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Associations of serum uric acid levels with arterial wave reflections and central systolic blood pressure ☆

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ABSTRACT

Background: Uric acid may be involved in the pathogenesis of hypertension. We investigated the roles of four major hemodynamic parameters of blood pressure, including arterial stiffness, wave reflections, cardiac output (CO), and total peripheral resistance (TPR), in the association between uric acid and central systolic blood pressure (SBP-c).

Methods: A sample of 1303 normotensive and untreated hypertensive Taiwanese participants (595 women, aged 30–79 years) was drawn from a community-based survey. Study subjects' baseline characteristics, biochemical parameters, carotid-femoral pulse wave velocity (cf-PWV), amplitude of the backward pressure wave decomposed from a calibrated tonometry-derived carotid pressure waveform (Pb), CO, TPR, and SBP-c were analyzed.

Results: In multi-variate analyses adjusted for age, waist circumference, body mass index, creatinine, total cholesterol, smoking, and heart rate, uric acid significantly correlated with Pb and cf-PWV in men, and Pb and TPR in women. The correlation between uric acid and Pb remained significant in men and women when cf-PWV was further adjusted. In the final multi-variate prediction model (model $r^2 = 0.839$) for SBP-c, the significant independent variables included uric acid (partial $r^2 = 0.005$), Pb (partial $r^2 = 0.651$), cf-PWV (partial $r^2 = 0.005$), CO (partial $r^2 = 0.062$), TPR (partial $r^2 = 0.021$), with adjustment for age, sex, waist circumference, body mass index, creatinine, total cholesterol, smoking, and heart rate.

Conclusions: Uric acid was significantly independently associated with wave reflections, which is the dominant determinant of SBP-c. Uric acid was also significantly associated with SBP-c independently of the major hemodynamic parameters.

1. Introduction

An elevated level of serum uric acid may be associated with the development of hypertension [1–3] and hypertension-related target organ damage [4], especially in patients with type 2 diabetes mellitus, metabolic syndrome, or obesity. The association of uric acid with hypertension [5,6] may partly explain the association of hyperuricemia with cardiovascular mortality, all-cause mortality, and mortality from heart failure and stroke [7,8]. In addition, lowering uric acid in the hyperuricemic adolescents with newly diagnosed hypertension or obese prehypertensives may become a therapeutic strategy in the management of hypertension [9,10].

How uric acid modulates blood pressure remains unclear [2,3]. Blood pressure is determined by both steady and pulsatile hemodynamics, including cardiac output, total peripheral resistance, arterial stiffness, and arterial wave reflections [11–13]. Only a few studies investigated the relationship between uric acid and various hemodynamic determinants of blood pressure, with inconsistent or even contradictory results [14–19]. For instance, the association between hyperuricemia and increased arterial stiffness has not been established [14–19]. In

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addition, a controversial inverse relationship between uric acid and arterial wave reflections in female newly diagnosed, never-treated hypertensives has been reported [14]. Therefore, in this cross-sectional study, we investigated the complex associations of serum uric acid with cardiac output, total peripheral resistance, arterial stiffness, arterial wave reflections, and central aortic systolic blood pressure (SBP-c). Central blood pressure is a more relevant blood pressure measurement and has been shown to predict target organ indices and cardiovascular mortality better than brachial blood pressure [20].

2. Methods

2.1. Study population

The study cohort of 1303 normotensive and untreated hypertensive [brachial systolic blood pressure (SBP-b) ≥140 mm Hg or brachial diastolic blood pressure (DBP-b) ≥90 mm Hg] Taiwanese participants (595 women aged 30–79 years) was drawn from a previous community-based survey conducted in 1992–1993 [21]. Baseline comprehensive cardiovascular evaluation included complete medical history and physical examination, carotid artery tonometry, non-directional Doppler flow velocimetry, and echocardiography, as previously described [21]. None of the participants had a previous history of diabetes mellitus, angina pectoris, or peripheral vascular disease, and none had clinical or echocardiographic evidence of other significant cardiac diseases. All participants gave informed consent, and the study was approved by the institutional review board at Johns Hopkins University.

2.2. Blood pressure variables

SBP-b and DBP-b were measured manually using a mercury sphygmomanometer and a standard-sized cuff (13×50 cm) by experienced cardiologists. Two measurements separated by at least 5 min were taken from the right arm of participants after they were seated for at least 5 min. A third measurement was taken when the difference of SBP-b between the first two measurements was greater than 10 mm Hg. Reported blood pressure values represented the average of the two or three consecutive measurements. Brachial pulse pressure (PP-b) was calculated as (SBP-b–DBP-b) and brachial mean blood pressure was calculated as [DBP-b + (PP-b/3)]. SBP-c, DBP-c, and PP-c were derived from the ensemble averaged right common carotid artery pressure waveform calibrated to DBP-b and mean blood pressure. Carotid artery pressure waveforms were registered noninvasively using an arterial tonometer [22].

2.3. Arterial stiffness

Carotid femoral pulse wave velocity (cf-PWV, current gold standard for arterial stiffness) was measured using sequential non-directional Doppler (Parks model 802; Parks Medical Electronics, Aloha, Oregon, USA) flow velocity at the right carotid and femoral arteries and a simultaneous ECG [21].

