Derangement in autonomic functions with elevated blood pressure

Arsalan Moinuddin, Sukhmani Saini, Ashish Goel, Rajesh Misra, Ashutosh Bajpai*
*Department of Physiology,Department of Biochemistry**
Himalayan Institute of Medical Sciences, SRHU, Jollygrant, Dehradun, India

Received : September 2016
Accepted : November 2016

Address for correspondence
Dr. Arsalan Moinuddin,
Assistant Professor,
Department of Physiology,
Shridev Suman Subharti Medical College,
Dehradun, Uttarakhand, India-303121
Contact no: 8003720999
Email: drarsalan.moinuddin@gmail.com

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

Introduction

Prehypertension exhibits approximately 62% of cardiovascular disease and 49% of ischemic heart disease (IHD) global morbidity burden as stated by W.H.O. These patients succumb to sudden coronary death, myocardial infarction and stroke more easily as evident by Framingham Heart Study (1, 2) which exhibited a twofold relative risk of CVD amongst pre hypertensives. Factors such as smoking, alcohol intake, and lack of physical activity may cause obesity and synergistically results in blunted reflex response of heart rate and sympathetic nerve activity to volume expansion along with enhanced afferent arteriolar reactivity to angiotensin II and catecholamines thus playing a key role in the pathogenesis of high BP (3, 4)

Findings elucidating elevated blood pressure in off springs of positive family history of hypertension are heterogeneous. H F Lopes et al in Brazil and Jin-Shang Wu et al in China found BP and heart rate significantly higher in children of hypertensive parents along with altered cardiac autonomic function. (5, 6) But the aforementioned findings are inconsistent amongst pre hypertensives which as per Joint National Committee (JNC VII) are individuals with systolic pressure of 120-139 mm Hg and/or a diastolic pressure of 80-89 mm Hg. The aim of this reclassification is to identify individuals who are at high risk of developing hypertension along with efforts to limit their rate of BP progression

Autonomic nervous system (ANS) primarily regulates the blood pressure by inducing rapid changes in peripheral resistance and cardiac output. It's two components; parasympathetic and sympathetic nervous systems acts precisely and antagonistically to each other to maintain sympathovagal balance (7, 8). 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. power spectral density analysis include low frequency (LF) (0.04 to 0.15 Hz) which predominantly depicts sympathetic drive whilst high frequency (HF) (0.15 to 0.40 Hz) is a major contributor of parasympathetic modulation. These signal parameters of HRV are extracted and analyzed as recognizable beat pattern that infers inter beat interval i.e. time between consecutive beats using computer software to estimate autonomic dysfunction. (9, 10)

Thus, we explored the effects of family history of hypertension, pre-hypertension and hypertension on autonomic functions amongst natives of Uttarakhand region.

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 >140/90mmHg).

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

	NT(-) (n=25)	NT(+) (n=25)	PreHTN (n=25)	HTN (n=25)	'p' value
Age	33.44 ± 1.27	33.04 ± 0.46	33.72 ± 1.31	34.72 ± 1.07	> 0.05
Male%	68	60	56	64	> 0.05
BMI (kg/m^2)	22.34 ± 0.37	23.24 ± 0.73	25.50 ± 0.95	25.36 ± 0.94	< 0.05
WHR	0.9 ± 0.01	0.9 ± 0.01	0.9 ± 0.10	0.9 ± 0.01	< 0.05
HR (bt/min)	73.88 ± 1.38	78.48 ± 1.63	86.84 ± 2.19	94.22 ± 2.16	< 0.05
SBP (mmHg)	104.64 ± 1.71	110.00 ± 0.88	125.84 ± 1.67	149.56 ± 2.82	< 0.05
DBP (mmHg)	71.12 ± 1.19	72.56 ± 1.75	82.72 ±1.07	94.64 ± 1.66	< 0.05
Smoking%	52	40	64	44	< 0.05
Alcohol consumption %	16	12	68	36	< 0.05
Physical activity%	34	32	26	25	< 0.05

Values are Mean ± SEBMI= 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 second. Six such cycles were recorded each minute for 5 minutes with the simultaneousrecording 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. Categoricalvariables (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 amongstall four groups. Smoking%and alcohol % were significantly higher in PreHTN group as compared to the remaining three groups, andsubjects 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(+),

Table 2: Univariate Analysis (One way ANOVA) for the comparison of Cardiac Autonomic Function parameters among normotensive with (NT+) and without (NT-) family history of hypertension, Pre-hypertension (PreHTN), and Hypertension (HTN)

