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Original Article

Physiology Section

Assessment of Cardiac Autonomic Functions in Prehypertensive Individuals with and without a Family History of Hypertension: A Cross-sectional Study

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ABSTRACT

Introduction: Individuals with prehypertension are at an increased risk of developing hypertension. Family history is one of the paramount non modifiable risk factors for developing hypertension. Hence, it becomes mandatory to assess the cardiac autonomic functions, which play an important role in the regulation of Blood Pressure (BP), in prehypertensive individuals with a family history.

Aim: To compare the variations in parameters of cardiac autonomic function tests in prehypertensive individuals with and without a family history of hypertension.

Materials and Methods: This cross-sectional study was conducted at the Institute of Physiology and Experimental Medicine, Madras Medical College, Chennai, Tamil Nadu, India from October 2020 to October 2021. The study included 30 prehypertensive individuals without a family history of hypertension and 30 prehypertensive individuals with a family history of hypertension, aged between 20 and 50 years, of both genders. They were recruited from the non communicable diseases Outpatient Department (OPD) at Rajiv Gandhi Government General Hospital, Chennai, Tamil Nadu, India. The prehypertensive range refers to a Systolic Blood Pressure (SBP) of 120-139 mmHg or a Diastolic Blood Pressure (DBP) of 80-89 mmHg. After obtaining informed consent, baseline parameters such as resting Heart Rate Variability (HRV) using AD instruments powerlab recorder, deep breathing test, Valsalva maneuver, isometric handgrip test, and Cold Pressor Test (CPT) were evaluated. The data obtained was statistically analysed using a Student's t-test.

Results: The mean age of prehypertensive individuals without a family history was 36.90±4.6 years, and in prehypertensive individuals with a family history, it was 36.43±5.3 years. The male to female ratio was higher. The resting SBP and DBP, as well as the basal heart rate, were significantly increased in the prehypertensive subjects with a family history. Time domain variables such as the mean RR, Root Mean Square of Successive Difference (RMSSD), and pRR50 were reduced in prehypertensive individuals with a family history. Among the frequency domain variables, the total power was reduced, while the low-frequency component and LF:HF ratio were significantly increased. The E/I ratio and Valsalva Ratio (VR) were also significantly reduced in prehypertensive individuals with a family history. Thus, the results emphasise that there is significant autonomic dysfunction in prehypertensive individuals with a family history of hypertension compared to prehypertensive individuals without a family history.

Conclusion: Cardiac autonomic function tests in prehypertensive individuals with a family history indicate a definite sympathovagal imbalance in the form of sympathetic overactivity. This may substantiate the role of genetic predisposition in them. Chronic activation of the sympathetic nervous system makes them more prone to developing early hypertension.

Keywords: Cold pressor test, Deep breathing test, Heart rate variability, Isometric handgrip, Sympathovagal balance, Valsalva ratio

INTRODUCTION

As of the year 2020, more than 31.5% of the adult population worldwide is affected by elevated BP, accounting for approximately one billion people [1]. The Joint National Committee's seventh report (JNC 7), introduced at the American Society of Hypertension annual scientific conference in 2003, defines hypertension as arterial BP of 140/90 mmHg. Individuals with a systolic pressure of 120-139 mmHg or a diastolic pressure of 80-89 mmHg are defined as having "prehypertension" [2]. More than one out of every four adults worldwide is affected by prehypertension [3]. Among the Indian urban population, the prevalence of prehypertension accounts for about 32% [4]. Several risk factors predispose individuals to hypertension, with family history being one of the most important non modifiable risk factors [5].

Family history refers to having a blood relative such as a mother, father, or siblings who have or had high BP. Numerous family studies conducted among parents and siblings, as well as between siblings and children, establish the hereditary nature of hypertension [6-8]. Genetic factors contribute to approximately 30% of the BP variance, with twin studies showing a range of 25-65% [6, 7]. Individuals with a family history of hypertension may also share common environments and other potential factors that increases their risk [8]. The risk for prehypertension can escalate when genetic factors combine with other risk factors such as obesity, dyslipidaemia, and smoking [9].

