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ORIGINAL ARTICLE

Correlation of serum uric acid with heart rate variability in hypertension

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KEYWORDS
Uric acid;
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Abstract
Background: Autonomic dysfunction with dominant sympathetic tone is a common finding among hypertensives and prehypertensives. Uric acid is one of the independent predictors of hypertension. There are very few studies which have shown a relationship between the autonomic tone and uric acid generation pathway among prehypertensives and hypertensives. Aim of the study was to estimate and correlate serum uric acid levels with autonomic function as measured by heart rate variability (HRV) among prehypertensives and hypertensives.
Methods: Cross-sectional study of three groups, prehypertensives, hypertensives and normotensives, classified according to Joint National Committee VII criteria, with 35 subjects in each group were included in this study. Serum uric acid levels were estimated by using colorimetric assay kit. HRV was analyzed after recording lead II Electrocardiogram using RMS Vagus HRV software (RMS, India). One-way ANOVA and Pearson's correlation was done using SPSS 18.0 software.
Results: Mean uric acid levels were 5.62 ± 2.21 mg/dL in normal subjects, 7.06 ± 2.87 mg/dL in prehypertensives and 9.77 ± 2.04 mg/dL in hypertensives. There was statistically significant negative correlation between uric acid and time domain parameters of HRV in the whole sample and among prehypertensives and positive correlation with low frequency power (LF) in ms^2 and n.u.
Conclusions: Serum uric acid levels were high in prehypertensives and hypertensives as compared to normal subjects. Further, there was statistically significant correlation seen between uric acid levels and sympathetic domain parameters particularly among prehypertensives.

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PALABRAS CLAVE
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Prehipertensión;
Hipertensión

Relación entre el ácido úrico sérico y la variabilidad de la frecuencia cardíaca en pacientes hipertensos

Resumen
Antecedentes: La distonía neurovegetativa con tono simpático dominante es un hallazgo habitual entre los pacientes hipertensos y prehipertensos. El ácido úrico es uno de los factores pronóstico independientes de la hipertensión. Existen muy pocos estudios que hayan manifestado una relación entre el tono neurovegetativo y el proceso de producción de ácido úrico entre hipertensos y prehipertensos. El objetivo de la investigación fue calcular e interrelacionar los niveles de ácido úrico con la función neurovegetativa conforme a la variabilidad de la frecuencia cardíaca (HRV) entre pacientes prehipertensos e hipertensos.
Métodos: Estudio transversal de tres grupos, prehipertensos, hipertensos y normotensos, clasificados conforme a los criterios del séptimo informe del Joint National Committee, con 35 integrantes en cada grupo. Los niveles de ácido úrico se calcularon con un equipo de análisis colorimétrico. Se análizo la HRV una vez quedó registrada la DII del ECG por medio del software RMS Vagus HRV (RMS, India). La relación entre ANOVA y Pearson se realizó con el software SPSS 18.0.
Resultados: Los niveles medios de ácido úrico fueron 5,62 ± 2,21 mg/dL en individuos normales, 7,06 ± 2,87 mg/dL en prehipertensos y 9,77 ± 2,04 mg/dL en hipertensos. La relación entre el ácido úrico y los parámetros de tiempo de la HRV fue negativa en significación estadística durante toda la muestra y entre los prehipertensos, y fue positiva con baja frecuencia (BF) en ms^2..
Conclusiones: Los niveles de ácido úrico sanguíneo fueron altos en los prehipertensos e hipertensos en comparación con los pacientes normales. Asimismo, existió una relación de significación estadística entre los niveles de ácido úrico y los parámetros simpáticos, sobre todo entre los prehipertensos.

Introduction

Hypertension arises from complex and interrelated etiologies, which features early markers that are often present before blood pressure (BP) elevation is sustained. The seventh report of the Joint National Committee (JNC), defined prehypertension as systolic BP ranging between 120 and 139 mmHg and/or diastolic BP ranging between 80 and 89 mmHg. It is this category which is advised lifestyle modifications and not pharmacotherapy for reducing the BP to normal levels.[1] Thus early identification of prehypertensives will help in reducing hypertension disease burden. Prehypertensives are 65% more likely to have at least one adverse cardiovascular risk factor, than normotensives.[2]