2.4. Arterial wave reflections

The calibrated carotid pressure waveform was analyzed to identify the inflection point resulting from the wave reflection using the zero-crossing timings of the fourth derivative of the pressure wave [22]. The augmented pressure (Pa) was the pressure amplitude above the inflection point, and the augmentation index (AI) was calculated as Pa divided by PP-c (Fig. 1). The carotid pressure waveform was also separated into its forward and reflected components to calculate the transit time-independent parameter of wave reflection intensity using the validated triangulation method [22,23]. This method creates a triangular-shaped flow wave by matching the onset, peak, and end of the flow wave to the timings of the foot, inflection point, and incisura of the carotid pressure wave (Fig. 1). Because the calculation of both the forward and the backward pressure components involves the product of flow and characteristic impedance (Zc), which itself has flow in the denominator, calibration of the flow waveform is not needed. Thus, the forward and backward components of the pressure wave can be constructed using the following equations:

$$Pf(t) = [Pm(t) + Zc \times F(t)]/2 \quad (1)$$

$$Pb(t) = [Pm(t) - Zc \times F(t)]/2 \quad (2)$$

where Pm(t) is the carotid pressure wave, F(t) is the approximated triangular-shaped flow wave, Pf(t) is the forward pressure component, and Pb(t) is the backward pressure component. Pf and Pb are the amplitudes of Pf(t) and Pb(t), respectively, with the latter being a transit-time independent index of wave reflections (Fig. 1) [22,24].

2.5. Biochemical variables

Overnight fasting serum and plasma samples were drawn for uric acid, C-peptide, and other biochemical measurements. Serum uric acid, cholesterol, triglycerides, and creatinine were measured with a Hitachi autoanalyzer 736-60 (Hitachi Ltd., Tokyo, Japan). Serum high-density lipoprotein cholesterol (HDL) was measured using a precipitation method (Kodak Ektachem HDL Kit; Eastman Kodak, Rochester, New York, USA). Serum low-density lipoprotein cholesterol was calculated from the Friederwald formula. Plasma glucose concentration was determined by a hexokinase/glucose-6-phosphate dehydrogenase method [Glucose (HK) Reagent Kit; Gilford Systems, Oberlin, Ohio, USA]. Fasting serum C-peptide was measured by radioimmunoassay (GP serum M1221, Novo, Bagaswaerd, Denmark) [25]. We also calculated homeostasis model assessment estimated by C-peptide (HOMA-CP) for insulin resistance index [26].

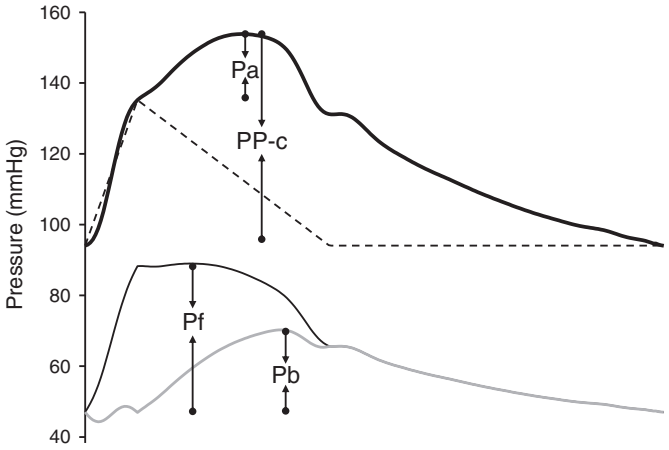

Fig. 1. Illustrations of augmented pressure (Pa), amplitude of backward pressure wave (Pb), amplitude of forward pressure wave (Pf), and carotid pulse pressure (PP-c). Pa and PP-c are derived from the calibrated carotid pressure waveform (thick solid line). Pb and Pf are derived from the forward (dark solid line) and backward (gray solid line) components decomposed from the carotid pressure waveform using a triangular flow wave (dashed line).

3. Statistical analysis

Differences of the basic characteristics between genders were examined with independent *t* test. Pearson's correlation coefficients of uric acid and SBP-c with other variables were calculated. Multiple linear regression analysis was performed for cf-PWV, CO, TPR, Pb, AI, Pa, and SBP-c, respectively, as dependent variable and with uric acid and other confounders as independent variables. Additional path analysis was performed to test the fit of the correlation matrix against several causal models incorporating the complex relationships between the independent variable (uric acid, cf-PWV, Pb) and the dependent variable (SBP-c). All statistical procedures were carried out using the SAS statistical package 8.0 with statistical significance set at $p<0.05$. The Path analysis was conducted using the SAS CALIS procedure. The maximum likelihood method was used for parameter estimation on the variance–covariance matrix.

4. Results

4.1. Basic characteristics of study subjects with hemodynamic parameters

There are total 1303 subjects including 647 hypertensive and 656 normotensive subjects. Characteristics of the study population stratified by hypertension status and gender are shown in Table 1. In both normotensive and hypertensive groups, females have lower serum uric acid, weight, height, waist circumference, DBP-b, triglycerides, and creatinine, and higher HDL than males. No significant differences between females and males were observed for heart rate, C-peptide, and HOMA-CP. For the hemodynamic parameters, females had higher Pb, AI, Pa, and TPR, males had higher CO, and females and males had similar cf-PWV, in both normotensive and hypertensive subjects.