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ORIGINAL ARTICLE

Relationship Between Serum Uric Acid and Electrocardiographic Alterations in a Large Sample of General Population: Data From the Brisighella Heart Study

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Abstract
Introduction Serum uric acid (SUA) may contribute to the increased cardiovascular damage through direct injury to the endothelium and alteration of cardiovascular function.
Aim To evaluate the association of SUA with the presence of the most recurrent electrographic alterations and with the length of the main ECG intervals in a large sample of general population.
Methods For this study, on the database of the Brisighella Heart Study, we evaluated the available data of 790 men and 849 women, excluding subjects affected by gout or taking antihyperuricemic agents, those taking drug increasing the QT interval and those using beta-blockers or non-dihydropyridine calcium channel blockers at the moment of the ECG registration. Multiple ascending stepwise regression analyses were carried out to determine the independent predictors of the predefined ECG alterations.
Results The prevalence of predefined ECG alterations was comparable between genders, with the exception of sinus bradicardia, left-anterior fascicular block, atrio-ventricular blocks and left ventricular hypertrophy (LVH), which appeared to be more frequent in men. The multivariate analysis revealed that SUA was associated to ischaemic alterations, LVH, sinus tachycardia and tachyarrhytmias. Age was associated to all evaluated ECG alterations beyond sinus tachycardia and LVH. Male sex was associated to sinus bradicardia, atrio-ventricular blocks, anterior-left fascicular block and LVH. Blood pressure was associated to different ECG alterations, but with clinically relevant OR with ischaemic alterations and LVH.
Conclusion SUA level is related the prevalence of both organic and rhythm ECG alterations in a wide sample of general population.

Keywords Electrocardiogram · Arrhythmias · Epidemiology · Serum uric acid

The Brisighella Heart Study: the members are listed in Appendix.

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1 Introduction

Uric acid (UA) is a diprotic acid which represents the final product of purine catabolism. In normal conditions its serum level is lower than 6 mg/dL in women and 7 mg/dL in men [1], due to a homeostatic regulation mainly ruled out by the kidney. Higher levels are defined as hyperuricemia, which could be the result both of overproduction or underexcretion, as many are the factors that could influence SUA. Some endogenous, such as age, sex, renal function and high cellular turnover conditions, and some others exogenous, such as purine intake and alcohol consumption.

The importance of determining SUA is due to the fact that, since it was initially considered to be an inert composite, it has been widely demonstrated that UA possesses opposite properties depending on its serum level: antioxidant at physiological concentrations and, on the contrary, pro-oxydant in hyperuricemia [2]. Thus, focusing on pathologies characterized by inflammation and oxidative stress, numerous proves have been collected so far to affirm that UA contributes to the development of some of the most important cardiovascular diseases, from hypertension to chronic heart failure and to the vast field of coronary artery diseases [3]. Its detrimental effects on the cardiovascular system include mediating immune response upon cell injury [4], increasing endotoxin-stimulated tumor necrosis factor-alpha production and hence proinflammatory immune activation [5]. Therefore, high levels of SUA may contribute to the increased cardiovascular damage through direct injury to the endothelium and alteration of cardiovascular function [6]. However there is a lack of studies about the relationship between UA and electrographic documented alterations. Thus, the aim of this study was to evaluate the association of SUA with the presence of the most recurrent electrographic alterations and with the length of the main ECG intervals in a large sample of general population.

2 Methods

The Brisighella Heart Study (BHS) is a prospective, population-based longitudinal epidemiological investigation involving 2,939 randomly selected subjects (1,491 men and 1,448 women), aged 14–84 years, free of cardiovascular disease at enrolment, resident in the northern Italy rural town of Brisighella. The study started in 1972 and it is still on-going. The town of Brisighella was originally selected as the site for the study, because of the homogeneity of lifestyle 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 [7, 8].

The BHS protocol and its sub-studies have been approved by the Ethical Board of the University of Bologna and all volunteers involved gave their signed consent to the participation to the study.