Autonomic dysfunction plays a crucial role in the pathogenesis of hypertension. Autonomic dysfunction can be easily studied by measurement of heart rate variability (HRV). It has been demonstrated that there is decreased parasympathetic activity in prehypertension and hypertension group.[3] Previous studies have reported either similar[4,5] or reduced[6–8] HRV in hypertensives as compared with normotensives. Untreated middle-aged hypertensives showed low frequency (LF) power, high frequency (HF) power and LF/HF similar to normotensive controls.[9] Hypertensives on treatment had decreased SDNN (standard deviation of all NN intervals), LF, LF/HF and unchanged HF power.[10] In the Framingham study, all time domain and frequency domain variables of HRV were reduced in untreated hypertensive men and women.[11] Hypertensives had greater LF n.u. (68 ± 3 versus 54 ± 3) and lower HF n.u. (24 ± 3 versus 33 ± 2) than normotensives; n.u. representing normalized units.[12] Though most of studies have shown reduced HRV among hypertensives, not many studies have documented HRV among prehypertensives.

Various biomarkers like plasma catecholamines, highly sensitive C-reactive protein (hs-CRP), plasma renin activity, uric acid (UA), etc. are recognized in hypertension, but their link with the autonomic tone remains untested. Uric acid, an end-product of purine metabolism is generated from xanthine by the enzyme xanthine oxidase among human beings. Normal serum concentrations are generally <420 mmol/l (<7 mg/dL) for men and <350 mmol/l (<6 mg/dL) for women.[13] There have been large amount of evidence accumulating about the causative association between UA and cardiovascular diseases like hypertension, heart failure, stroke, metabolic syndrome. An elevated UA level has been shown to be associated with increased cardiovascular morbidity and mortality.[14] In fact, hypertensive patients with hyperuricemia have a 3–5 fold increased risk of coronary or cerebrovascular disease compared with patients with normal UA levels.[15] Recent guidelines by European Society of Hypertension–European Society of Cardiology recommend UA measurement as a routine laboratory investigation in hypertensive patients.[16] However, this has not been considered a risk factor for hypertension by either the American Heart Association[17] or the JNC VII.[1]

Uric acid is now measured routinely across laboratories. Considering, it is easily assayed and available at a reasonable cost, screening for hyperuricemia would be cost effective for subjects with prehypertension and hypertension. Autonomic dysfunction tests, on the other hand, are not routinely investigated unless indicated. In this study we hypothesized that UA levels are increased among prehypertensives and hypertensives and this might correlate with sympathetic activity as measured by HRV due to interaction between autonomic nervous system and UA synthesis pathway which may play a role in the causation of prehypertension, hypertension.

Materials and methods

Rationality for sample size

Employing nMaster 1.0 software (nMaster 2.0 sample size software, Department of Biostatistics, CMC, Vellore) based on Erden et al., 2011 study,[18] the correlation between night time blood pressure and uric acid was 0.260. With a power of 80% and alpha error of 5% the sample size was calculated to be 105. Thus the sample size in each group was set at 35.

Patient characteristics

Subjects in the age range of 18–60 years; with BP in range of normotension, pre-hypertension and hypertension (newly diagnosed) as per JNC VII criteria[1] were included. Postmenopausal women, individuals with gout, myocardial infarction, diabetes mellitus, peptic ulcer, recurrent asthma, bronchitis, sinusitis, renal dysfunction, malignant diseases, obesity, diabetes mellitus, and dyslipidemia, patients taking any drug known to affect serum UA levels (such as allopurinol, probenecid, etc.), patients on drugs affecting autonomic nervous system function, secondary hypertension were excluded.

This was a cross sectional study. The sample composed of 35 subjects with pre-hypertension, 35 with hypertension and 35 with normotension. The hypertensive subjects needed for the above study were recruited from out-patient department of the tertiary care hospital. Prehypertensives and healthy normal subjects were recruited by history and clinical examination, from relatives accompanying patients and staff of the hospital. The study was ethically cleared by the institutional ethical review committee. The subjects were informed in detail about the objectives of the study, the tests to be analyzed, and also the rights to withdraw from participating in the study. Informed consent was taken from each subject.

A detailed history about the general health of the subjects, physical activity, dietary habits, stress levels at work (measured on 10-point scale by visual analog scale), general stress based on perceived stress scale, smoking and drinking and drug history was recorded by a pre-designed, pretested questionnaire. The anthropometric measurements were recorded for all the subjects in light clothing without shoes. Height and weight was measured and body mass index (BMI) in kg/m^2 was calculated for each subject. Waist and hip circumference (cm) was measured and waist hip ratio (WHR) was then calculated.

