Sympathovagal Imbalance in Young Prehypertensives: Importance of Male-Female Difference

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Abstract: *Introduction:* Although the prevalence of prehypertension is high, the pathophysiological mechanisms and the effects of gender in its causation have not yet been fully understood. *Methods:* Body mass index, waist-to-hip ratio, basal heart rate, blood pressure, rate pressure product and spectral indices of heart rate variability were reordered and analyzed in young normotensive (n = 344) and prehypertensive (n = 69) subjects. Each group was categorized into male and female subgroups. *Results:* Ratio of low-frequency to high-frequency powers (LF-HF ratio) of heart rate variability spectrum, the sensitive marker of sympathovagal imbalance (SVI), was significantly more increased ($P < 0.001$) in male prehypertensives compared with female prehypertensives. Although SVI in prehypertensives was found to be due to both sympathetic activation in the form of increased low-frequency power normalized (increased LF_{nu}) and vagal inhibition in the form of decreased high-frequency power normalized (decreased HF_{nu}), contribution of vagal withdrawal was more in males. LF-HF ratio was significantly correlated with body mass index, waist-to-hip ratio, basal heart rate, blood pressure and rate pressure product by Pearson correlation analysis. Furthermore, multiple regression analysis demonstrated an independent relationship between LF-HF ratio and gender ($P = 0.000$) and prehypertension status ($P = 0.000$) in both normotensives and prehypertensives. *Conclusions:* Vagal inhibition plays an important role in addition to sympathetic activation in alteration of SVI in the genesis of prehypertension, especially in males. Gender and prehypertension status play important role in the causation of SVI. It was suggested that vagal tone of prehypertensives should be maintained at a higher level to prevent their further rise in blood pressure.

Key Indexing Terms: Prehypertension; Gender; Heart rate variability; LF-HF ratio; Body mass index; Sympathovagal imbalance. **[Am J Med Sci 2013;345(1):10–17.]**

Prehypertension has recently been accepted as an established risk factor for hypertension.[1–4] Prehypertension *per se* has also been observed to be associated with adverse cardiovascular events.[5–7] The prevalence of prehypertension has increased tremendously throughout the globe, mainly due to lack of healthy lifestyle in the general population.[2,8–10] Especially in Indian subcontinent, increased prevalence of prehypertension is primarily due to increased incidence of diabetes and central obesity, sedentary life, excess consumption of alcohol and change in food habits.[11,12] However, irrespective of the causes and associated risk profiles, the physiological mechanisms responsible for progression from the state of normotension to prehypertension have not yet been fully elucidated. Although the sympathetic overactivity has been reported as a major physiological mechanism for genesis of essential hypertension,[13–15] there is paucity of data on the pathophysiological basis of the causation of prehypertension. Recently, we have reported that in addition to sympathetic overactivity, vagal withdrawal contributes to the progression from prehypertension to hypertension.[16]

The progression of normotensive adolescents to hypertensive adults linked to the change in status of body mass index (BMI) has been reported to be sex dependent.[17] Moreover, there is report of gender difference in the metabolic characteristics of prehypertensives.[18] However, no study has been conducted yet to assess the difference in the nature of sympathovagal imbalance (SVI) involved in the genesis of prehypertension in males and females. Spectral analysis of heart rate variability (HRV) has recently been clinically used to assess autonomic functions and dysfunctions in various disorders.[19] Therefore, in this study, we have assessed SVI in young male and female normotensive and prehypertensive subjects by performing spectral analysis of HRV to understand the gender difference in autonomic dysfunctions involved in the causation of prehypertension in young adults.

METHODS

After obtaining the approval of Research Council and Institutional Ethics Committee, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India, 420 subjects were recruited from first-year MBBS, MSc (Medical Biochemistry) and BSc (Medical Laboratory Technology) courses of JIPMER of 2008, 2009 and 2010 batches. They were classified as normotensives and prehypertensives based on their level of systolic and diastolic blood pressure (SBP and DBP) as per JNC-7 classification.[20]

1. Normotensive group (n = 344; 207 males and 137 females): subjects having SBP 100 to 119 mm Hg and DBP 60 to 79 mm Hg.
2. Prehypertensive group (n = 69; 48 males and 21 females): subjects having SBP 120 to 139 mm Hg and DBP 80 to 89 mm Hg.

Subjects receiving any medication; subjects with history of diabetes, smoking and hypertension and hypertensive patients already receiving medication were excluded from the study. Moreover, subjects performing regular athletics and body building exercises were excluded from the study.

Subjects were asked to report to autonomic function testing (AFT) laboratory of Physiology Department at about 9 AM after a light breakfast, without tea or coffee. After obtaining the informed consent, their age, height, body weight, BMI and waist-to-hip ratio (WHR) were recorded. BP of all the subjects was recorded in AFT laboratory. The temperature of AFT laboratory was maintained at 25°C for all the recordings. Omron (SEM 1 Model), the automatic blood pressure monitor (Omron Healthcare Co., Kyoto, Japan), was used for BP recording. The cuff size of Omron was 121 mm (width) × 446 mm (length). The

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length of the cuff tube was 600 mm. For BP recording, the subject was asked to seat upright with back straight on a wooden armed chair keeping one forearm on a wooden table kept in front and close to the subject. The height of the table was such that the middle of the arm placed on the table approximately coincided with the level of the heart. The subject was asked to keep the other forearm on the side hand rest of the chair. The BP cuff was tied just tight (neither too tight nor loose) on the arm approximately 2 cm above the cubital fossa. It was ensured that the BP cuff was at the level of the heart. After 5 minutes rest in the same sitting posture, the "Start" button of Omron was pressed that automatically inflated and deflated the cuff, and SBP, DBP and basal heart rate (BHR) were noted from the display screen of the equipment. For each subject, SBP, DBP and BHR were recorded in each arm 2 times at an interval of 5 minutes between the recordings, and for each parameter, the mean of the 4 recordings was considered. Rate pressure product (RPP) was calculated using the formula,[21] RPP = SBP × heart rate × 10^{-2}.