S.no	Cardiac Autonomic Function Parameters		NT(-)(n=25) Mean ± SE	NT(+)(n=25) Mean ± SE	PreHTN(n=25) Mean ± SE	HTN (n=25) Mean ± SE	'p' value
1.	Parasympathetic Modulation	HFpower (nu)	45.18 ± 2.92	34.64 ± 2.32	29.46 ± 2.25**	28.80 ± 3.77**	<0.001
		E/I ratio	1.31 ± 0.02	1.33 ± 0.02	1.20 ± 0.02**††	1.10 ± 0.02$^{**††\#\#}$	<0.001
2.	Sympathetic modulation	LF power (nu)	53.55 ± 2.94	63.02 ± 2.53	63.05 ± 2.54*	68.94 ± 3.72**	<0.001
3.	Sympathovagal balance	LF/HF ratio	1.45 ± 0.16	2.08 ± 0.19	2.81 ± 0.40*	3.54 ± 0.39**†	<0.001

Values are Mean ± SE; Bonferroni post hoc test: 1. Compared with NT(-): *p < 0.05,p < 0.001;2. Compared with NT(+):†p <0.05, ††p <0.001; 3. Compared with preHTN: #p<0.05,##p<0.001**

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. Compared with NT(-) both preHTN and HTN have significantly reduced HF power (nu) and E/I ratio but they have elevated LF power (nu) and LF/HF ratio. However, the differences in LF power (nu) and LF/HF ratio although significant were less marked between

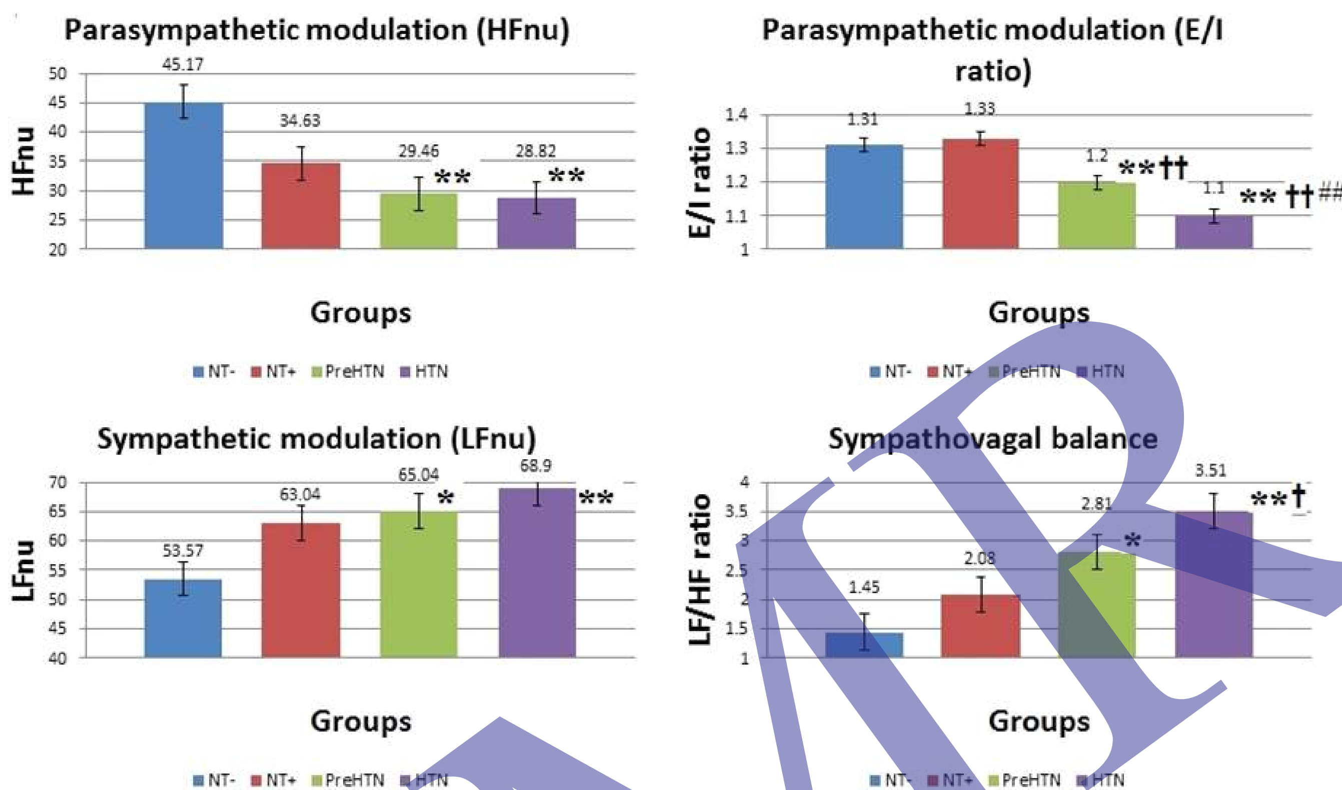

Figure: 1 Analysis of Covariance (ANCOVA) used for comparison and depict ADJUSTED MEANS of Cardiac Autonomic Function parameters among normotensive with (NT+) and without (NT-) family history of hypertension, Pre-hypertension (PreHTN), and Hypertension (HTN)

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(+) geousp.

