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CARDIAC AUTONOMIC DYSFUNCTION CONTRIBUTES TO PREHYPERTENSION STATUS.

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ABSTRACT We aimed to elucidate the role of autonomic dysfunction in subjects with prehypertension. We identified 150 asymptomatic subjects without hypertension who underwent comprehensive Cardiovascular Autonomic function tests. In our study, the prevalence of prehypertensives was 24%. Body Mass Index (BMI) was significantly higher in prehypertensive than normotensive subjects (P =0.04). Comparison of the two parasympathetic tests i.e, the mean value of 30:15 ratio and Valsalva ratio were comparable between two groups. Comparison of the sympathetic tests revealed that in case of prehypertensive subjects the mean of SBP and DBP before and after HGT and CPT was significantly higher than normotensives. Thus, these findings reflect increased sympathetic reactivity in prehypertensive subjects. Our study confirmed that prehypertension is associated with autonomic dysfunction, which is reflected by an elevated sympathetic tone that was intriguingly associated with high BMI. We emphasize that adaptation to a healthier lifestyle will help improve sympathovagal homeostasis and prevent the occurrence of hypertension.

KEYWORDS : : autonomic nervous system; parasympathetic activity; prehypertension; sympathetic activity, body mass index.

INTRODUCTION

One major change in JNC 7 report was the addition of a new blood pressure category called prehypertension (120-139 mm Hg systolic or 80-89 mm Hg diastolic).1 As a result, persons who were once considered to have normal blood pressure became labeled as prehypertensives. Prehypertension is a major public health concern affecting more than 1 out of every 4 adults worldwide.2 Overall prevalence of prehypertension all over the world was reported to be 31% (1999-2000).1 In India, it was found to be more than 45%. Patients with prehypertension have increased risk of developing hypertension3 and may be associated with adverse cardiovascular outcomes4 compared with persons who have normal blood pressure (BP).5 Though hypertension is common in middle-aged and elderly population, prehypertension is relatively more common in young adults, especially in those who have family history of hypertension and also higher Body Mass Index (BMI).[6]

Prehypertension is not a simple precursor state of hypertension with high normal BP. Rather, it is a pathologic condition with a spectrum of changes in autonomic and metabolic domains and target organ damage, which warrants increased clinical attention.7 Prehypertension
tends to progress to hypertension over a relatively short time and is a risk factor for the development of microalbuminuria and cardiovascular disease, with consequently increased mortality. Ishikawa et al. in his study found that the incidence of hypertension in the subjects with prehypertension at baseline was 3.57 times higher than in those with normal BP at baseline.[8]

Although prehypertension has a strong genetic predisposition,9 little is known about the pathophysiological mechanisms responsible for pressure elevation. It is unclear, however, whether and how much autonomic dysfunction contributes to this precursor state of hypertension.10,11 Only limited data are available to support the association between prehypertension and autonomic dysfunction.12 Various studies have verified autonomic dysfunction in the prehypertensive individuals.13 Some studies have also demonstrated that decreased parasympathetic tone, along with increased sympathetic activity, underlies the pathogenesis of prehypertension.14,15

Equivocal conclusions cited above, based on the difference in methodology of assessing cardiovascular autonomic nervous system (ANS) states in prehypertensives, necessitates systemic and thoroughly planned study to know the possible role of the autonomic nervous system on the development of prehypertension to hypertension. Medical undergraduate students, transcending adolescence, are entering into adulthood. Clinical and academic challenges may have an adverse effect on their lifestyle, predisposing vulnerable subjects to hypertension. So this study aimed at estimating the incidence of prehypertension in apparently healthy medical students and to find the association between prehypertension and autonomic dysfunction.

MATERIAL & METHODS

A total of 150 healthy young adults were included in this study with age range from 18 to 25 years. The study was conducted in the Department of Physiology at Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana (Ambala) from 2014 to 2015. The study was approved by the institutional ethical committee. Informed and written consent of all the participants was taken before conducting the study. The non-smoker, non-alcoholic, with systolic (SBP) and diastolic blood pressure (DBP) < 140/90 mm/Hg were included in the study. Exclusion criteria included i) Subjects with SBP ≥ 140 and or DBP ≥ 90 mm/Hg ii) Subjects on antihypertensive drugs or any other medication. iii) Under-going regular physical training. iv) With history of acute or chronic illness like diabetes mellitus, renal disease or any neuro-psychiatric disorder which can affect autonomic function. Subjects were divided into two groups based on blood pressure

Group A (N= 36) Prehypertension subjects
Group B (N= 114) Normotensive subjects

A detailed history was taken and general physical examination of all the volunteers was done with the main emphasis on cardiovascular diseases, renal diseases. None of the subjects took any medication at the time of the study. All the students were explained about the procedure of tests and tested under similar laboratory conditions in comfortable environment. Subjects were instructed not to have heavy meals/tea/coffee at least 2 hours before the test and were asked to rest just before the commencement of the test, and then all basal parameters like heart rate, blood pressure and respiratory rate were measured. Various Cardiovascular Autonomic function tests that were performed are as follows.

