0.001
DBP (mmHg)	79.61 ± 8.80	86.60 ± 10.71*	81.55 ± 9.34$^{\#}$	91.48 ± 11.62*$^{\#\$}$	34.230	<0.001
Creatinine (umol/L)	62.76 ± 13.56	64.05 ± 20.42	69.03 ± 13.61*	77.81 ± 22.16*$^{\#\$}$	12.044	<0.001
FPG (mmol/L)	5.43 ± 0.87	5.48 ± 0.91	5.33 ± 0.58	5.77 ± 0.88	2.597	0.051
UA (umol/L)	284.49 ± 62.91	295.55 ± 58.66*	424.72 ± 49.97*$^{\#}$	446.80 ± 55.74*$^{\#}$	147.790	<0.001
TC (mmol/L)	5.05 ± 1.14	4.94 ± 1.11	5,14 ± 1.23	4.96 ± 1.04	0.639	0.590
HDL-C (mmol/L)	1.31 ± 0.36	1.26 ± 0.30*	1.20 ± 0.29*	1.12 ± 0.29*$^{\#}$	5.944	0.001
LDL-C (mmol/L)	3.18 ± 0.86	3.11 ± 0.85	3.35 ± 0.86	3.16 ± 0.71	1.002	0.391
TG (mmol/L)	1.67 ± 1.44	1.73 ± 1.37	2.31 ± 1.89*$^{\#}$	2.46 ± 2.11*$^{\#}$	5.436	0.001
HCY (umol/L)	12.42 ± 6.22	13.34 ± 7.87	15.03 ± 8.94*	15.16 ± 6.52*	3.099	0.026
Statins (No.)	55	75	11	20	—	0.034
Diuretic (No.)	0	5	0	3	—	0.314
ACEI/ARB (No.)	0	135	0	30	—	0.967
CCB (No.)	0	110	0	23	—	0.845
Beta blockers (No.)	0	40	0	9	—	0.909
Allopurinol (No.)	0	0	8	9	—	0.682
Benzbromarone (No.)	0	0	5	10	—	0.433
Duration of hypertension (years)	0	10.13 ± 9.2	0	13.1 ± 10.2	—	0.06

Note: * *vs.* group 1 $p < 0.05$, $^{\#}$ *vs.* group 2 $p < 0.05$. $^{\$}$ *vs.* group 3 $p < 0.05$. group 1: subjects without hypertension and hyperuricemia; group 2: hypertension subjects without hyperuricemia; group 3: hyperuricemia subjects without hypertension; Group 4: subjects with hypertension and hyperuricemia; BMI, body mass index; CFPWV, carotid-femoral pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; UA, uric acid; TC, cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; HCY, homocysteine; ACEI, angiotensin converting anzyme inhibitior; ARB, angiotensin II receptor antagonist; CCB, calcium channel blocker. Proportions analysis about usage of Diuretic, ACEI/ARB, CCB, Beta blockers between group 2 and group 4 were analyzed by χ^2-test. Proportions analysis about usage of Allopurinol, Benzbromarone between group 2 and group 4 were analyzed by χ^2-test.

tion of stroke, heart failure [13]. Our present study has shown that the level of CF-PWV was higher in hypertension subjects compared to non-hypertension subjects with lower level of HDL-C, the similar result to our previous research [14].

Serum uric acid is a final oxidation product of dietary or endogenous purine metabolism in humans. Recent studies have shown the role of serum uric acid in vascular-related diseases such as hypertension and metabolism. A large cross-sectional study about 46,561 Taiwanese showed that serum uric acid had significant associations with the presence of metabolic syndrome, diabetes mellitus, and hypertension. Higher serum uric acid significantly increased the risks for developing hypertension in all different age subgroups in male [15]. In another prospective observational study including 23,525 non-metabolic syndrome subjects who had been followed up for at least 5 years, the result showed that the higher serum uric acid level group was found to show a higher risk for the development of hypertension with odds ratio of 2.27, and there was significant difference between subgroups (different level of serum uric acid) about triglycerides [16]. In a prospective study about the relationship between serum uric acid and heart failure incidence in hypertension subjects, the result showed that hyperuricemia was associated with detrimental effects in terms of the incidence of heart failure in hypertensive patient [17]. Georgiopoulos *et al.* [18] found that serum uric acid is independently associated with the presence of diastolic dysfunction in hypertension subjects. These

Table 3 Pearson correlation between CFPWV and study variables among entire study group

	r	*p* value
Age (year)	0.419	<0.001
BMI (Kg/M^2)	0.026	0.514
SBP (mmHg)	0.414	<0.001
DBP (mmHg)	0.232	<0.001
Creatinine (umol/L)	0.168	<0.001
FPG (mmol/L)	0.134	0.001
UA (umol/L)	0.187	<0.001
TC (mmol/L)	0.028	0.498
HDL-C (mmol/L)	–0.036	0.375
LDL-C (mmol/L)	0.010	0.806
TG (mmol/L)	0.096	0.019
HCY (umol/L)	0.055	0.192

Note: BMI, body mass index; CFPWV, carotid-femoral pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; UA, uric acid; TC, cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; HCY, homocysteine.

studies showed that hyperuricemia might be associated with hypertension.