After rest of 10 min the BP was recorded twice with a gap of 5 min in supine position on the right arm of subjects using sphygmomanometer. In order to record electrocardiogram (ECG) subjects were instructed to abstain from coffee or tea intake and smoking on the day of recording. All the recordings were done between 08.00 and 10.00 am in order to avoid diurnal variation in HRV. After 15 min of rest, Lead II ECG was recorded for a duration of 10 min using RMS Vagus HRV (RMS Vagus, India) hardware and was analyzed using fast Fourier transformation using the given software. The parameters analyzed were time domain parameters such as SDNN, RMSSD (square root of the mean of the sum of the squares of differences between adjacent NN intervals), NN50 (number of pairs of successive NNs that differ by more than 50 ms), pNN50 (proportion of NN50 divided by total number of NNs). The frequency domain parameters included were absolute power in very low frequency (VLF), low frequency (LF) range, high frequency (HF) range given in millisecond square units (ms^2) and normalized units (n.u.) and ratio of low frequency to high frequency (LF/HF).

After an overnight fast of 12 h, 5 mL of blood sample was drawn under aseptic precautions from the anterior cubital vein between 08:00 and 09:00 am from all subjects. Samples were centrifuged; serum was separated within 30 min of collection and stored at $-20\,^{\circ}C$ until analysis. Serum UA levels were measured using UA MR Enzymatic colorimetric assay kit (Linear Chemicals). This assay was based on the principle that UA is oxidized by uricase to allantoin with the formation of hydrogen peroxide; in the presence of peroxidise, a mixture of dichlorophenol sulphonate and 4-aminoantipyrine is oxidized by hydrogen peroxide to form a quinoneimine dye proportional to the concentration of UA in the sample.

Statistical analysis

Data was analyzed using SPSS 18.0 software (SPSS Inc., Chicago, USA). Quantitative data was described in terms of descriptive statistics such as mean and standard deviation (SD). To test the differences in mean values between the three groups with regard to various quantitative parameters, one-way ANOVA was employed. To test for associations between categorical variables Chi square test was employed and data was presented as percentage of subjects. Mann–Whitney *U* test was used to compare mean UA levels based on gender and alcohol intake. For HRV parameters which showed skewed distribution non-parametric Kruskal–Wallis test was employed. Pearson's/Spearman's correlation coefficient was used to assess the correlation between UA and HRV parameters. Multivariate backward stepwise linear regression analysis was employed to find out the independent predictors of UA after univariate analysis. *P* value of <0.05 was considered statistically significant.

Results

Baseline population characteristics

The three groups differed based on mean age comparison, with more number of subjects above the age of 40 years being hypertensives. There was a significant difference in the three groups based on gender classification with

Table 1 Clinical characteristics, blood pressure and uric acid of the study population.

Data based on questionnaire	*N* (%)	Normotension 35 (100%)	Prehypertension 35 (100%)	Hypertension 35 (100%)	*P*
Age (years)	Mean ± SD	23.71 ± 9.9	28.76 ± 11.9	48.37 ± 5.8	<0.001[b]
Gender	Males	28.6	51.2	73.7	0.009[a]
	Females	71.4	48.8	26.3	
Diet	Vegetarian	35.7	39	26.3	0.63[a]
	Non-veg	64.3	61	73.7	
Smoking	Yes	0	2.4	10.5	0.13[a]
	No	100	97.6	89.5	
Alcohol intake	Yes	7.1	7.3	47.4	<0.001[a]
	No	92.9	92.7	52.6	
Involved in physical activity	Yes	46.4	48.8	42.1	0.89[a]
	No	53.6	51.2	57.9	
BMI	(kg/m^2)	21.71 ± 4.1	23.64 ± 3.8	27.84 ± 3.0	<0.001[b]
Waist hip ratio		0.80 ± 0.8	0.84 ± 0.2	0.92 ± 0.5	0.003[b]
Stress at work	(Range 0–10)	4.96 ± 2.2	5.52 ± 2.3	7.79 ± 0.6	<0.001[b]
Perceived stress scale		17.89 ± 7.1	19.59 ± 5.4	21.68 ± 4.6	0.096[b]
Systolic BP	(mmHg)	112.5 ± 4.7	124.39 ± 5.7	148.79 ± 6.4	<0.001[b]
Diastolic BP	(mmHg)	73.43 ± 6.1	81.66 ± 3.2	93.89 ± 5.9	<0.001[b]
Serum uric acid	(mg/dL)	5.62 ± 2.2	7.06 ± 2.9	9.77 ± 2.0	<0.001[b]

All values are given in mean ± SD and percentage of total number of subjects; *n* is the number of subjects; *P* value of <0.05 was considered significant.