TESTS OF CARDIOVASCULAR AUTONOMIC FUNCTION:

Parasympathetic tests:

1. Heart rate response to Standing.
2. Heart rate changes during the Valsalva manoeuvre.

Sympathetic tests:

1. Blood pressure response to sustained Hand Grip Test.
2. Blood pressure response to Cold Pressor Test.

Heart rate response to Standing (Lying to Standing test):

In this test heart rate response to standing was assessed. Each subject initially took supine rest on a couch for 5 min; ECG limb leads were

attached, baseline ECG was recorded. Then subject attained standing posture within 3 seconds. A continuous ECG (lead II) was recorded during the procedure for measuring heart rate. 30:15 ratio was calculated as the ratio of the longest R-R interval at or around 30th beat after standing / shortest R-R interval at or around 15th beat after standing. The normal value of 30:15 ratio is ≥ 1.04.[16]

Heart rate changes during the Valsalva manoeuvre (Valsalva Ratio):
The test was done in sitting posture. The subject blows into a mouth piece attached to sphygmomanometer to raise the pressure to 40 mmHg for 15 seconds. At the end of 15 seconds, the pressure was released. A continuous ECG (lead II) was recorded 1 minute before the manoeuvre, during the manoeuvre and 40 seconds following the release of strain period. Valsalva Ratio is calculated as the ratio of the longest R-R interval after the strain / shortest R-R interval during the strain. The normal value of Valsalva Ratio is > 1.21.[16]

Blood pressure response to sustained Hand Grip Test (HGT):
The baseline blood pressure was recorded. The subject was asked to press handgrip dynamometer at 30% of maximum voluntary contraction (MVC) for 15 seconds. Blood pressure was recorded just before the release of hand grip after 1 minute and 5 min of grip release. Maximum rise in diastolic blood pressure above baseline was noted. A rise of more than 10 mmHg in diastolic blood pressure after the test was considered normal.[17]

Blood pressure response to Cold Pressor Test (CPT):
First, the baseline blood pressure was recorded and then the subjects were instructed about the test. They were instructed to indicate to the investigator if they were not able to keep the hand immersed in water for 1 minute. The cold water of 10oC was prepared. Subject immersed the right hand in cold water up to the wrist without touching the bottom of cold water bath, for 1 minute. After that hand was removed from water, it was covered by the towel. The blood pressure was recorded from left hand just at the end of 1 minute of immersion and again at 1 minute after hand was withdrawn from the cold water. A rise of 10mmHg in diastolic blood pressure after test was considered normal.[16]

Each test was performed after a resting period of 10 minutes, in supine or sitting position. Blood Pressure recording was done by using an Omron (SEM 1 Model), the automatic blood pressure monitor (Omron Healthcare Co. Ltd, Kyoto, Japan). The heart rate was measured from R-R interval of ECG using lead II of Electrocardiograph machine (CADIART 108T-DIGI, BPL LIMITED). Hand grip strength was measured from Handgrip Dynamometer.

Statistical analyses
The collected data was tabulated and analyzed with the help of Statistical Package for Social Sciences SPSS for WINDOWSTM (version 20). Student's independent t-test for quantitative differences was used for data analysis. The inter-group comparison was done by one way ANOVA with post hoc test. Mean ± standard deviations were calculated and t-test was applied for measuring statistical significance in the difference of means. $P < 0.05$ was considered statistically significant and $P \leq 0.001$ was considered highly significant.

RESULTS
In our study, the total number of Prehypertensives (Group A) were 36 (24%) and Normotensives (Group B) were 114 (76%). Table 1 shows the comparison of various anthropometric parameters (age; weight; height; and BMI) between Group A and Group B. The mean age in Group A and Group B was comparable (P = 0.547). The mean BMI of Group A was higher than Group B 25.77 ± 4.36 Kg/m² and 23.47 ± 4.99 Kg/m² respectively and it was statistically significant (P = 0.014). The mean basal heart rate of Group A and Group B was similar (P= 0.897) as shown in Table 2. The mean SBP of Group A was 122.72 ± 4.95 mm/Hg and Group B was (103.83 ± 6.98 mm/Hg) (P < 0.001). The mean DBP of Group A was 71.89 ± 9.02 and Group B was 63.18 ± 8.03 (P < 0.001).

The comparison of the two parasympathetic tests between Group A and Group B is shown in Table 3. The mean value of 30:15 ratio in Group A and Group B was 1.32 ± 0.15 and 1.27 ± 0.15 respectively (P = 0.115). Also the mean of Valsalva ratio was 1.67 ± 0.22 and 1.71 ± 0.29 (P = 0.427). There was no statistically significant difference found in the values of both the parasympathetic tests in between the two groups (P > 0.05).

