Original Article

The Effect of Gender on Heart Rate Variability and Uric Acid Levels among Subjects with Different Blood Pressure Profiles

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ABSTRACT

Context: Autonomic function is said to be different between males and females. Uric acid (UA) levels also vary with gender. We tried to explore if these differences exist among the subjects grouped based on their blood pressure (BP) profiles. Aims: The aim of this study was to compare the level of UA and autonomic function differences between males and females classified according to their BP levels. **Settings and Design:** This was a cross-sectional study conducted on 105 subjects classified into three groups according to Joint National Committee (JNC) VII criteria. **Materials and Methods:** Heart rate variability (HRV) was analyzed in Lead II electrocardiogram recording and UA levels were measured among 105 subjects after classifying them based on their BP levels according to JNC VII criteria. **Statistical Analysis:** Statistical analysis was performed using SPSS 18.0 version software. Chi-square test and Mann – Whitney U-test was used. **Results:** Males had significantly higher UA levels. The time domain parasympathetic parameters of HRV were higher among females on comparison with males indicating vagal withdrawal among males. The sympathetic parameters in the frequency domain were higher among males. This difference in HRV was observed among all BP profile groups. **Conclusions:** Males have a higher degree of vagal withdrawal and sympathetic activity as shown by HRV markers and UA levels. It is thus suggested that males could undertake more preventive measures and therapy at an earlier date than females. Further, treatment of male patients with hypertension should be much more vigorous than females.

Key words: Blood pressure, gender, heart rate variability, uric acid

INTRODUCTION

Males and females are different. We all know about this. The parameters, which are different, are many. Recently, gender differences have been proven to be important in terms of causation of certain metabolic and non-communicable disorders that include hypertension, diabetes and cancers. Autonomic dysfunction or dysautonomia co-exists in a variety of disorders such as hypertension, diabetes and neurological problems. Heart rate variability (HRV), blood pressure (BP) variability and baroreflex sensitivity are the usual methods to assess the normality of autonomic functions in an individual and are now used by many scientists around the world for research purposes also.

Heart rate variability measures the variations of the time intervals between consecutive heartbeats, which can be modulated by variations in the activation of sympathetic or the parasympathetic system. HRV can be analyzed using time domain and frequency domain and autoregression methods as described by the task force group.[1] In the time domain method, we include the analysis of the square root of variation of RR intervals (SDNN) and square root of the mean squared differences of successive RR intervals (RMSSD), number of pairs of successive NNs that differ by more than 50 ms (NN50) and proportion of NN50 divided by the total number of NNs (pNN50) (RR interval is also called the normal to normal or simply NN interval). All the time domain parameters give us an idea about the high frequency oscillations in the heart beats and thus are said be a reflection of parasympathetic influence on the heart. Frequency domain parameters include total power (TP), very low frequency (VLF), low frequency (LF), high frequency (HF), all in absolute

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units (ms^2) and LF normalized units (n.u), and HF n.u in n.u and LF/HF ratio. TP is an indicator of the global autonomic function. VLF component is usually considered an ambiguous measure as it lacks a valid physiological explanation. The LF power has been shown to be modulated by both sympathetic and parasympathetic activity, while HF power depicts the parasympathetic activity. LF/HF is a marker of sympathovagal balance, with higher level seen in sympathetic over activity. Normalization of LF and HF minimizes the effect of changes in VLF power and emphasizes changes in sympathetic and parasympathetic regulation respectively.[1]

Soon after the discovery of HRV as a measure of autonomic function, it was proven that decreased HRV is a bad prognostic marker of morbidity and mortality, especially in patients with myocardial infarction.[1] Previous studies has identified gender differences in HRV, but the results have been conflicting.[2-4] This is especially true among woman, where HRV has been shown to be similar,[5] lower than[6] and also greater than males.[7] HRV decrease is found among hypertensives and prehypertensives.[8,9] This finding further extends depending on the gender of the individual. It has been concluded that vagal inhibition plays an important role in addition to sympathetic activation, which leads to the genesis of prehypertension, especially in males.[10]