[a] Chi square test.

[b] One-way ANOVA.

more number of males as hypertensives and more number of females as normotensives. Uric acid levels among males were 8.95 ± 2.54 mg/dL and among females were 5.49 ± 2.11 mg/dL ($P < 0.001$). Stress levels at work as measured by visual analog scale was significantly higher among hypertensives. The smoking, diet history and physical activity did not vary significantly between the three groups. Alcohol intake was more among hypertensives and this was statistically significant on comparison with other two groups. Uric acid among alcoholics was 9.46 ± 2.16 mg/dL and among non-alcoholics it was 6.75 ± 2.83 mg/dL ($P = 0.001$). Based on anthropometric measurements we found there was a significant difference between the three groups with hypertensives having higher BMI, WHR (Table 1).

There were statistically significant differences in the systolic and diastolic BP and serum UA levels in between the three groups. Prehypertensives and hypertensives had significantly higher BP and UA as compared to normotensives (Table 1). On applying post hoc Tukey's test to test for differences in UA levels, it was seen that normotensives ($P < 0.001$) and prehypertensives ($P = 0.001$) differed significantly from hypertensives; but the difference between normotensives and prehypertensives was not significant ($P = 0.056$).

Time domain parameters (SDNN, RMSSD) had decreased significantly among hypertensives whereas the frequency domain parameters did not show a significant difference between the groups compared on HRV analysis; this indifference persisted after natural logarithmic conversion of HRV parameters (not shown in tables). We observed no significant elevation in LF power or LF/HF among hypertensives compared with prehypertensives included in this study (Table 2).

Pearson's correlation analysis

On correlation analysis of serum UA with age, anthropometric measurements and BP levels, there was a significant positive correlation between serum UA and age ($r = 0.458$, $P < 0.001$), waist hip ratio ($r = 0.263$, $P = 0.013$), BMI ($r = 0.242$, $P = 0.023$) and systolic BP ($r = 0.558$, $P < 0.001$) (not shown in tables).

We conducted Pearson's/Spearman's correlation analysis (HRV parameters with skewed distribution on Kolmogorov–Smirnov test) (Table S1, supplement file) to study UA and HRV relationship. They were NN50, pNN50, HF n.u., HF ms^2. On correlation analysis of the whole sample, it was observed that UA was negatively correlated with all the time domain parameters (SDNN, RMSSD, NN50, pNN50). This was observed further among prehypertensives (Fig. 1). Uric acid also showed positive correlation with LF (ms^2) ($r = 0.219$) and negative association with HF (ms^2) ($r = -0.297$) in the whole sample; but the positive correlation with LF (ms^2) was significant among prehypertensives ($r = 0.319$). Further, UA levels were positively correlating with LF/HF among normotensives and hypertensives but not with prehypertensives. There was statistically no significant correlation between other HRV parameters and serum UA (Tables 3 and 4).

Since the baseline age and gender differences were significant, we conducted correlation analysis after age and sex stratification. We observed that UA and HRV parameters failed to show any correlation except among male prehypertensives who were aged between 36 and 58 years, where UA was negatively correlating with VLF ms^2 ($r = 0.532$, $P = 0.034$), LF ms^2 ($r = 0.773$, $P < 0.001$), SDNN

Table 2 Comparative data of Heart rate variability analysis between the three groups.

