



## Original Article

# High serum uric acid is associated to poorly controlled blood pressure and higher arterial stiffness in hypertensive subjects



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## ABSTRACT

**Introduction:** Serum uric acid (SUA) has been associated to incident hypertension and increased risk of cardiovascular diseases.

**Materials and methods:** Among the 2191 subjects enrolled during the last population survey of the Brisighella Heart Study, we identified 146 new cases of arterial hypertension and 394 treated but uncontrolled hypertensive patients with different levels of SUA. Their hemodynamic characteristics have been compared with those of age- and sex-matched normotensive (N. 324) and controlled hypertensive (N. 470) subjects. Then, by logistic regression analysis, we evaluated which factors were associated with a worse BP control under pharmacological treatment.

**Results:** SUA levels were significantly higher in untreated hypertensive and uncontrolled hypertensive patients when compared to normotensives and controlled hypertensive patients. Pulse wave velocity (PWV) was significantly higher ( $p < 0.001$ ) in undiagnosed and uncontrolled hypertensive patients, while controlled hypertensive patients had PWV values comparable to normotensive controls. A similar trend has been observed for the augmentation index (AI). A worse BP control was associated with SUA levels (OR 1277, 95% CI 1134–1600 per mg/dL), AI (OR 1066, 95%CI 1041–1092 per unit), and PWV (OR 1201, 95% CI 1089–1423, per m/s), but not with age, body mass index, nor estimated glomerular filtration rate.

**Conclusion:** Based on our data, SUA seems to be associated with an inadequate BP control in subjects treated with antihypertensive drugs, and subjects with both uncontrolled BP and relatively high SUA levels have also an increased arterial stiffness that (per se) could be a cause of worse BP control under treatment.

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## 1. Introduction

Uric acid (UA) is the final product of purine catabolism and is formed from xanthines and hypoxanthines mainly in the liver and intestine. While this metabolic pathway has been well preserved during the evolution in most of the living species, men as well as apes, Dalmatian dogs and some birds have lost the functionality of the final step in the UA degradation (uricase) with a consequent rise in the circulating levels of uric acid [1]. In normal conditions, the serum levels of UA (SUA) are lesser than 6 mg/dL in women and 7 mg/dL in men [2], due to a complex homeostatic regulation mainly involving the kidney transport systems. Hyperuricemia might result from either an overproduction and/or a reduced UA renal excretion, thus explaining the large number of factors able to affect SUA levels. Among them are encompassed both physiological conditions, including age, sex, renal function, and the rate of cellular

turnover, and exogenous/dietary factors, such as purine intake, fructose intake, and alcohol consumption [3].

During the last two decades, a large body of evidence has been published showing that even moderately increased levels of SUA are associated with incident hypertension [4,5] and an increased risk of cardiovascular diseases (CVD) [6,7]. An analysis from the Framingham Heart Study found an increased risk of progression of BP level in subjects with hyperuricemia. In a subsample of 3157 individuals not on antihypertensive treatment at the follow-up examination, SUA was positively associated with an increase in both systolic (SBP) and diastolic blood pressure (DBP) 4 years later and after adjustment for the most relevant confounding risk factors [8]. In addition, the presence of hyperuricemia has been associated with the extent of BP control. For instance, data from the NHANES surveys shows that the prevalence of hyperuricemia was 6–8% among healthy US adults, 10–15% among adults with uncontrolled BP, 22–25% with uncontrolled BP and one additional CVD risk factor, and 34–37% with uncontrolled BP and two additional CVD risk factors. This results in a cumulative relative risk for hyperuricemia of 4.5 (95% CI 3.5–5.6) in subjects with uncontrolled BP with and without

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additional CVD risk factors when compared to subjects with adequate BP control [9].

However, despite these interesting observations, few data are available about the relationship between SUA levels and BP control in pharmacologically treated hypertensive population, nor if the eventual worse BP control is related to SUA per se or to concomitant risk factors or vascular aging.

The aims of our study were to compare the BP, SUA levels, and peripheral hemodynamic characteristics of normotensive subjects, undiagnosed, controlled and uncontrolled hypertensive subjects, and to evaluate if SUA levels are associated with a different BP control in pharmacologically treated patients.

## 2. Materials and methods

The Brisighella Heart Study (BHS) is a prospective, population-based longitudinal epidemiological investigation involving 2939 randomly sampled Caucasian subjects (1491 men and 1448 women), aged 14–84 years, free of cardiovascular disease at enrolment and all resident in the northern Italian rural town of Brisighella. The study started in 1972 and it is still ongoing. The town of Brisighella was originally selected because of the homogeneity of life-style among its residents, with a very low rate of migration. Subjects were clinically evaluated at baseline and every 4 years thereafter by collecting an extensive amount of clinical and laboratory data [10]. All-cause mortality and morbidity, as well as the incidence of the main CVD risk factors, were recorded throughout the duration of the entire study [11].

The BHS protocol and its substudies, largely described elsewhere [12], have been approved by the Ethical Board of the University of Bologna and all volunteers involved gave their signed consent to participate in the study.

Briefly, the standard visit includes an update of medical history (familial and personal history, with a special attention to life-style habits and pharmacological treatments), physical examination (including anthropometric measurements, BP values, heart rate, and respiratory rate), the collection of a fasting blood sample, and standard electrocardiography [13,14].