The previous studies have reported either similar[11,12] or reduced[13-15] HRV in hypertensives as compared with normotensives. Findings of few studies: Untreated middle-aged hypertensives showed LF n.u, HF n.u, and LF/HF similar to normotensive controls. It was observed that age, HR and BP were independent determinants of decreased absolute measures of HRV. Association of BP with HRV was found to be independent of HR.[16] Huikuri *et al.*, observed that, hypertensives on treatment, had decreased SDNN, VLF and LF components of HRV, unchanged TP and HF powers, and decreased LF/HF. They hypothesized that use of β blockers led to similar HF component observed among hypertensives and normotensives.[17] In the Framingham study, all time domain and frequency domain variables of HRV were reduced in untreated hypertensive men and women.[18] Hypertensives had greater LF n.u (68 ± 3 vs. 54 ± 3) and lower HF n.u (24 ± 3 vs. 33 ± 2) than normotensives.[19] Twenty-four hour monitoring of HRV among hypertensives showed that there was a small nocturnal increase in HF and a loss of the circadian rhythm of the LF component.[20] These data indicate that there is reduced responsiveness of neural regulatory mechanisms among hypertensives. In another study[21] where α index was used to assess the overall gain of the baroreceptor mechanisms it was confirmed that neural buffering mechanisms were attenuated in essential hypertension.[22]

Uric acid (UA) is a product of purine metabolism. Nevertheless, gender differences exist due to the uricosuric action of estrogen.[23,24] Hyperuricemia is said to be present when the levels of UA crosses 450 μmol/l or >7.0 mg/dl in men, and >360 μmol/l or >6.0 mg/dl in women.[25] It has been reported that the level of UA is elevated among hypertensives.[26-29] Although, UA levels are considerably different in males and females, most of the prior studies have been done among males and if both genders were included, gender specific analysis was not included. Thus, it remains largely unknown. Not many studies have looked into UA levels based on gender and BP profiles. Thus, this study aimed at comparing HRV differences based on gender and BP profiles of the subjects.

MATERIALS AND METHODS

This was a cross-sectional study. Hundred and five subjects in the age range of 18-60 years were included. They were then classified according to their BP in the range of normotension, prehypertension and hypertension (newly diagnosed) as per Joint National Committee (JNC) VII criteria.[30] All subjects needed for the above study were recruited by history and clinical examination from the out-patient department of the hospital attending for general or master health checkup. This 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. Nonvegetarians, alcoholics, postmenopausal women, individuals with gout, myocardial infarction, diabetes mellitus, peptic ulcer, recurrent asthma, bronchitis, sinusitis, renal dysfunction, malignant diseases, obesity, insulin resistance, and dyslipidemia, patients taking any drug known to affect serum UA levels (allopurinol, diuretics, probenecid, benzbromarone, sulfinpyrazone, diclofenac, fenofibrate, pirenzepine, ethambutol, aspirin and other nonsteroidal antiinflammatory drugs, losartan, atorvastatin), patients on drugs affecting autonomic nervous system function, secondary hypertension were excluded. A detailed history about the general health of the subjects, physical activity, dietary habits (with vegetarian being defined as the one who never takes any nonvegetarian food such as meat, etc.), stress levels at work (measured on ten point scale by visual analog scale), general stress based on perceived stress scale, smoking and drinking and drug history was recorded by a predesigned, pretested questionnaire. The anthropometric measurements were recorded for all the subjects in light clothing without shoes. Height and weight was measured in standing posture. Height was measured with a horizontal wall mounted height meter to the last complete 0.1 cm and weight with a digital weighing scale to the last complete 0.1 kg. Body mass index (BMI) in kg/m^2 was calculated for each subject. Waist circumference (cm) was measured with a standard measuring tape at the midpoint between the iliac crest and the lower ribs measured at the sides. Hip circumference was measured with tape at the point of maximum hip circumference. Waist hip ratio was then calculated.