Tests such as heart rate responses to the Valsalva maneuver, standing up, and deep breathing, as well as BP responses to standing up, sustained handgrip, and the CPT, are used in standard cardiovascular autonomic assessment [10, 11]. The pathophysiological mechanisms contributing to hypertension are complex. However, physiological studies on the cardiovascular system have long documented the role of the Autonomic Nervous System (ANS) in modulating cardiovascular functions and its influence over BP, both at rest and in response to environmental stimuli [12,13]. Heart rate responses to various stimuli serve as indicators of cardiac parasympathetic integrity, while BP changes indicate sympathetic influence. Therefore, primary prevention, which primarily focuses on non pharmacological lifestyle changes, has

been recommended for individuals at an increased risk of developing systemic arterial hypertension. Among them, individuals with a family history of hypertension would benefit most from primary prevention.

The aim of this study was to estimate and compare the variations in parameters of cardiac autonomic function tests in prehypertensive subjects with and without a family history of hypertension.

MATERIALS AND METHODS

This hospital-based cross-sectional study was conducted at the Institute of Physiology and Experimental Medicine, Madras Medical College, and Rajiv Gandhi Government General Hospital, Chennai, Tamil Nadu, India from October 2020 to October 2021. The study commenced after obtaining clearance from the Institutional Ethical Committee (IEC Reg.No.ECR/270/Inst./TN/2013/RR-16).

Inclusion criteria: All prehypertensive subjects with a SBP of 120 to 139 mmHg and a DBP of 80 to 89 mmHg, regardless of gender, aged between 20 to 50 years, were included in the study.

Exclusion criteria: Subjects with a history of systemic disorders such as diabetes mellitus, primary autonomic insufficiency, other cardiovascular diseases, respiratory, hepatic, renal, or neurological diseases, hypothyroidism, anaemia, neoplasia, any secondary infections, use of antidiabetic, antihypertensive, lipid-lowering agents, glucocorticoids, antipsychotics, oral contraceptives, smokers, alcoholics, pregnancy, postpartum period, or any infectious disease were excluded from this study. Subjects with a parental history of cardiovascular diseases and deaths were also excluded from the study.

Sample size calculation: The sample size was calculated based on the prevalence of prehypertension which was found to be 14.5% in a previous study [12]. A minimum sample size of 48 was needed to ensure a 10% precision and a 95% confidence interval. The sample size was calculated using the formula:

$$n=\frac{Z^2 1\text{-}\alpha/2\ p(1-p)}{d^2}$$

where, p: Expected proportion, d: Absolute precision, 1-α/2: Desired confidence level.

All 60 prehypertensive subjects were divided into two groups based on the presence or absence of a family history:

Group I: Thirty prehypertensive individuals without a family history of hypertension were enrolled.

Group II: Thirty prehypertensive individuals with a family history of hypertension were enrolled.

Family history of hypertension refers to a parental history of hypertension, either with one parent or both parents [13].

Data collection: Once the subjects were selected, informed written consent was obtained from both groups. They were instructed to report to the research lab of the Institute of Physiology and Experimental Medicine, Madras Medical College, at around 10 AM, with instructions to have breakfast before 8 AM and to avoid coffee or tea for atleast two hours prior to the test.

A detailed history, general, and systemic examination of the subjects were conducted to follow the inclusion/exclusion criteria. The anthropometric parameters such as height, weight, and Body Mass Index (BMI) were recorded. After five minutes of rest, the SBP, DBP, and basal heart rate were recorded in the supine position using an Omron digital BP apparatus. BP and HR were recorded on both arms twice with a five-minute interval between each recording. The mean of the four recordings was then calculated.

The subjects were explained the procedure and were subjected to a set of autonomic function tests, including resting HRV as stated by Ewing DJ and Clarke BF [14]. Disposable electrodes were placed after cleaning with alcohol wipes, and then connected to the Power-lab recorder. Lead II ECG was recorded for evaluation. A 15 minute rest in the supine position was given before each test. A baseline recording of respiration, ECG, and simultaneous R-R interval was taken for 30 seconds before each test commenced.

Resting HRV: The subject was asked to lie comfortably in the supine position, and ECG was recorded for a period of five minutes for short-term analysis [15]. The AD instruments Labchart pro 8 evaluation software analysed the recording using the power spectrum and displayed the HRV analysis report. Artifacts and ectopics were removed, and the mean RR (normal range: 654.6-1141.4 ms), RMSSD (normal range: 40-100), pRR50 (normal range: 10-25), TP (normal range: 600-1500 ms2), LF (nu) (normal range: 40-60), HF (nu) (normal range: 45-65), and LF:HF ratio (normal range: 0.5-1.5) were calculated [16].