The comparison of the two sympathetic tests i.e. Blood pressure response to HGT and CPT between Group A and Group B is shown in Table 4. In Group A the mean of SBP before HGT was found higher (124.97 ± 6.47 mm/Hg) than for Group B (106.61 ± 8.17 mm/Hg) (P < 0.001). Similarly, on the comparison of two groups for SBP after HGT, it was found higher in Group A than Group B and the difference was statistically highly significant (P < 0.001). But the SBP difference HGT for two groups was not significant (P = 0.953). Mean of DBP before HGT for Group A and Group B was 73.53 ± 9.26 and 66.38 ± 6.65 mm/Hg respectively and it was statistically highly significant (P < 0.001). Mean of DBP after HGT for Group A was significantly higher than Group B (P = 0.016). But the DBP difference HGT for two groups was not significant (P = 0.511).

On the comparison between Group A and Group B, there was statistical highly significant difference found between SBP before and after CPT (P < 0.001). But the mean SBP difference CPT for Group A and Group B was not significant (P = 0.751). Mean of DBP before and after CPT for Group A was highly raised than Group B (P < 0.001). But, the mean of DBP difference CPT for Group A and Group B was not statistically significant (P = 0.556).

DISCUSSION
Prehypertension is an emerging and remarkably common risk factor for not only hypertension but also increased the risk of cardiovascular morbidity and mortality. Though hypertension is common in middle-aged and elderly population, prehypertension is relatively more common in young adults, especially in those who have the family history of hypertension and also high Body Mass Index (BMI).18,19
In our study, the prevalence of prehypertensives was 24%. BMI was significantly higher in prehypertensive than normotensive subjects (P =0.04). The mean basal heart rate did not show any significant difference between prehypertensives and normotensives. But, both mean basal SBP and DBP of prehypertensives were significantly high compared to that of normotensives (P < 0.001) (Table 2).

Comparison of the two parasympathetic tests (Table 3), the mean value of 30:15 ratio and Valsalva ratio were comparable between two groups. (P > 0.05). While comparison of the sympathetic tests revealed that in case of prehypertensives the mean of SBP and DBP before and after HGT and CPT was higher than normotensives. Thus, these findings reflect increased sympathetic reactivity in prehypertensive subjects, as BP response to handgrip is an important sympathetic function test.20 A report by Wang et al. has also revealed increased sympathetic activity in prehypertensives.21From our study the exact cause of sympathetic imbalance in prehypertensive subjects cannot be fully ascertained but it could be suggested that adiposity contributes to these autonomic dysfunctions as BMI was significantly higher in prehypertensive than normotensive subjects. Thus, the degree of adiposity in these high-risk (prehypertensive) subjects could be a key determinant for the occurrence of prehypertension.22 Our study confirmed that prehypertension is associated with autonomic dysfunction, which was reflected by an elevated sympathetic tone that was associated with high normal BP states, and intriguingly, it was also coupled with high BMI alterations.

Various other studies have demonstrated that increased sympathetic activity, along with decreased parasympathetic tone, underlies the pathogenesis of prehypertension.14,15 Pal GK at el in his study observed that autonomic imbalance in prehypertensives was due to proportionate increased sympathetic activity and vagal inhibition, whereas in hypertensives, vagal withdrawal was more prominent than sympathetic overactivity.23 Our study did not find any alteration in parasympathetic function.

Davis et al. in his study "Autonomic and Hemodynamic Origins of Prehypertension" revealed that there was an overall increase in plasma norepinephrine levels as blood pressure and heart rate increased; the increment in norepinephrine can be suggested as a cause for increased sympathetic activity.[24]

Increased adiposity could be a key determinant for the development of prehypertension in susceptible individuals as obesity has been reported to be associated with increased sympathetic and decreased parasympathetic activity.22,25 It was suggested that alteration in plasma levels of leptin, neuropeptide-Y and α-MSH (melanocyte-

stimulating hormone) might be involved in activation of sympathetic activity that leads to hypertension in obese patients.26 Therefore, we assume that SVI caused by increased adiposity is among the major predictors of increase in blood pressure in prehypertensives. Though the exact mechanism of increased blood pressure induced by sympathetic activation in obesity is not known, it has been suggested that retrograde inflammation could be the pathophysiologic link as increased sympathetic activity induces a proinflammatory state by IL-6 production, which in turn results in an acute phase response.27 This was further supported by the study of Schmid et al. that increase in BMI is significantly associated with an increase in sympathetic tone and increased blood pressure in young healthy overweight subjects.28 Inspite of the limitations that we have not performed direct assessment of sympathetic activity, nor measured cardiac functions and there is less sample size of prehypertensive subjects, the present study emphasizes the necessity to improve vagal tone in individuals having blood pressure in prehypertensive range so that the sympathovagal balance is restored in these subjects and they do not progress to the stage of clinical hypertension. As the practice of regular aerobic exercises such as morning walk, swimming, cycling etc. have been reported to decrease blood pressure, improve vagal tone and cardiac health, and reduce body weight prehypertensive subjects should be encouraged to practice such program to prevent an increase in their BMI and progression to hypertension.[27,29,30]

CONCLUSION

The result of this study suggests that there is sympathetic overactivity in prehypertensive young individuals. Adopting a healthier lifestyle can help to delay the development of hypertension in later life. We have emphasized that adaptation to a healthier lifestyle will help improve sympathovagal homeostasis and prevent the occurrence of hypertension.

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