Blood pressure measurements were taken from each subject (using the dominant arm) in the seated position using validated oscillometric devices with a cuff of appropriate size, in the morning before daily drug intake and after the patient had rested for 10 min in a quiet room. Three consecutive BP measurements were obtained at 1-min intervals, and the mean of the three readings was calculated [15]. Hypertension was defined as average SBP/DBP > 140/90 mmHg. The same values have been used as cut-off to define the degree of BP control in treated subjects.

Arterial stiffness parameters (augmentation index—AI, carotid-femoral pulse wave velocity—PWV) were estimated by the use of the Vicorder® device (Skidmore Medical Ltd., Bristol, UK), a validated brachial cuff-based device that estimates central BP using a brachial-to-aortic transfer function [16,17].

Blood biochemistry was evaluated according to standardized methods [18] by trained personnel and including fasting plasma glucose (FPG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (gGT), creatinine, estimated glomerular filtration rate (eGFR), SUA, and creatinine phosphokinase (CPK) [19].

For the purpose of the present study, during the last periodical survey, on 2191 screened subjects, we excluded subjects in secondary prevention for CVD, the ones affected by resistant hypertension, those assuming high daily doses of alcohol (>3 drinks per day), and those pharmacologically treated with urate lowering treatments (mainly allopurinol). Then, we identified 146 new cases of arterial hypertension and 394 treated but uncontrolled hypertensive patients. Thus, we

compared the BP values and peripheral hemodynamic characteristics of the former populations with those of age- ( $58 \pm 14$  years old) and sex-matched normotensive subjects (N. 324) and controlled hypertensive (N. 470) patients.

Descriptive values are expressed as mean  $\pm$  standard deviation (SD) or number and percentage. Continuous parameters have been described separately by ANOVA or Kruskal–Wallis analysis of variance followed by post hoc test, if normally or not normally distributed. The different levels of prevalence, expressed as absolute number and percentage, were compared by chi-square test followed by Fischer's exact test. A regression analysis was carried out to evaluate the relationship between blood pressure and arterial stiffness. Logistic regression analysis was then carried out to detect factors independently associated with uncontrolled BP, defined as BP > 140/90 mmHg [20], independently from the type of treatment, including as covariates age, gender, BMI, physical activity intensity, smoking habit, antihypertensive treatment (YES/NO), SUA, eGFR, AI, and PWV. We also repeated including mean arterial pressure in the prediction model to further evaluate the weight of BP per se in the prediction of the arterial stiffness parameters. A *p* value less than 0.05 was regarded as statistically significant. Statistical analyses were performed using the SPSS 21.0 statistical software package (IBM Corporation, Armonk, NY, USA).

## 3. Results

Demographic, anthropometric, and laboratory data of the general study population and the different subsets of subjects are summarized in Table 1. Uncontrolled hypertensive patients were significantly heavier and had higher LDL-C and lower HDL-C levels when compared to other groups. SUA levels were superimposable in normotensives and controlled hypertensive patients ( $5.1 \pm 1.3$  mg/dL and  $5.1 \pm 1.2$  mg/dL, respectively, *p* > 0.05), while significantly higher values were observed in untreated and uncontrolled hypertensive patients (Table 1).

Male/female ratio was homogeneously distributed in the different subgroups with a slight but not significant higher prevalence of male subjects among the newly diagnosed and uncontrolled hypertensive patients. The prevalence of active smokers was significantly lower in non-hypertensive subjects (*p* < 0.05) who also showed a higher degree of moderate-to-high physical activity when compared to the all other groups (*p* < 0.05) (Table 2).

The use of antihypertensive drugs was equally distributed in controlled and uncontrolled hypertensive patients, with a comparable proportion of patients treated with monotherapy (56% vs. 60% of patients, respectively). No significant differences have been observed in the distribution of the main classes of BP lowering drugs controlled and uncontrolled hypertensive patients (ACE inhibitors 34% vs. 37%, ARBs 12% vs. 13%, calcium-channel blockers 29% vs. 33%, beta-blockers 12% vs. 13%, diuretics 5% vs. 2%, and other drugs 8% vs. 2%, respectively, all *p* > 0.05). A combination of two drugs was used by 28% and 27% of the patient populations, while in the remainder of the hypertensive population (16% vs. 13%, *p* > 0.05), a combination of three or more drugs was prescribed.

Augmentation index and PWV were significantly related to the mean arterial blood pressure level in the whole population (AI: *B* = 0.101, 95% CI 0.048–0.155, *beta* = 0.110, *p* < 0.001; PWV: *B* = 0.049, 95% CI 0.031–0.068, *beta* = 0.150, *p* < 0.001) and in uncontrolled hypertensives (AI: *B* = 0.113, 95% CI 0.088–0.138, *beta* = 0.256, *p* < 0.001; PWV: *B* = 0.047, 95% CI 0.038–0.056, *beta* = 0.302, *p* < 0.001), but not in the other population subgroups (*p* > 0.05).

Pulse wave velocity was significantly higher (*p* < 0.001) in undiagnosed hypertensive ( $9.8 \pm 2.4$  m/s) and uncontrolled hypertensive ( $10.3 \pm 4.3$  m/s) patients, whereas no difference has been observed in the levels of PWV in controlled hypertensives ( $8.4 \pm 2.1$  m/s) and normotensive control ( $8.2 \pm 1.9$  m/s, *p* > 0.05). Similar results have been observed for AI (Table 3).

In our cohort, age, gender, BMI, intensity of physical activity, smoking habit, antihypertensive treatment, and eGFR were not

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