		Normotension	Prehypertension	Hypertension	*P*
ECG parameters					
Time domain measures of HRV					
SDNN	ms	51.04 ± 25.8	47.06 ± 22.4	35.0 ± 12.6	0.09
RMSSD	ms	37.76 ± 19.8	38.47 ± 18.7	25.25 ± 13.1	0.03*
NN50		117.61 ± 114.1	138.83 ± 128.7	58.74 ± 81.4	0.06
pNN50	%	21.74 ± 20.3	21.97 ± 19.9	8.30 ± 11.9	0.03*
Frequency domain measures of HRV					
VLF power	(ms^2)	297.89 ± 97.8	287.8 ± 132.1	272.84 ± 150.1	0.48
LF power	(ms^2)	158.75 ± 64.3	159.39 ± 59.1	156.68 ± 64.2	0.99
HF power	(ms^2)	172.11 ± 52.9	172.95 ± 73.6	152.16 ± 60.6	0.48
LF	(n.u.)	49.22 ± 14.3	48.41 ± 14.4	50.53 ± 14.5	0.77
HF	(n.u.)	50.74 ± 14.4	51.57 ± 14.4	49.47 ± 14.5	0.76
LF/HF		0.96 ± 0.5	2.48 ± 9.2	1.25 ± 0.9	0.75

All values are given in mean ± SD; n.u; Normalized unit.
* *P* value of <0.05; HRV parameters analyzed by non-parametric Kruskal–Wallis test.

($r = 0.654$, $P = 0.006$) and RMSSD ($r = 0.507$, $P = 0.045$) (not shown in tables). After deletion of non-vegetarians and alcoholics the correlation analysis was repeated. We found that uric acid continued to remain negatively correlated with HF n.u. and ms^2 among normotensives and prehypertensives (Supplementary Table S2).

Multivariate linear regression analysis

We further tried to find the independent predictors of UA by multivariate linear backward stepwise regression analysis in the overall sample. We observed that systolic BP was the only independent predictor of UA ($P < 0.001$; $\beta = 0.558$; $r^2 = 31.1$). Further on subgroup analysis, SBP was the predictor for UA only among prehypertensives ($P = 0.006$; $\beta = 0.424$; $r^2 = 17.9$).

Discussion

In this study, we evaluated the relationship between the autonomic function as measured by HRV and serum UA levels among individuals with prehypertension and hypertension and compared the same with normotensives. This may be among the first few studies to show correlation between autonomic nervous system and UA generation pathway, by measurement of HRV.

Hypertensives in this study belong to older age group, predominantly males. Stress levels during work was higher among hypertensives. The smoking, diet history and physical activity did not vary significantly between the three groups. Alcohol intake was more among hypertensives. Hypertensives had higher BMI and waist hip ratio. All time domain parameters (indicators of parasympathetic activity) were

Table 3 Pearson's correlation analysis between serum uric acid and HRV parameters.

HRV parameters	Overall sample ($n = 105$)		Normotension ($n = 35$)		Prehypertension ($n = 35$)		Hypertension ($n = 35$)	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Time domain parameters								
SDNN	−0.290	0.006*	−0.038	0.85	−0.327	0.04*	0.043	0.86
RMSSD	−0.298	0.005*	−0.091	0.65	−0.367	0.02*	0.236	0.33
NN50	−0.198	0.06	−0.04	0.84	−0.213	0.18	0.171	0.48
pNN50	−0.318	0.003*	−0.075	0.70	−0.378	0.02*	0.155	0.53
Frequency domain parameters								
VLF power (ms^2)	−0.024	0.82	0.1	0.61	−0.013	0.93	0.005	0.99
LF power (ms^2)	0.219	0.04*	0.224	0.25	0.319	0.04*	0.199	0.42
HF power (ms^2)	−0.225	0.04*	−0.342	0.08	−0.132	0.41	−0.221	0.36
LF (n.u.)	−0.261	0.01*	0.281	0.15	0.257	0.10	0.382	0.11
HF (n.u.)	−0.26	0.01*	−0.281	0.15	−0.257	0.11	−0.382	0.11
LF/HF	−0.013	0.90	0.462	0.01*	−0.055	0.73	0.525	0.02*

Values given are Pearson's correlation value (*r*) and *P* value; *n* is the number of subjects.
* *P* value of <0.05.