A detailed description of the protocol of the BHS and the full protocol have been largely described elsewhere [9]. Briefly, all-cause mortality and morbidity, as well as the incidence of the main cardiovascular risk factors, were recorded throughout the duration of the entire study. During each survey we perform an update of familial and personal history (with a specific attention to life-style habits and pharmacological treatments), a physical examination (with a specific attention to anthropometric measurements, blood pressure measuring, heart and breath rate evaluation), and we collect a fasting blood sample [10, 11]. Hematochemical analyses have been evaluated according to standardized methods [12] by trained personnel and include fasting plasma glucose (FPG), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), non-HDL cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, creatinine, SUA, and creatine-phosphokinase (CPK). Glomerular filtration rate was derived using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [13].

Standard 12-lead resting ECG recordings were performed using a Marquette MAC 12 electrocardiograph (Marquette Medical Systems, Inc., Milwaukee, WI) with signals sampled at 250 Hz per channel. A representative P-QRS-T cycle was then derived by selective averaging using the Dalhousie ECG Analysis Program [14]. The automated diagnosis of the ECG software was confirmed in blind manner by a trained cardiologist. Sinus bradycardia was defined by a sinusal rhythm with a heart rate lower than 60 beats per minute (BPM); same but non sinusal frequencies were grouped and considered as bradyarrhytmias. Sinusal frequencies higher than 100 BPM were defined as sinus tachycardia; same but non sinusal frequencies were grouped and considered as tachyarrhytmias. Left ventricular hypertrophy was calculated according to the Sokolow–Lyon formula, as recommended by current guidelines [15], and the diagnosis was further confirmed by the R-wave voltage in lead aVL, that seems to present a greater diagnostic ability in detecting left ventricular hypertrophy at a population level [16].

Signs of previous myocardial infarction were detected by the presence of Q waves, according to current recommendations from European guidelines [17]. We excluded unspecific and/or uncommon alterations from our analysis.

For this study, considering the 2012 population survey, we evaluated the available data of 790 men and 849 women, excluding subjects affected by gout or taking antihyperuricemic agents, those taking drug increasing the QT interval at the moment of the ECG registration [18] and those using beta-blockers or non-dihydropyridine calcium channel blockers.

Continuous parameters have been described separately by sex, being the most part of them differently distributed between genders, in particular ECG wave intervals, and their values have been compared by *t* test for independent samples. Univariate regression analysis with Bonferroni's correction and the Pearson correlation coefficients were used to assess the association between sampled

anthropometric, biochemical, clinical parameters and ECG intervals.

Multiple ascending stepwise regression analyses were carried out to determine the independent predictors of the predefined ECG alterations. All variables at $p \leq 0.2$ in univariate analysis were candidates to the model.

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

The main clinical and laboratory characteristics of the studied population, grouped by sex, are resumed in Table 1. All the considered continuous parameters were significantly higher in men, except for HDL-C, Apo-AI and estimated Glomerular Filtration Rate that were significantly higher in women, while age and LDL-C were similar between the genders.

The ECG diagnoses, distributed by sex, are resumed in Table 2. For each considered electrocardiographic alteration the percentage of diagnosed ECG was comparable between the two sexes, with the exception of sinus bradicardia, left-anterior fascicular block, atrio-ventricular blocks and left ventricular hypertrophy which appeared to be more frequent in men.

The multivariate analysis (Table 3) revealed that SUA was associated to previous myocardial infarction, left ventricular hypertrophy, sinus tachycardia and tachyarrhytmias. Age was associated to all evaluated ECG alterations beyond sinus tachycardia and left ventricular hypertrophy. Male sex was associated to sinus bradicardia, atrio-ventricular blocks, anterior-left fascicular block and left ventricular hypertrophy. Blood pressure was associated to different ECG alterations, but with clinically relevant OR with ischaemic alterations and left ventricular hypertrophy (Table 4).