After 15 minutes of supine rest on a couch in AFT laboratory, ECG was recorded for 5 minutes for short-term HRV analysis following the standard procedure as described earlier.[22] For recording of HRV, recommendation of the Task Force on HRV was followed.[23] For the purpose, ECG electrodes were connected and Lead II ECG was acquired at a rate of 1,000 samples/sec during supine rest using BIOPAC MP 100 data acquisition system (BIOPAC, Goleta, CA). These data were transferred from BIOPAC to a windows-based PC with Acqknowledge software version 3.8.2. Ectopics and artefacts were removed from the recorded ECG. HRV analysis was done using the HRV analysis software version 1.1 (Bio-signal Analysis group, Kuopio, Finland). Frequency domain such as total power (TP), normalized low-frequency power (LF_{nu}), normalized high-frequency power (HF_{nu}), ratio of LF to HF powers (LF-HF ratio) and time-domain indices such as mean heart rate (mean-RR), square root of the mean-squared differences of successive normal to normal intervals (RMSSD), the number of interval differences of successive NN intervals greater than 50 ms (NN50) and the proportion derived by dividing NN50 by the total number of NN intervals (pNN50) were calculated. Of total 420, 7 subjects reported as hypertensives receiving antihypertensive drugs. Their recordings were not considered for statistical analysis.

Statistical Analysis of Data

SPSS version 13 (SPSS Software, Chicago, IL) and GraphPad InStat softwares (GraphPad Software, San Diego, CA) were used for statistical analysis. All the data were presented as mean ± SD. Normality of data was tested by Kolmogorov-Smironov test. For parametric data, the level of significance between the groups was tested by Student's unpaired *t* test and for nonparametric data, Welch's corrected *t* test was used. Statistical analysis of data within the 4 groups was done by 1-way ANOVA and *post hoc* by Tukey-Kramer test. The association between LF-HF ratio with BMI, WHR, BHR, blood pressure and RPP was assessed by Pearson correlation analysis. The independent relation of various factors such as BMI, WHR, BHR, SBP, DBP, RPP, prehypertension status and gender with LF-HF ratio was assessed by multiple regression analysis. The *P* values < 0.05 were considered statistically significant.

RESULTS

Age, Anthropometric and Cardiovascular Parameters

Comparison of age and anthropometric parameters between the groups was done because these parameters are known to influence HRV indices and blood pressure. Although there was no significant difference in age between normotensives and prehypertensives, the body weight, BMI, WHR, BHR, SBP, DBP and RPP of prehypertensives were significantly more increased ($P < 0.0001$) compared with the normotensives (Table 1).

Although there was no significant difference in body weight between males and females of normotensive and prehypertensive groups, the body weight of prehypertensive males and females was significantly more increased than that of their respective normotensive controls (Table 2). In normotensive group, the BMI of females was significantly higher ($P < 0.05$) than that of males. However, in prehypertensive group, there was no significant gender difference in BMI. Although BMI of prehypertensive males was significantly more increased ($P < 0.05$) than the normotensive males, the BMI was not significantly different in female prehypertensives than in normotensives. Waist circumference (WC) of normotensive females was significantly decreased ($P < 0.01$) than that of the normotensive males, whereas there was no significant difference in waist circumference between prehypertensive males and females (Table 2). In normotensive group, WHR of males was significantly high ($P < 0.001$) compared with that of females, and in prehypertensive group, WHR was also significantly increased in males compared with females ($P < 0.05$). Among males, although WHR was significantly more increased in normotensives compared with prehypertensives ($P < 0.001$), the difference was not significant between female normotensives and prehypertensives. For BHR, there was no significant difference between normotensive males and females and prehypertensive males and females (Table 2). However, BHR of prehypertensive males was significantly more increased ($P < 0.001$) compared with that of normotensive males. SBP among the normotensive groups was significantly high ($P < 0.001$) in males compared with females, but it was not significant between prehypertensive males and females. Among males, SBP of prehypertensives was significantly more increased ($P < 0.001$) than that of normotensives and, among females, SBP had a similar significant difference between prehypertensives and normotensives. For DBP and RPP, differences between the groups were almost similar to that of the SBP (Table 2).

TABLE 1. Age, anthropometric and basal cardiovascular parameters of normotensive and prehypertensive subjects

Parameters	Normotensive group (n = 344)	Prehypertensive group (n = 69)	*P*
Age (yr)	19.85 ± 2.40	20.20 ± 2.16	0.2619
Body weight (kg)	57.25 ± 3.50	60.56 ± 4.10	<0.0001
BMI (kg/m^2)	22.10 ± 3.45	24.04 ± 4.25	<0.0001
WC (cm)	79.80 ± 5.90	82.60 ± 5.74	<0.0001
WHR	0.784 ± 0.08	0.842 ± 0.08	<0.0001
BHR (per min)	71.20 ± 7.56	77.60 ± 8.30	<0.0001
SBP (mm Hg)	107.80 ± 6.50	127.65 ± 5.70	<0.0001
DBP (mm Hg)	69.80 ± 4.72	85.56 ± 4.30	<0.0001
RPP (mm Hg/min)	76.75 ± 5.80	99.05 ± 6.20	<0.0001

Data are presented as mean ± SD. The *P* values <0.05 were statistically considered significant.

BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; BHR, basal heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RPP, rate pressure product.