After the rest of 10 min the BP was recorded twice with a gap of 5 min in the supine position on the right arm of subjects using sphygmomanometer. Systolic and diastolic BP was defined as the first and the fifth Korotkoff sounds. The average of the two readings was taken as the final BP.[31] We then classified the subjects into groups, based on JNC VII criteria. As we included only healthy individuals, we did not have a Stage II hypertension group. In order to record Lead II 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 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 the total number of NNs). The frequency domain parameters included were absolute power in VLF, LF range, HF range given in ms^2 units and n.u. and the ratio of LF/HF.

After an overnight fast of 12 h, 5 mL of a 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°C until analysis. Serum UA levels were measured using UA MR enzymatic colorimetric assay kit (Linear Chemicals, India). 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 sulfonate 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 were analyzed using SPSS 18.0 Software (SPSS Inc., Chicago, USA). Quantitative data were described in terms of descriptive statistics such as mean and standard deviation. 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 and HRV parameters based on gender. $P < 0.05$ was considered as statistically significant.

RESULTS

There was a significant difference between the age distribution of males and females, with males in higher age group than females. Further, most of the males were nonvegetarians. About 27% of males were consuming alcohol and about 7% were smokers. The two groups did not vary based on their involvement in physical activity. The BMI of either gender was within normal limits, though males had higher BMI when compared with females. Waist hip ratio of males was higher than females. Stress at work and perceived stress scale scores were comparable between the two groups. Systolic and the diastolic BP were significantly higher among males. Furthermore, serum UA levels were significantly higher among males [Table 1].

Table 1: Clinical characteristics of the population

Baseline clinical characteristics	Female (mean ± SD) (*n* = 54)	Male (mean ± SD) (*n* = 51)	*P*
Age (years)	27.80±12.6	35.14±13.9	0.01
Diet (%)			
Vegetarian	46.7	23.3	0.02
Nonvegetarian	53.3	76.7	
Smoking (%)			
Yes	0	7	0.11*
No	100	93	
Alcohol intake (%)			
Yes	4.4	27.9	0.003
No	95.6	72.1	
Involved in physical activity (%)			
Yes	44.4	48.8	0.68
No	55.6	51.2	
BMI (kg/m^2)	22.99±4.7	24.92±3.6	0.03
Waist hip ratio	0.82±0.1	0.88±0.1	0.02
Stress at work (range 010)	5.50±2.3	6.19±2.2	0.15
Perceived stress scale	19.04±5.7	19.98±6.1	0.46
Systolic BP (mm Hg)	120.18±11.9	131.84±14.2	<0.001
Diastolic BP (mm Hg)	79.22±7.2	84.26±9.7	0.007
Serum uric acid (mg/dl)	5.49±2.1	8.96±2.5	<0.001

All values are given in mean ± SD and percentage of total number of subjects, *n*: Number of subjects. *Calculated by Fisher's exact test, $P < 0.05$ was considered significant, SD: Standard deviation, BP: Blood pressure, BMI: Body mass index

Table 2: Gender based comparison of HRV

HRV Parameters	Female (mean ± SD) (*n* = 54)	Male (mean ± SD) (*n* = 51)	*P*
SDNN (ms)	49.89±24.7	41.36±19.3	0.08
RMSSD (ms)	38.80±19.3	31.82±17.3	0.08
NN50	131.04±120.3	97.77±115.1	0.19
pNN50%	22.99±19.9	14.71±17.8	0.04
VLF power (ms^2)	446.49±1172.6	356.20±396.4	0.63
LF power (ms^2)	184.25±250.9	185.02±172.0	0.99
HF power (ms^2)	146.10±203.6	161.83±179.5	0.70
LF (n.u)	54.17±15.1	61.00±15.2	0.04
HF (n.u)	44.45±14.9	35.29±14.1	0.004
LF/HF	1.5±0.9	2.22±1.4	0.006

All values are in mean ± SD. HRV: Heart rate variability, VLF: Very low frequency, LF: Low frequency, HF: High frequency, SD: Standard deviation, n.u: Normalized units

Table 3: Gender differences of HRV classified according to different BP profiles (JNC VII)

