Derangement in autonomic functions with elevated blood pressure

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ABSTRACT

Background: Prehypertension exhibits approximately 62% of cardiovascular disease and 49% of ischemic heart disease (IHD) global morbidity burden. Heart Rate Variability (HRV) is a fundamental non-invasive technique to assess the autonomic influence on cardiovascular system using time domain and frequency domain methods. We explored the effects of family history of hypertension, pre-hypertension and hypertension on autonomic functions amongst natives of Uttarakhand region. Methodology: This cross sectional analytical study was designed to explore effects of family history of hypertension, pre-hypertension and hypertension on autonomic functions on 100 subjects divided in four groups using HRV analysis. Results: Autonomic function Analysis of our results showed an increased sympathetic activity among family history of hypertension, pre-hypertension and hypertension as evident by a significant increase in Low frequency normalized unit (LFnu), an increased LF/HF ratio and a significantly reduced High frequency Normalized unit (HFnu) and E/I ratio (p<0.05). Conclusion: Thus, altered cardiac autonomic functions are one of the early manifestations of raised blood pressure and can potentially be used in predicting hypertension at an early stage.

Keyword: Cardiovascular disease, Autonomic Functions, Heart rate, Variability, Hypertension
Methodology

**Study design:** This cross-sectional analytical study was designed to explore effects of family history of hypertension, pre-hypertension and hypertension on autonomic functions in Uttarakhand region. Volunteers; aged 20-40 years of both genders were selected from Himalayan Institute of Medical Sciences (HIMS), Dehradun. The research was carried out in the Autonomic Function Lab of the Department of Physiology, HIMS over a period of 12 months after obtaining written consent from all participants and approval by the institutional ethics committee.

**Sample population:** 100 participants were included in the analysis after excluding subjects with history of CVD, obesity, diabetes mellitus, renal and endocrine disorders. They were divided into 4 groups of 25 each as per the Seventh Report of the Joint National Commission (JNC 7) criteria: (i) NT (-) (BP < 120/80 mm Hg i.e, normotensive without history of hypertension), (ii) NT (+) (BP < 120/80 mm Hg i.e, normotensive with history of hypertension), (iii) pre-hypertension (BP of 120 to 139/80 to 89 mm Hg), and (iv) hypertension (BP of >140/90 mmHg).

**Sample size:** A sample size of 25 for each group was calculated through Cohen's flexible algorithm using Fischer's F distribution by comparing means between four group(s) F= 0.7 / 2 * 1 = with 'α' = 0.05, 'β'= 80%, '0.35 difference b/w the and effect size (es) which is two groups / 2 * within the group SD = 0.7

**Anthropometric measurements**

All anthropometric parameters i.e. weight (kg), height, waist and hip circumference (cm) were recorded were recorded care footed with minimal clothing. BMI, WHR were subsequently calculated from the aforementioned parameters

**Heart Rate Variability measurements**

HRV was performed between 8:30 am and 11 am in an isolated chamber at 25°C temperature. The subjects were abstained from smoking, devouring alcohol and caffeine for the last 12 hours and were kept in supine position for 15 minutes before commencing the test. After application of electrolyte jelly (providing interface between source and the electrode) surface electrodes (aided by elastic straps) were employed and ECG was recorded unremittingly for 5 minutes on a computerized polygraph; physiopac (Model; Windows) to obtain beat to beat R-R interval. Recording is in the form of Welch’s periodogram (Spectral window’s width: 1024, sampling rate: 1000 samples/sec) and Fourier transform analysis gives central frequency bands of spectral components as Low frequency power; LF (0.04-15Hz) showing predominantly sympathetic modulation, High frequency power; HF (0.15-0.4Hz) exhibiting parasympathetic modulation and their ratio LF/HF ratio depicting sympathovagal balance.