Table 2 Mean ECG wave intervals in men and women participants to the population survey

	Men (N. 790)		Women (N. 849)	
	Mean	SD	Mean	SD
Heart rate (bpm)	63.25	10.38	67.67	10.95
PR (ms)*	163.25	86.91	103.88	72.01
RR (ms)*	999.95	173.88	908.18	155.71
QRS (ms)*	86.97	19.90	80.44	10.18
QT (ms)*	393.29	29.88	388.41	30.35
cQT (ms)*	397.06	48.93	411.23	44.41
JT (ms)	306.32	65.25	308.02	30.91

* $p < 0.05$ men vs. women

4 Discussion

Beyond the most well known cardiovascular risk factors UA has also been supposed to contribute to the development of cardiovascular diseases. Thus, despite the need of further prospective and randomized trials to better establish the burden of this assumption, mainly due to the fact that hyperuricemia is commonly associated with metabolic syndrome and renal function impairment which are themselves cardiovascular risk factors, medical literature has widely described the involvement of SUA in several clinical entities as incident hypertension [19], stroke [20],

Table 1 Clinical and laboratory characteristics of men and women participants to the population survey

	Men (N. 790)		Women (N. 849)	
	Mean	SD	Mean	SD
Age (years)	53.34	17.929	52.96	18.16
Body mass index (kg/m^2)*	26.84	3.79	26.09	5.10
Waist circumference (cm)*	94.00	11.15	87.46	13.64
Systolic blood pressure (mmHg)*	135.06	15.90	130.99	18.42
Diastolic blood pressure (mmHg)*	85.10	10.34	81.19	9.99
Fasting plasma glucose (mg/dL)*	108.90	18.90	102.19	17.28
LDL-cholesterol (mg/dL)	135.25	34.85	134.51	34.42
Triglycerides (mg/dL)*	121.11	73.73	104.97	60.67
HDL-cholesterol (mg/dL)*	43.12	9.86	49.11	10.78
Apolipoprotein B (mg/dL)*	90.71	21.45	86.55	21.06
Apolipoprotein A (mg/dL)*	133.48	25.64	152.02	27.79
Serum uric acid (mg/dL)*	4.57	1.36	4.37	1.33
Creatinine (mg/dL)*	1.19	0.88	0.84	0.16
Estimated glomerular filtration rate (mL/min/1.73 m^2)*	58.81	11.05	69.51	13.23

* $p < 0.05$ men vs. women

Table 3 ECG diagnosis in men and women participants to the population survey

ECG characteristics	Gender		Total
	Men (N. 790)	Women (N. 849)	
Normal*	523 (66.7 %)	688 (81.4 %)	1211 (74.3 %)
Sinus tachycardia	2 (0.3 %)	4 (0.5%)	6 (0.4 %)
Tachyarrhytmias	33 (4.2 %)	30 (3.6%)	63 (3.9 %)
Sinus bradicardia*	93 (11.9 %)	30 (3.6%)	123 (7.6 %)
Right branch block	42 (5.4 %)	37 (4.4%)	79 (4.8 %)
Left branch block	5 (0.6 %)	7 (0.8%)	12 (0.7 %)
Left-anterior fascicular block*	35 (4.5 %)	16 (1.9%)	51 (3.1 %)
Atrio-ventricular blocks*	13 (1.7 %)	6 (0.7 %)	19 (1.2 %)
Pace-maker rythm*	4 (0.5 %)	1 (0.1 %)	5 (0.3 %)
Previous ischaemia	19 (2.4 %)	19 (2.3 %)	38 (2.3 %)
Left ventricular hypertrophy*	15 (2.0 %)	7 (0.9 %)	22 (1.3 %)

* $p < 0.05$ men vs. women

Table 4 Multinomial regression analysis of the factors and covariates associated with the different ECG abnormalities compared with the normal group

ECG abnormality	Variables	OR	95 % Confidence interval	
			Lower limit	Upper limit
Sinus bradicardia	Age	1.02	1.00	1.03
	Systolic blood pressure	0.98	0.96	0.99
	Intense physical activity	0.74	0.58	0.94
	Male sex	2.27	1.58	4.05
Tachyarrhytmias	Age	1.06	1.04	1.08
	Diastolic blood pressure	1.02	1.01	1.04
	Serum uric acid	1.11	1.01	1.36
	Current smoking	1.19	1.07	1.41
Sinus tachycardia	Serum uric acid	2.21	1.05	4.16
	Fasting plasma glucose	1.02	1.00	1.04
Right branch block	Age	1.03	1.02	1.05
	Systolic blood pressure	1.01	1.00	1.03
Left branch block	Age	1.05	1.00	1.09
Atrio-ventricular blocks	Age	1.07	1.03	1.11
	Male sex	3.28	1.46	6.52
Anterior-left fascicular block	Age	1.08	1.05	1.12
	Male sex	2.58	1.77	5.21
Pace-maker rythm	Age	1.14	1.01	1.28
	Serum uric acid	1.96	1.09	3.97
Previous ischaemia	Age	1.15	1.12	1.18
	LDL-cholesterol	1.39	1.13	1.83
	Serum uric acid	1.35	1.04	1.75
	Systolic blood pressure	1.19	1.08	1.38
	Current smoking	1.44	1.23	1.65
Left ventricular hypertrophy	Diastolic blood pressure	1.36	1.09	1.72
	Body mass index	1.03	1.01	1.06
	Serum uric acid	1.09	1.08	1.18
	Male sex	2.77	1.61	6.11