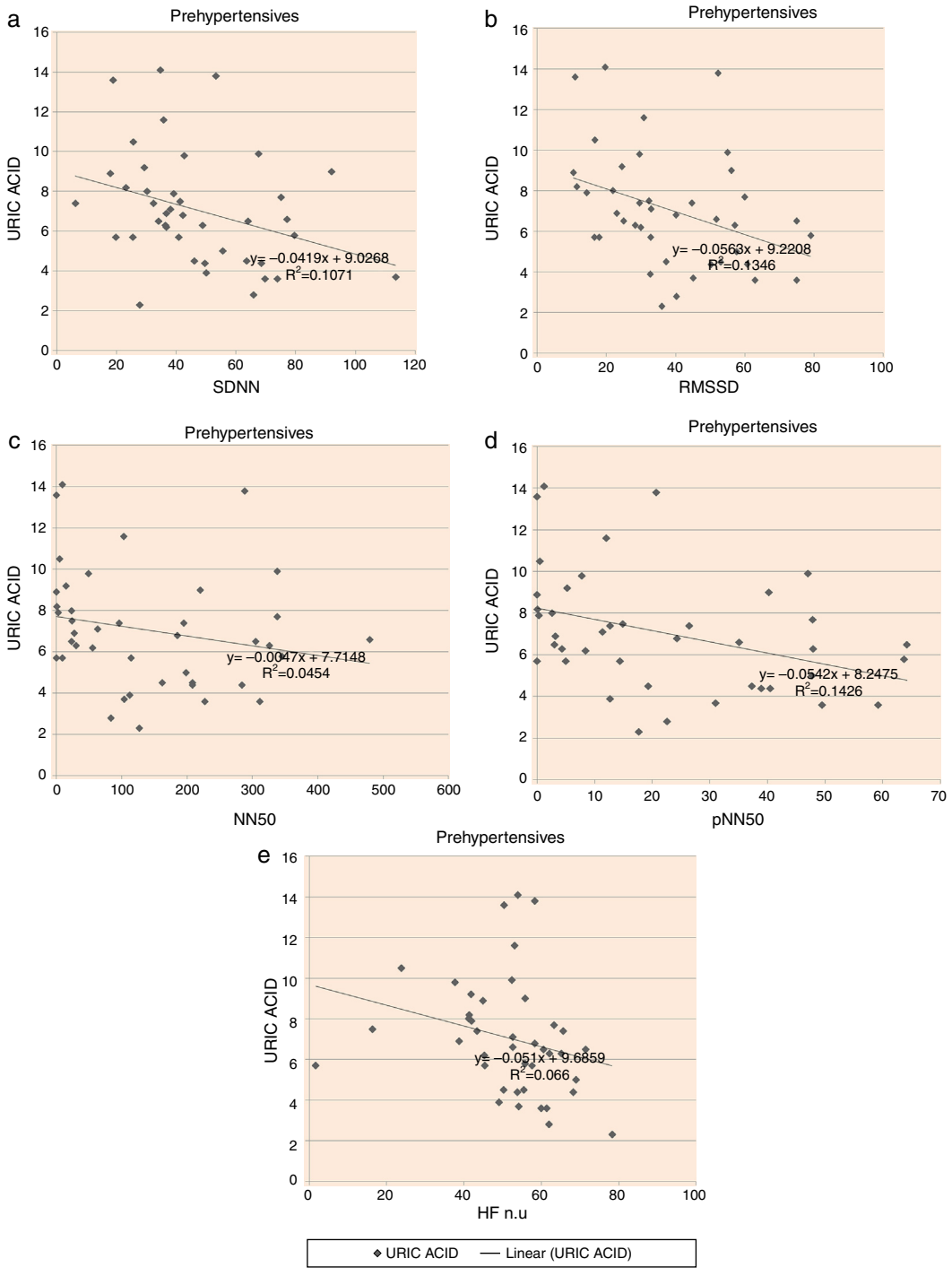

Figure 1 (a–e): Scatter plots showing the correlation between uric acid and various HRV parameters among prehypertensives. (a) Scatter plots showing the correlation between uric acid and SDNN among prehypertensives. (b) Scatter plots showing the correlation between uric acid and RMSSD among prehypertensives. (c) Scatter plots showing the correlation between uric acid and NN50 among prehypertensives. (d) Scatter plots showing the correlation between uric acid and pNN50 among prehypertensives. (e) Scatter plots showing the correlation between uric acid and HF n.u. among prehypertensives.

lower among hypertensives and prehypertensives.[19] Sympathetic dominance has been proven to be one of the chief causative factors of hypertension.[3,11] However frequency domain parameters did not vary significantly among the different groups.

In this study we found significantly higher UA levels among prehypertensives, which is near the upper limit of normal UA levels (reference range > 6 mg/dL/354 μmol/L in females and between 6.5 and 7 mg/dL/383–413 μmol/L in males).[20,21] Females had lower UA levels which could be due

Table 4 Spearman's correlation analysis of the parameters that showed skewed distribution on Kolmogorov–Smirnov test (Parameters shown in Supplementary Table S1).