**E/I Ratio measurement**

E/I ratio was measured to assess and reinforce parasympathetic modulation. Respiratory excursions were obtained using stretch sensitive strain gauze with Velcro straps tethered around the chest and connected

| Table: 1 Comparison of demographic and clinical characteristics among normotensive with (NT+) and without (NT-) family history of hypertension, Pre-hypertension (PreHTN), and Hypertension (HTN) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Age             | 33.44±1.27      | 33.04±0.46      | 33.72±1.31      | 34.72±1.07      |
| Male%           | 68              | 60              | 56              | 64              |
| BMI (kg/m²)     | 22.34±0.37      | 23.24±0.73      | 25.50±0.95      | 25.36±0.94      |
| WHR             | 0.9±0.01        | 0.9±0.01        | 0.9±0.10        | 0.9±0.01        |
| HR (bt/min)     | 73.88±1.38      | 78.48±1.63      | 86.84±2.19      | 94.22±2.16      |
| SBP (mmHg)      | 104.64±1.71     | 110.00±0.88     | 125.84±1.67     | 149.56±2.82     |
| DBP (mmHg)      | 71.12±1.19      | 72.56±1.75      | 82.72±1.07      | 94.64±1.66      |
| Smoking%        | 52              | 40              | 64              | 44              |
| Alcohol consumption % | 16          | 12              | 68              | 36              |
| Physical activity % | 34          | 32              | 26              | 25              |

Values are Mean ± SE
BMI = Body mass index; WHR = Waist hip ratio; HR = Heart rate; SBP (systolic blood pressure) = Average of 3 systolic blood pressure readings; DBP (diastolic blood pressure) = Average of 3 diastolic blood pressure readings

'a' Analysed with one way ANOVA
'b' Analysed with Chi square test
to the polygraph machine. The subject took slow deep inspiration for 5 seconds followed by slow deep expiration for another 5 seconds thus making each respiratory cycle last for 10 seconds. Six such cycles were recorded each minute for 5 minutes with the simultaneous recording of ECG. Finally, ratio of the longest R-R interval during expiration to the shortest R-R interval during inspiration (E/I ratio) was calculated from above obtained respiratory and ECG tracings.

**Statistical Analysis**

Dataset was analyzed using SPSS (Statistical Package for the Social Sciences; version 20.0 for Windows). One-way Analysis of variance (ANOVA) followed by post hoc Bonferroni was used for comparing continuous variables (anthropometric indices, HRV parameters, and E/I ratio) between the groups. Categorical variables (history of smoking, alcohol intake and physical activity) were compared using appropriately chosen Pearson chi-square or Fisher exact test. Analysis of covariance (ANCOVA) was used to compare HRV parameters after adjusting for differing confounders (age, gender, BMI, WHR, history of smoking and alcohol intake) in one way ANOVA.

**Demographic and clinical characteristics**

Normotensives with family history of hypertension (NT+), pre hypertensives (PreHTN) and hypertensives (HTN) were slightly older, have raised BMI, WHR, and resting heart rate than normotensives without family history of hypertension (NT-) (Table 1). This difference was statistically non-significant (p > 0.05) thus maintaining homogeneity amongst four groups. Smoking% and alcohol% were significantly higher in PreHTN group as compared to the remaining three groups, and subjects in both (NT-) and (NT+) groups were physically more active than PreHTN and HTN subjects.

**Univariate analysis (one way ANOVA) of Cardiac Autonomic function tests**

Table 2 shows comparative univariate analysis of cardiac autonomic function tests among NT(-), NT(+), PreHTN and HTN groups. Both the parameters of parasympathetic tone i.e. HFnu and E/I ratio, component of predominantly sympathetic modulation LFnu and LF/HF ratio, index of sympathovagal balance differs among the aforementioned groups.
the aforementioned groups as compared to HFnu and E/I ratio. In addition, subjects in both PreHTN and HTN groups have significantly lower E/I ratio as compared to NT(+) group. Also hypertensive subjects have raised sympathovagal balance than NT(+) subjects.

For the above analysis the covariance included age, gender, BMI, WHR, history of smoking, history of alcohol intake with data presented as ADJUSTED MEANS. HFnu: high frequency normalized unit, E/I ratio: Ratio between R-R intervals during expiration & inspiration, LFnu: low frequency normalized unit, LF/HF ratio: low frequency/high frequency ratio

Covariant analysis (ANCOVA) of Cardiac Autonomic function tests adjusted for confounders.