acute coronary syndrome [19, 21, 22] and chronic heart failure [23, 24]. What we decided to focus on instead was the relationship between SUA and pure electrocardiographic alterations, without any referral to clinics, in a group of general population, as to our knowledge no other study had analyzed the relationship

before, with the only exception of few works on atrial fibrillation (AF) we will discuss further.

According to our results, speaking about electrocardiographic alterations indicative of organic cardiac modifications, UA was found to be associated firstly with signs of previous myocardial infarction and it is worthy to underline its Odds Ratio, comparable with that of LDL-C and higher than that of SBP, revealing the strength of the parameter. Another correlation was UA with signs of left ventricular hypertrophy. The explanation of this findings is based on the microvascular damage induced by UA on the coronary wall which in time may lead to the loss of endothelium-dependent vasodilatation. UA reduces the compliance of vessel walls due to a lower NO bioavailability both by blocking L-arginine uptake [25] and by facilitating its degradation [26] as observed in murine and cellular models. Moreover UA can trigger microvascular inflammation stimulating the production of chemokines and inflammatory markers [27]. Additionally, UA stimulates renin-angiotensin system (RAS) [28] and vascular smooth cell proliferation [29], thus substantiating the relationship with electrocardiographic signs of left ventricular hypertrophy.

Considering instead tracings of rhythm alterations, we found UA was associated with tachyarrhytmias, which consisted principally of atrial fibrillation, and with sinus tachycardia. The results confirmed the recent TROMSO study [30] which showed the direct influence of baseline SUA on the risk of developing atrial fibrillation in a wide sample of general population and another study in which the authors supposed the larger left atrium dimension observed in hyperuricemic patients to represent the possible cause [31]. Anyway, we think that the inflammatory and oxidative properties of UA may play a part even this time, as inflammatory markers have been associated to the development of arrhythmias [32]. As for sinus tachycardia, it could be framed considering the higher heart rate as compensatory of the increased myocardial oxygen request due to the over-mentioned UA induced ventricular remodelling, while sinus bradicardia was not found to be associated with UA level. No correlations were found with bundle branch and atrio-ventricular blocks. As for bundle branch blocks the result could be partially in contrast with one previous study [33] which demonstrated a relatively high prevalence of the ECG alteration in patients on haemodialysis compared to general population, assuming that UA accumulation could play a part in altering the electric cardiac conduction. Anyway, the study population was not comparable with ours, as it was composed of patients with final-stage renal function impairment, leading to higher values of SUA, without considering any other potential confounding factors.

This study has some relevant limitations, the main of which is the transversal design of the study that did not allow concluding if SUA was higher in subjects developing ECG alterations before the change itself. The second one is that we did not exclude from the selection patients already taking lipid-lowering drugs or antihypertensive drugs (beyond beta-blockers or non-dihydropyridine calcium channel blockers) as the choice was made to preserve the sample representativity of the whole Brisighella Heart Study cohort, excluding however the main iatrogenic causes of rhythm alterations. Finally, our results could not directly applicable to different populations, since the Brisighella Heart Study cohort as specific characteristics, among which relevant could be highly prevalent sinus bradycardia, observed in all study surveys [7, 8, 10, 12].

To conclude, even if confounding factors could hamper the interpretation of UA involvement in the development of cardiovascular diseases and even if its burden to be considered as a new cardiovascular risk factor still has to be established with further trials, we demonstrated that UA serum level is related to the development of both organic and both rhythm ECG alterations in a wide sample of general population.

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Appendix: The Brisighella Study Group

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