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 Kotpalliwar 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. TolgaDoğru et al similar results of significantly altered LF, HFand 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.

References

- Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in non-hypertensive participants in the FraminghamHeart Study: a cohort study. Lancet 2001; (358);1682-6.
- Pitzalis MV,Iacoviello M, Massari F, Guida P, Romito R, Forleo C et al. Influence of gender and family history of hypertension on autonomic control of heart rate, diastolic function and brain natriuretic peptide. J Hypertens 2001 Jan;19(1);143-8
- Dogru Mt, Simsek V, Sahin O, Ozer N. Differences in autonomic activity in individuals with optimal, normal, and high-normal blood pressure levels.Turk KardiyolDernArs. 2010; 38(3);182-8
- Pal GK, Pal P, Nanda N, Lalitha V, Dutta Tk, Adithan C. Sympathovagal Imbalance in Young Prehypertensives: Importance of Male-Female Difference. Am J Med Sci. 2012 ; (22);68-84
- Lopes HF, Silva HB, Consolim-ColomboFM, BarretoFilho JA, Riccio GM, GiorgiDM, Krieger EM.Autonomic abnormalities demonstrable in young normotensive subjects who are children of hypertensive parents. Braz J Med Biol Res.2000 Jan;33(1);51-4.
- WuJS, LuFH, Yang YC, Lin TS Chen JJ, WuCH, Huang YH, Chang CJ. Epidemiological study on the effect of pre-hypertension and family history of hypertension on cardiac autonomic function. J Am CollCardiol. 2008 ;51(19):1896-901
- Anna Myredal. Cardiovascular regulation

and vascular structure in prehypertension andcoronary heart disease. Sweden, University of Gothenburg; 2009. [Cited 2012 March24]Availablefromhttps://gupea.ub.gu.se/bitstream/2077/20809/4/gupea_2077_29809_4.pdf

- Arthur C Guyton & John E Hall. Text book of medical physiology. 11th ed. Pennsylvania: Elseviers& Saunders; 2006;(1);25-36
- Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the NorthAmerican Society of Pacing and Electrophysiology. Circulation 1996;(93);1043-65.
- Basics of Heart Rate Variability: Applied to Psychophysiology.http://www.thoughttechnology.com/pdf/pdf/MAR95300%20Heart%20Rate%20Variability%20applied%20to%20psychophysiology.pdf/ Accessed 2nd October 2011
- Bracho M, Esis C, Silva E, Villasmil J, Gonzalez A, Bermudez G et al. Anthropometric Measures As Predictors of Prehypertension in Adolescents. Journal of Hypertension. 2010;(28);e479-e480
- Kotpalliwar MK, Wanjari A, Acharya S. Prevalence of Prehypertension in Young Healthy Individuals and its Associated Risk Factors. 2013; 2(3); 242-248.
- Beck CC, Lopes Ada S, Pitanga FJ. Anthropometric indicators as predictors of high blood pressure in adolescents. Arq Bras Cardiol 2011; 96(2); 126
- Maver J, Strucl M, Accetto R. Autonomic nervous system and microvascular alterations in normotensives with a family history of hypertension. Blood Press 2004;(13);95–100.
- Piccirillo G, Viola E, Nocco M, Durante M, Tarantini S, Marigliano V. Autonomic modulation of heart rate and blood pressure in normotensive offspring of hypertensive subjects. J Lab Clin Med 2000;(135);145–52.
- Maver J, Strucl M. Microvascular reactivity in normotensive subjects with a familial predisposition to hypertension. Microvasc Res 2000; (60);241– 8.
- Pal GK, Chandrasekaran A, Hariharan AP, Dutta Tk, Pal P, Nanda N, Venugopal L Body mass index contributes to sympathovagal imbalance in prehypertensives.BMC Cardiovasc Disord. 2012 ;(12);54
- G. K. pal, D. amudharaj, Pravati Pal, K. Saranya, V. Lalitha, M. Gopinath, T. K. Dutta and C. adithan. Study of sympathovagal imbalance by spectral analysis of heart rate variability in young prehypertensives. Indian J PhysiolPharmacol 2011; 55 (4) ; 357–363
- Thornton RM, Wyss JM, Oparil S. Impaired reflex response to volume expansion in NaCl-sensitive spontaneously hypertensive rats. Hypertension 1989; (14); 518-23.
- Tahawi Z, Orolinova N, Joshua IG, Bader M, Fletcher EC. Altered vascular reactivity in arterioles of chronic intermittent hypoxic rats. J ApplPhysiol 2001; (90); 2007-13.