Figure 1 compares the adjusted means of different components of cardiac autonomic function tests between the groups using ANCOVA (adjusted for confounders). Compared with NT (-), both preHTN and HTN group showed significant decline in HF power (nu) and E/I ratio but exhibited elevated LF power (nu) and LF/HF ratio. PreHTN and HTN groups have diminished E/I ratio when compared with NT(+) group. In addition, HTN group exhibited significant reduction in E/I ratio than PreHTN group but elevated sympathovagal balance compared with NT(+) group.

Discussion:

Increased adiposity was thought to have an influence on autonomic functions and in turn somewhat correlated with elevated blood pressure. Our study exhibited higher BMI and WHR in NT(+), prehHTN and HTN groups. These findings are in concordance with Bracho, M et al (11) and Kotpallivar M. K. et al (12) and Carmem Cristina Beck et al (13) who found BMI and WHR as major risk predictors of prehypertension.

It's difficult to ascertain the exact cause of altered adiposity suggested that adiposity contributes to these autonomic dysfunctions as BMI and WHR were significantly higher NT (+), preHTN and HTN as compared to NT(-). Obesity can either be a cause or exhibits association with increased sympathetic and decreased parasympathetic activity.
Amongst NT(+) subjects, we exhibited a significant reduction in parasympathetic tone which is evident by a decreased E/I ratio and HF power. This is in corroboration with a few studies showing low HF in normotensives with family history of HTN (14). We also reported a rise in LF power (nu) and LF/HF ratio in these subjects indicating greater sympathetic outflow which is in concordance with both Piccirillo G (15) and Marver J (16). However, heterogeneity occurs as far as increased sympathetic tone in normotensives with FHH is concerned which perhaps incurs due to classification or selection bias.

As for the effect of prehypertension on autonomic functions, we have observed a raised LF and LF/HF ratio along with diminished HF and E/I ratio in preHTN group perhaps suggest an increased sympathetic and a decreased parasympathetic activity. Moreover, an increased HR indicates lower vagal tone as lower resting HR is a sensitive index of higher parasympathetic activity.

These results are in close proximity with many previous studies. E.g. G K Pal et al elucidated a significant rise and fall in LFnu and HFnu respectively along with raised LF-HF ratio among prehypertensive subjects (17).

The same author further reiterated that pre-hypertensives showed higher sympathetic discharge as evident by a considerable decline in vagal modulation with increased LFnu (18). In a Turkish study M. Tolga Doğru et al similar results of significantly altered LF, HF and LF/HF ratio indicating that high-normal BP patients have increased sympathetic activity and decreased parasympathetic activity making them more vulnerable to hypertension (3).

The abovementioned altered autonomic parameters can be related to a hemodynamic transition from NT(+) to preHTN and HTN characterized by high cardiac output. This phenomenon can perhaps be manifested by various pharmacological blockade studies high sympathetic and low parasympathetic tone.

Other pathophysiologic mechanisms proposed to unveil correlation between elevated blood pressure and sympathetic over activity include gradual impairment of cardiopulmonary volume receptors. This is evident by a blunted reflex response to sympathetic activity and HR on volume expansion (19). Furthermore, lack of either production or release of NO may cause altered arteriolar reactivity again exhibited by a rise in the peripheral resistance (20).

Overall there is decrease in parasympathetic tone; diminished HFnu and E/I ratio and an increase in sympathetic tone; elevated LFnu and sympathovagal balance (LF/HF ratio) among (NT+), (PreHTN), and (HTN) as compared to (NT-). These findings are consistent with ANCOVA too after adjusting covariance for confounders which include age, gender, BMI, WHR, history of smoking, history of alcohol intake thus reiterating the fact deranged cardiac autonomic functions are one of the early manifestations of raised blood pressure and can potentially be used in predicting hypertension at an early stage.

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