Our present study found that CF-PWV was significantly higher in hypertension subjects with hyperuricemia compared to hypertension without hyperuricemia subjects, and positive correlation between CF-PWV and serum uric acid was found. However, there was significant difference about gender composition, BMI between these groups (Table 2). Baltimore Longitudinal Study of Aging [19] showed that higher serum uric acid was associated with greater increase in pulse wave velocity in men. Another study [20] showed that high-normal serum uric acid or greater was associated with greater risk of arterial stiffness in apparently healthy women. There was a positive relationship between mild hyperuricaemia and aortic stiffness in essential hypertensive subjects [21]. However, another study [22] found all the metabolic components were correlated to brachial-ankle PWV in the male and female subjects except low HDL-C and high serum uric acid in the male group. In addition, our present study also showed that there was difference about HDL-C, TG between these four groups. We all know that BMI, hypertension, HDL-C, TG, and glucose are the members of metabolic syndrome. These studies disclosed the strong association between hyperuricemia and metabolic syndrome, obesity, hypertension, type 2 diabetes mellitus, non-alcoholic fatty liver disease, hypertriglyceridemia, acute kidney injury, chronic kidney disease, coronary heart disease, heart failure and increased mortality among cardiac and chronic kidney disease patients [18, 23].

In a cross-sectional study among healthy participants of the ELSA-Brasil, Baena CP *et al.* [24] found that serum uric acid was significantly associated to PWV in men but not in women. Another study also showed that serum uric acid levels were significantly associated with carotid-radial PWV in a younger Caucasian population [25]. What are the mechanisms? Corry *et al.* [26] showed that serum uric acid stimulated vascular smooth muscle cell proliferation and oxidative stress *via* the vascular renin-angiotensin system. Khosla UM found that hyperuricemia induced endothelial dysfunction [27]. Recent study found that use of allopurinol in patients with chronic kidney disease was associated with improvements in endothelial function and left ventricular hypertrophy, and PWV improvement [28, 29]. Muraya N found that benzbromarone had a direct antioxidant effect *in vivo* to reduce the levels of advanced oxidation protein products [30]. And PWV was correlated with oxidative stress [31]. So oxidative stress and endothelial dysfunction might be the linkage between uric acid and PWV. Our present study showed that serum uric acid was independent associated with CFPWV, so there might be some other mechanism such as arterial stiffness about the role of serum uric acid in the development of hypertension. However, allopurinol was not associated with CFPWV and benzbromarone was not a protective factor for CFPWV in the present study, and nonstandard medication and small sample size might be the reasons. In addition, Cicero AF *et al.* [32] found that serum uric acid appeared to be significantly correlated to hypertension and IMT, but not to aortic stiffness. So more studies should be investigated in future study.

A major limitation of our study is its cross-sectional design; another limitation is that the subjects' numbers of each group were not balanced, especially subjects with hypertension and hyperuricaemia lies on a small fraction of the study sample (58/651, 8.9%) and could be due to chance. In addition, our present study showed that CF-PWV was significantly higher in hypertension subjects with hyperuricemia compared to hypertension without hyperuricemia subjects (Group 4 *vs.* Group 2), with higher levels of SBP and DBP in Group 4 than Group 2, There might be reasons that hyperuricemia might be associated with hypertension [15]. However, whether increasing CF-PWV was entirely due to the blood pressure or the hyperuricemia should be investigated. In addition, time of duration of hypertension and hyperuricemia might be associated with CF-PWV, and our present study showed that the duration of hypertension was 10.13 ± 9.2 years in group 2 compared to 13.1

Table 4 Multiple linear regression analysis for the relationship between CFPWV and study variables among entire study group (A and B)

A Independent associating factors of CFPWV in all subjects

	Unstandardized β	95% CI for β	Std. Error	Standardized β	*t*	*p* value
constant	0.737	[–1.320, 2.794]	1.044	—	0.706	0.481
SBP (mmHg)	0.031	[0.021, 0.042]	0.005	0.310	5.838	<0.001
Age (year)	0.078	[0.054, 0.102]	0.012	0.330	6.389	<0.001
Benzbromarone	1.953	[0.705, 3.202]	0.634	0.172	3.081	0.002
Statin	–0.662	[–1.128, –0.196]	0.237	–0.143	–2.797	0.006
UA (umol/L)	0.003	[0.000, 0.006]	0.001	0.126	2.220	0.027

B Excluded variables by multiple linear regression analysis in all subjects

Characterisitics	Beta in	*t*	*p* value
Gender	0.023	0.391	0.696
BMI (Kg/M^2)	–0.055	–1.012	0.313
DBP (mmHg)	–0.031	–0.407	0.685
Creatinine (umol/L)	0.048	0.871	0.384
FPG (mmol/L)	0.058	1.100	0.272
TC (mmol/L)	–0.072	–1.369	0.172
HDL-C (mmol/L)	0.018	0.338	0.736
LDL-C (mmol/L)	–0.068	–1.032	0.194
TG (mmol/L)	–0.017	–0.317	0.751
HCY (umol/L)	–0.049	–0.910	0.364
Duration of hypertension	0.066	1.253	0.211
Diuretic	0.030	0.589	0.556
ACEI/ARB	–0.090	–1.706	0.089
CCB	–0.020	–0.371	0.711
Beta blockers	0.026	0.500	0.618
Allopurinol	–0.106	–1.822	0.070

Note: BMI, body mass index; CFPWV, carotid-femoral pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; UA, uric acid; TC, cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; HCY, homocysteine; ACEI, angiotensin converting anzyme inhibitior; ARB, angiotensin II receptor antagonist; CCB, calcium channel blocker.

± 10.2 years in group 4 without significant difference (p = 0.06). However, we did not collect the data about the duration of hyperuricemia in group 3 and group 4. So large sample and prospective study need to be investigated in future.

In conclusion, our present study showed that CF-PWV was significantly higher in hypertension subjects with hyperuricemia compared to hypertension without hyperuricemia subjects, and serum uric acid was an independent associating factor of CFPWV.

Competing Interests

None.

Data Sharing Statement

No additional data are available.

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Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.

Ethics Approval

From the ethics committee of Peking University Shougang Hospital, China. (No IRBK-2017-022-01, May, 2, 2017)

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