Deep breathing test: The subject was then asked to breathe deeply and slowly according to verbal instructions, with inspiration for five seconds and expiration for five seconds. Each cycle lasted for 10 seconds, and six cycles were performed for a period of one minute. The E:I ratio, which is the ratio of the average RR interval during expiration to the average RR interval during inspiration in the six cycles of the deep breathing test, was taken from the recordings [13]. In young individuals, the E:I ratio is typically more than 1.2. The E:I ratio is influenced by factors such as age, resting heart rate, BMI, etc. [17].

Valsalva maneuver: The subject was asked to blow into a disposable mouthpiece (a 10 cc disposable syringe) connected to a modified sphygmomanometer, sustaining a pressure of 40 mmHg for 15 seconds while continuous recording was done throughout the maneuver and for 30 seconds after its completion. The ratio of the longest RR interval after the maneuver, reflecting the overshoot bradycardia after release, to the shortest RR interval during the maneuver, depicting the tachycardia during strain, was taken as the VR [18]. A VR ratio greater than 1.21 is considered a normal response [18].

Sustained handgrip: The subject was instructed to compress the grip force transducer of AD instruments with their dominant hand maximally. The transducer was connected to the Power-lab recorder, which recorded the grip force signals and displayed the grip force in Newtons. The maximum grip force, representing the maximum voluntary contraction, was determined. The subject was then asked to apply a force of 30% of the maximum grip force for two minutes. The BP in the opposite limb was recorded during the procedure at one minute. The difference in diastolic BP above the baseline was measured [13]. Normally, this difference should be higher than 15 mmHg [17].

CPT: The subject was instructed to immerse their hand into a basin of cold water at 4°C for two minutes. The BP in the opposite limb was recorded during the procedure after one minute of immersion. The difference in diastolic BP above the baseline was recorded [19]. A rise in diastolic BP of 10 to 20 mmHg from the baseline is considered a normal response [20].

STATISTICAL ANALYSIS

The recorded data were analysed using the statistical software package SPSS Version 26.0 for Windows (USA). The Student's t-test was used for statistical analysis as the test of significance at a 95% confidence level.

RESULTS

A total of 30 prehypertensive s without a family history of hypertension and 30 prehypertensive s with a family history of hypertension, aged 20 to 50 years, were included. Group I consisted of 21 men and 9 women, with a proportion of 70:30, while Group II consisted of 20 men and 10 women, with a proportion of 67:33. The proportions of gender in the two groups showed that they were comparable. In the present study, there was no significant difference in BMI between the two study groups [Table/Fig-1].

Variables	Study group	Mean±SD	p-value
Age (years)	Group I	36.90±4.664	0.756
	Group II	36.43±5.354	
BMI (kg/m^2)	Group I	27.38±2.007	0.705
	Group II	27.10±3.054	
Resting SBP (mmHg)	Group I	131.70±3.807	0.038*
	Group II	134.00±3.629	
Resting DBP (mmHg)	Group I	81.20±3.274	0.027*
	Group II	83.23±3.137	
BHR (beats/minute)	Group I	79.13±3.721	0.014*
	Group II	81.70±3.446	

[Table/Fig-1]: Comparison of baseline parameters among both the study groups.
BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BHR: Basal heart rate; Statistical test: Student's t-test. *p-value <0.05 statistically significant

The time domain variables, such as mean RR, RMSSD, and pRR50, showed a significant reduction in Group II compared to Group I. The frequency domain variable, total power, was significantly reduced in Group II compared to Group I. The LF nu was significantly increased in Group II. Although the HF nu was elevated in Group II, it was not statistically significant [Table/Fig-2].

Variables	Study group	Mean±SD	p-value
Mean RR (ms)	Group I	754.43±35.484	<0.001***
	Group II	703.30±53.050	
RMSSD	Group I	30.11±1.2972	<0.001***
	Group II	26.83±2.5652	
pRR50	Group I	7.911±0.8997	0.021*
	Group II	7.421±0.4180	
TP (ms^2)	Group I	855.06±118.63	0.043*
	Group II	805.9±104.67	
LF (nu)	Group I	55.40±4.193	0.015*
	Group II	58.26±3.718	
HF (nu)	Group I	29.74±2.563	0.616
	Group II	29.43±2.130	
LF:HF ratio	Group I	1.8±0.198	0.023*
	Group II	1.9±0.145	