HRV Parameters	Normotension (*n* = 35)			Prehypertension (*n* = 35)			Hypertension (*n* = 35)		
	Female (mean ± SD)	Male (mean ± SD)	*P*	Female (mean ± SD)	Male (mean ± SD)	*P*	Female (mean ± SD)	Male (mean ± SD)	*P*
SDNN (ms)	52.81±27.3	46.61±22.7	0.72	50.5±23.4	43.78±21.5	0.40	35.74±15.8	34.74±12.0	0.85
RMSSD (ms)	39.50±20.8	33.41±17.6	0.65	40.88±18.6	36.18±18.9	0.36	27.72±15.2	24.37±12.7	0.78
NN50	128.20±121.0	91.13±96.6	0.65	148.05±128.4	130.05±131.6	0.68	74.4±76.0	53.14±85.2	0.55
pNN50%	23.78±21.3	16.65±17.9	0.63	25.05±19.9	19.03±20.1	0.26	11.6±13.4	7.13±11.6	0.46
VLF Power	303.3±103.1	286.88±88.5	0.98	292.75±160.5	283.10±101.7	0.77	409.8±151.2	223.93±119.9	0.02
LF power	150.75±66.4	178.75±57.9	0.22	144.95±43.0	173.14±69.4	0.11	120.0±62.8	169.79±61.6	0.09
HF power	179.55±56.8	153.5±38.1	0.07	177.05±93.0	169.05±50.9	0.48	159.8±55.0	149.43±64.2	0.78
LF	47.72±15.7	52.98±10.0	0.13	46.69±18.1	50.05±9.9	0.14	42.58±10.3	53.37±15.0	0.17
HF	52.24±15.7	47.0±10.0	0.13	53.3±18.1	49.91±9.9	0.12	57.38±10.3	46.64±15.0	0.17
LF/HF	0.85±0.4	1.21±0.5	0.07	3.93±13.1	1.11±0.6	0.13	0.79±0.3	1.42±1.0	0.17

All values are given in mean ± SD, SD: Standard deviation, VLF: Very low frequency, LF: Low frequency, HF: High frequency

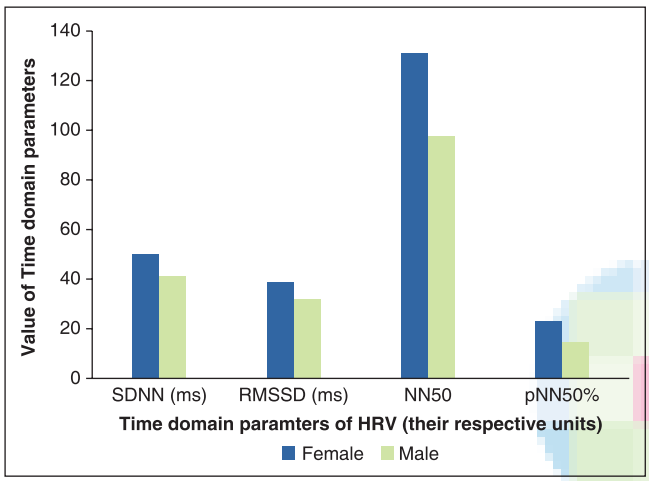

Figure 1: Comparison of time domain parameters of heart rate variability between males and females

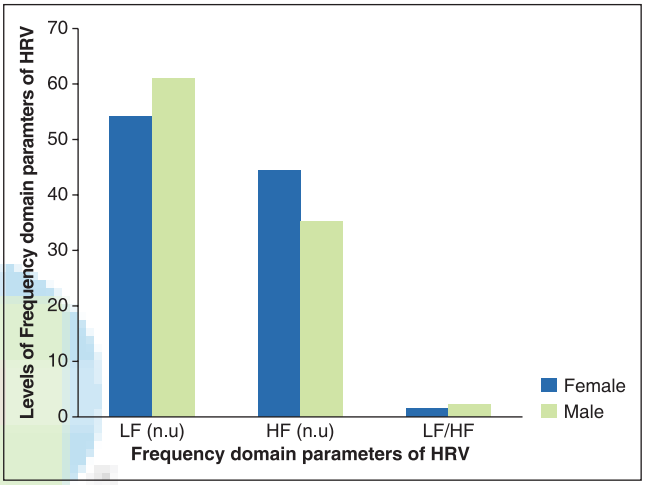

Figure 2: Comparison of frequency domain parameters of heart rate variability between males and females

Evident differences were observed between males and females HRV parameters, with males exhibiting higher LF n.u, LF/HF ratio (indicators of sympathetic activity) and decreased SDNN, RMSSD, NN50 and pNN50 (time domain parameters), HF n.u (indicators of vagal activity) [Table 2, Figures 1 and 2].