	Correlations			
Group	NN50	PNN50	HF n.u.[a]	HF ms^2
Normotensives				
r	−.089	−.056	−.384*	−.532**
P	.652	.776	.044	.004
Prehypertensives				
r	−.325*	−.438**	−.415**	−.266
P	.038	.004	.007	.092
Hypertensives				
r	.098	.093	−.160	−.104
P	.691	.706	.513	.673
Overall sample				
r	−.237*	−.312**	−.315**	−.297**
P	.026	.003	.003	.005

* Correlation is significant at the 0.05 level (two-tailed).
** Correlation is significant at the 0.01 level (two-tailed).
[a] Lomb–Scargle spectrum parameters.

to uricosuric action of estrogen.[22] We also found that hyperuricemia among hypertensives was more pronounced than among prehypertensives.

We observed that UA was negative correlating with the time domain parameters implying that higher the UA, higher is the sympathetic activity. This negative correlation of UA with HRV time domain parameters was evident among prehypertensives. On regression analysis, systolic BP was the only independent predictor of UA. This was especially true for prehypertensives. Nevertheless, it has been shown that increased UA leads to higher BP and not vice versa.[23]

Uric acid has been proven to be one of the independent risk factors for hypertension.[24,25] It is suggested that sympathetic overactivity in hypertension decreases renal clearance of UA, leading to higher plasma levels.[26] Impaired pressure natriuresis mechanism along with renal arteriosclerosis (ischemia[27]) caused by high levels of UA may lead to sodium-dependent hypertension.[28] Mechanisms indicated in causation of hypertension by UA are generation of reactive oxygen species,[29] impaired nitric oxide synthesis in the macula densa,[30] endothelial dysfunction, arresting endothelial cell proliferation, activation of renin–angiotensin aldosterone system,[27] synthesis of CRP contributing to microinflammation and subtle decrease in glomerular filtration rate (GFR) leading to impaired UA clearance.[31,32]

Though UA acts like an antioxidant, as serum levels increase, their prooxidant potential takes over the antioxidant property[21] via genesis of hsCRP. Vagal pathway has been shown to have anti-inflammatory activity and thus autonomic dysfunction can increase the production of proinflammatory cytokines and hs-CRP.[33,34] HRV negatively correlates with hs-CRP[35] and it has been shown that UA levels along with hs-CRP and autonomic dysfunction are independent predictors of nocturnal BP levels; SDNN was negatively correlating with age of subjects and hs-CRP levels.[18]

Significant correlation between LF power and UA was found among normal and preeclamptic woman.[36] Among heart failure patients, it was observed that UA was negatively associated with all HRV parameters but not the LF/HF ratio.[37] A recent large scale population based study supported the hypothesis that hypertension and UA have interaction effects to influence the progression of cardiovascular autonomic neuropathy.[38]

Through this study we have made a small attempt toward observing the simple test for uric acid among prehypertensives and hypertensives. The clinical implications of this study need to be authenticated by future clinical trials. This is important because hyperuricemia may soon change its status from being risk predictor to treatment target for patients at high cardiovascular risk. Epidemiological data show a connection between hyperuricemia and hypertension and uric acid lowering therapy has been shown to lower arterial BP.[39]

This study was a cross sectional study with a small sample size. A longitudinal study including more subjects will help in further confirming the hypothesis of this study. We have not measured serum creatinine and calculated GFR, as tested by most of the studies which have related BP with UA levels. However, testing for the same was not part of our objective. Some of the variables like lipid profile and sugar levels were not tested. Regards to HRV, we did not control for respiration. This may also affect HRV analysis, especially HF power. Further, allopurinol usage has not shown any significant effect on HRV parameters.[40] Even so, this study still has shown that UA to be significantly correlating with HRV parameters particularly among prehypertensives and thus can be included as a marker of sympathetic activity.

Conclusions

In this study serum UA levels significantly correlated with HRV parameters and thus can be used as a marker of sympathetic activity. This was especially true for the male prehypertensives, who were apparently healthy. Measurement of UA levels can thus be included in the litany of tests in routine laboratory diagnostics in order to identify individuals with impaired autonomic function (as indicated by UA) earlier and necessary actions taken.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or

subjects mentioned in the article. The corresponding author is in possession of this document.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.hipert.2015.06.001.

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