[Table/Fig-2]: Comparison of time domain and frequency domain variables of Heart Rate Variability (HRV) among the study groups.
RR: RR interval; RMSSD: Root mean square of successive differences between normal heartbeats; pRR50: Percentage of adjacent RR intervals that differ from each other by more than 50 ms; TP: Total power; LF (nu): Normalised low frequency power; HF (nu): Normalised high frequency power, Statistical test: Student's t-test

The E/I ratio and VR were significantly decreased in Group II compared to Group I. There was no significant variation in the difference in Isometric Handgrip (IHG) DBP and CPT DBP between the two groups [Table/Fig-3].

Variables	Study group	Mean±SD	p-value
E/I ratio	Group I	1.18±0.185	0.027*
	Group II	1.08±0.156	
VR	Group I	1.33±0.083	0.047*
	Group II	1.28±0.064	
IHG DBP	Group I	20.00±3.248	0.418
	Group II	19.33±2.644	
CPT DBP	Group I	9.87±1.408	0.482
	Group II	10.13±1.717	

[Table/Fig-3]: Comparison of E/I ratio, Valsalva Ratio (VR), diastolic BP of isometric handgrip test and cold pressor test among the study groups.
E/I ratio: Expiration inspiration ratio; VR: Valsalva ratio; IHG DBP: Difference from baseline diastolic BP of isometric hand grip test; CPT DBP: Difference from baseline diastolic BP of cold pressor test, Statistical test: Student's t-test; *p-value <0.05 was considered as significant; **p-value <0.01 was considered as highly significant; ***p-value <0.001 was considered as very highly significant

DISCUSSION

There was no significant difference in age between the two groups. The rise in resting BP in Group II could be attributed to the presence of a family history of hypertension, while in Group I, it could be attributed to the elevated BMI of 27.38±2.0, which falls within the overweight category of BMI classification, although there was no significant difference in BMI between the two groups. This warrants the need to investigate other factors such as lipid profile, catecholamine levels, etc., in these individuals. The elevated resting SBP and DBP are consistent with the results of Arun Kumar B and Nirmala N [21]. The higher basal heart rate in Group II compared to Group I could be attributed to altered vagal regulation caused by genetic predisposition in prehypertensive subjects with a family history of hypertension. This was similar to the results of Pal GK [22].

Among the time domain variables of resting HRV, a high variability of RR interval is considered an index of the ability of the cardiovascular system and ANS to cope with environmental challenges. Hence, the lower mean RR in Group II compared to Group I could be linked to impaired integrity of the ANS due to genetic predisposition in Group II. A similar decrease in mean RR in normotensives with a family history was observed in a study by Pitzalis MV [23]. RMSSD reflects the vagal modulation of heart rate and is therefore an important short-term measure of parasympathetic drive. The significant reduction in RMSSD in Group II reflects poor vagal control in that group. The percentage of adjacent NN intervals that differ from each other by more than 50 ms, known as pNN50, is closely related to parasympathetic activity. The results obtained show decreased vagal activity in Group II compared to Group I. In this study, the time domain variables were calculated using short-term resting HRV monitoring, which was comparatively less accurate than 24-hour Holter monitoring. Yet, the decrease in RMSSD and pRR50 in Group II indicates significant parasympathetic withdrawal in that group compared to Group I. A study by Jha A et al., also reported alterations in time domain variables in subjects with a family history [24].

The study reveals a highly significant variation in frequency domain parameters. Total power represents the total variance and corresponds to the sum of four spectral bands, influencing the LF and HF values. To minimise this effect, normalised HF and LF values were used. The LF (nu) was significantly increased in Group II compared to Group I, indicating higher sympathetic activity in Group II. There was no significant difference in the HF (nu) value, reflecting parasympathetic activity, between the two groups. The LF:HF ratio, a reliable measure of sympathovagal balance, was 1.8±0.198 in Group I and 1.9±0.145 in Group II. The p-value of the LF:HF ratio was 0.023, indicating a significant overall sympathovagal imbalance in both groups, but significantly greater in Group II with sympathetic overactivity and parasympathetic withdrawal. This was consistent with the results of Wadoo OK et al., and Pal GK [25,26]. [Table/Fig-4] shows comparison of present study with other studies [13,21-27].