On comparison of HRV based on different BP profiles, we did not find any statistically significant difference between males and females. However, males had higher LF power (ms^2), LF n.u (indicators of sympathetic activity) and LF/HF (indicator of sympathovagal balance) and lower HF power (ms^2), HF n.u, SDNN, RMSSD, NN50, and pNN50 (indicators of vagal activity) across all the BP groups [Table 3].

DISCUSSION

In this study, we tried to elicit the gender differences in HRV and UA levels among subjects with different BP profiles or ranges. As an auxiliary finding, we observed that the UA levels were high among subjects with prehypertension and hypertension, who also had increased sympathetic activity as observed using HRV analysis.

Most of the studies exploring the association between UA levels and cardiovascular disease have indicated higher levels of serum UA among males as compared with females.[32-35] In the present study, we observed a similar outcome. This might be due to the uricosuric action of estrogen.[24] High UA level is assumed to be a poor prognostic marker for cardiovascular and renal disease, as it acts on endothelium by various mechanisms such as increase in the inflammatory markers and inhibition of nitric oxide synthase enzyme.[36]

Not many studies have examined the gender based differences in autonomic functions. We observed a significantly higher sympathetic activity and lower parasympathetic activity among males. The time domain parameters, which are indicators of parasympathetic nervous activity were higher among females. Among the frequency domain parameters, the LF/HF, LF (n.u) and LF (ms^2) were higher among males; whereas, females had higher HF (ms^2) and HF (n.u). As reviewed previously, LF/HF, LF (n.u) and LF (ms^2) are sympathetic markers of HRV. HF (ms^2) and HF (n.u) are parasympathetic markers. Woman have a lower risk of

developing cardiovascular diseases due to differences in autonomic modulation on comparison with males.[2] Higher parasympathetic activity was observed among woman on comparing them with age matched men.[3,4] Further, it was shown that this autonomic modulation varies with age. Woman who are <30 years age have lower HRV (higher sympathetic activity) than males; this difference decreases between 30 and 50 years of age and tends to disappear in older age.[6] Even during periods of stress, woman have better parasympathetic input than males.[37]

This study further extended by comparing males and females in different BP groups. Vagal withdrawal was prominent among males where lower levels of SDNN, RMSSD and other time domain parameters were observed. In that, we noticed that the higher sympathetic activity observed in males was among normotensives, prehypertensives and hypertensives though none of the differences were statistically significant. This could be due to higher vagal withdrawal among males than sympathetic dominance.[38] Gender differences in BP has been shown previously.[39] However, the gender differences in HRV based on different BP profiles need further explanations and research.

However, every study has some limitations. First this was a cross sectional study involving a small sample. Further grouping them into hypertensives decreased the sample of males and females further. This is natural for all studies where subgroup analysis is involved. We did not classify subjects into different age groups, as HRV varies with age.[2,40] Blood levels of glucose, creatinine, lipid profile and other metabolic parameters along with inflammatory have not been included as it was not the primary objective of the study. The strength of the study is that this may be one among the first few studies that has analyzed autonomic functions differences between males and females subdivided based on their BP profiles. Our findings have significant clinical and speculative implications. The increased sympathetic activity amongst males indicates that they need to be treated more vigorously than females when presenting with any autonomic dysfunction associated disorder.

CONCLUSION

In this study, higher sympathetic and lower parasympathetic, nervous activity was found among males. Previous studies, which have explored gender differences in HRV, have been done on healthy adults. This study showed that males had higher sympathetic activity after dividing them according to their BP profiles. Thus, testing for autonomic functions serve as a prognostic marker to identify individuals prone to develop hypertension and other cardiovascular disorders. It further facilitates in taking up the gender specific treatment approach.

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