Authors name, publication year	Place of the study	Sample population	Sample size	Findings
Arun Kumar B and Nirmala N [21], 2020	Sri Venkateshwara Medical College and Research Centre, Puducherry, India	Normotensives, prehypertensives, hypertensives	90	Elevated resting systolic and diastolic BP in prehypertensives than normotensives.
Pal GK et al., [22], 2012	Jawaharlal Institute of Post-graduate Medical Education and Research, Puducherry, India	Normotensives, prehypertensives with normal BMI, prehypertensives with higher BMI	108	Elevated basal heart rate in prehypertensives.

Pitzalis MV [23], 2001	University of Bari, Bari, Italy	Normotensives with and without family history of hypertension	87	Decreased mean RR in normotensives with family history than subjects without family history.
Jha A et al., [24], 2018	BP Koirala Institute of Health Sciences, Dharan, Nepal	Normotensives with normotensive parents and hypertensive parents	60	Time domain variable RMSSD was decreased in subjects with family history.
Wadoo OK et al., [25], 2021	Government Medical College, Srinagar, India	Normotensives with hypertensive parents normotensive parents	60	LF nu and LF:HF ratio was higher in subjects with family history.
Pal GK et al., [13], 2011	Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India	Normotensive offsprings of hypertensive parents and Prehypertensive offsprings of hypertensive parents	172	LF:HF ratio was higher in prehypertensive offspring of two parents hypertensive.
Pal GK [26], 2013	Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India	Normotensives and prehypertensives	176	The E/I ratio was significantly decreased in prehypertensives.
Herlekar SS and Kapparrad D [27], 2022	Jawaharlal Nehru Medical College, Belagavi, Karnataka, India	Normotensive offspring without a family history of hypertension, Normotensive adolescents with positive family history of hyperetension and Prehypertensives	150	The VR was altered in normotensives with family history and in prehypertensives.
Present study, 2023	Madras Medical College, Chennai, Tamil Nadu, India	Prehypertensive individuals with and without a family history of hypertension	60	Elevated resting systolic BP, diastolic BP, basal heart rate, LF nu, LF:HF ratio and decreased mean RR, RMSSD, pRR50, E/I ratio, VR in prehypertensives with family history.

[Table/Fig-4]: Comparison of present study with other studies. [13,21-27].

Sinus arrhythmia is the key aspect of the deep breathing test. The heart rate increases during inspiration and decreases during expiration. The E/I ratio, which represents the ratio between the longest RR interval during expiration and the shortest RR interval during inspiration, was determined and compared between the two groups. The decrease in E/I ratio in Group II implies decreased vagal tone, which is significant with a p-value of 0.027. VR, the ratio of the longest RR interval after the Valsalva maneuver to the shortest RR interval during the maneuver, is a measure of parasympathetic function. The decrease in VR in Group II reflects a decrease in vagal activity. The Isometric Hand Grip (IHG) test is a simple yet reliable non invasive measure of sympathetic activity. It results in an increase in heart rate and BP during sustained IHG, mediated reflexly by sympathetic activity. This leads to an increase in DBP. In this study, there was no significant difference in IHG DBP between the two groups. The CPT assesses sympathetic activity. Reflex arterial vasoconstriction occurs when the hand is immersed in ice water, causing elevated BP due to activation of temperature receptors and nociceptors in the skin. However, there was no significant difference between the two groups in this study. Genetic predisposition leads to early and chronic stimulation of the sympathetic system. Because autonomic circuits are sensitised by genetic predisposition, long-term sympathetic dominance contributes to the development of hypertension and adverse cardiovascular events at a young age [28].

Limitation(s)

Due to time constraints, 24-hour ambulatory HRV measurements data on salt intake, physical activity, and serum lipid profile were not collected. If these limitations were better addressed, it could provide a better understanding of the complex pathophysiology of prehypertension.

CONCLUSION(S)

In the present study, the cardiac autonomic function tests in prehypertensive subjects with a family history of hypertension indicate that the sympathovagal balance has been impaired, with sympathetic overactivity evident from the time domain and frequency domain parameters of HRV, and parasympathetic withdrawal observed in the deep breathing test and VR. There is also a need to investigate other risk factors that influence BP. A prospective study with follow-up after lifestyle changes would provide a better understanding of the integrity of the ANS. Additionally, a catecholamine assay, which is regarded as a direct measure of the sympathetic system, could have been conducted.

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