The Study Of Autonomic Status And Hemodynamic Variables In Young Healthy Normotensive Subjects With And Without Parental History Of Essential Hypertension.

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Abstract: **Background & Objectives:** Normotensive subjects with a family history of hypertension are considered to be at increased risk of developing hypertension. Autonomic control of heart rate is impaired in hypertensive offsprings. Thus the purpose of study was to assess the autonomic activity and hemodynamic variables in young healthy normotensive subjects with parental history of essential hypertension**. Method:** Sixty young healthy normotensive subjects, with (n = 30) and without (n = 30) parental history of essential hypertension were examined. Autonomic functions were assessed by using heart rate variability analysis. **Results:** In the present study, no significant differences were observed in hemodynamic variables (blood pressure, cardiac output, stroke volume, heart rate, systemic vascular resistance, blood flow index, pulse arrival time, pulse termination time) in both groups. The low frequency power in normalized units was significantly higher ($P<0.05$) and high frequency power in normalized units was significantly lower ($P<0.05$) in subjects with positive parental history of essential hypertension. The Low frequency/High frequency ratio was significantly higher ($P<0.01$) in subjects with positive parental history of essential hypertension. **Interpretation & Conclusion:** The altered sympathovagal balance may be an early marker of increased cardiovascular responsiveness in subjects with genetic predisposition to hypertension.

Keywords: Autonomic activity, heart rate variability analysis, hemodynamic variables, impedance plethysmography

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Introduction: The autonomic drive to the heart with a normal sinoatrial (SA) node gives valuable insight the sympathovagal interplay[1]. The analysis of heart rate variability evaluates the SA node modulation by the two interactive limbs of autonomic nervous system, namely sympathetic and parasympathetic nervous system[2,3,4]. Hemodynamic variables were assessed on the principle of Impedance plethysmography (IPG). IPG is used for indirect assessment of blood volume changes in any part of the body in the electrical impedance of the body segment[5].

Hypertension is one of the major risk factors for cardiovascular mortality, which accounts for 20-25 % of all death[6]. Normotensive subjects with a family history of hypertension are considered to be at increased risk of developing hypertension. The children of two normotensive parents had 3% possibility of developing hypertension whereas this possibility is 45% in children of both hypertensive parents[7]. Autonomic control of heart rate is impaired in hypertensive offsprings. So, the early diagnosis does have significant effect on cardiovascular autonomic activity in children of hypertensive parents. Thus the present study was planned to assess the autonomic activity and hemodynamic variables in normotensive subjects of hypertensive parents.

Material and Method: The present study was carried out in the upgraded Department of Physiology, SMS Medical College, Jaipur. Sixty non alcoholic, non smoking, young healthy normotensive medical students of either gender aged 18-25 years were recruited for the study after obtaining written informed consent to a protocol that was approved by the institutional ethics review board. A detailed history of subjects was taken with main emphasis on the parental history of essential hypertension. Subjects were divided into two groups:

1) Subjects with parental history of Essential Hypertension (FH^+, n=30)

2) Subjects without parental history of Essential Hypertension (FH^-, n=30).

All subjects had normal medical history and physical examination. Autonomic evaluation was carried out in the morning from 10.00 to 12.00 noon, 2 hours after a light breakfast and after familiarizing the subjects with the test procedures. For the calculation of body mass index, body weight was measured in kilogram and height was measured in inch by using Stadiometer on scale (Feca 100 Jahre, Waagenbau). After 5 minutes of supine rest, blood pressure was taken by using mercury sphygmomanometer. Heart rate variability and hemodynamic variables were recorded by the

medical analyzer module based on principle of impedance plethysmography (NIVOMON, L & T)

Heart rate variability (HRV):- The analysis of signal was done in frequency domain measures. For short term analysis of HRV, impedance peripheral pulse in the right forearm was recorded in the supine position for 5 minutes after 10 minutes of supine rest. Room ambient temperature was maintained between 24-25^0 C. The impedance peripheral pulse wave signals were continuously amplified, digitized and stored in the computer for offline analysis in frequency domains. The detection of impedance peripheral wave was digitally done by medical analyzer, Non-invasive Vascular Monitor (NIVOMON, L & T). Abnormal beats and areas of artefacts were automatically and manually identified and excluded from the study.

In the present study, the power spectrum is subsequently divided into three frequency bands: Very low frequency (VLF) (<0.04 Hz), Low frequency (LF) (0.04-0.15 Hz) and High frequency (HF) (0.15-0.4Hz). Powers of spectral bands are calculated in absolute units (ms^2) and normalized units (nu)[4]. The normalized units were calculated as:

High frequency power in normalized units (HF nu) = (HF ms^2) / (LF ms^2 + HF ms^2) × 100)

Low frequency power in normalized units (LF nu) = (LF ms^2) / (LF ms^2 + HF ms^2) × 100)[8].

Hemodynamic variables: According to the procedure described by Barde et al, (2006), for the assessment of cardiac output (CO), stroke volume (SV), heart rate (HR) and systemic vascular resistance (SVR), non-invasive cardiac output (NICO) monitor was connected to subject via 4 spot electrodes in supine position. Amongst 4 spot electrodes used, two were current injecting electrodes (I_1, I_2), and other two were voltage-sensing electrode (V_1, V_2). V_1 was placed in the mid axillary line at the level of xiphisternum and V_2 was positioned at the base of neck. I_1 was placed at the top of the neck and I_2 was placed below the V_2[9].

IPG monitor was used for the estimation of blood flow index (BFI), pulse arrival time (PAT) and pulse termination time (PTT). Impedance plethysmography monitor was connected to subject in supine position. Selected investigation was upper extremities and right forearm leads were selected for data acquisition[5].

Statistical analysis: Data are presented as mean ± standard deviation (SD). Statistical analysis was performed by using Student Unpaired't' test for comparison between various measures of HRV and hemodynamic variables in subjects with and without parental history of essential hypertension. The data were analyzed with the use of SPSS version 10 software packages. All p values were two tailed. Differences were considered statistically significant for p values < 0.05.

Results: Table 1 depicts the demographic characteristics and hemodynamic variables of studied subjects and no significant difference was observed between systolic blood pressure (SBP), diastolic blood pressure (DBP), CO, SV, HR, SVR, BFI, PAT, and PTT in both groups.

Table 1: Demographic characteristics and hemodynamic variables of studied subjects

Basal parameters	Normotensive subjects with FH^+ (n=30)	Normotensive subjects with FH^- (n=30)
Age (yr)	20.03 ± 1.52	19.93 ± 1.66
Height (cm)	161.57 ± 7.04	164.23 ± 10.21
Weight (kg)	56.9 ± 8.11	55.97 ± 8.93
BMI (kg/m^2)	21.73 ± 2.20	20.67 ± 2.07
SBP (mmHg)	117.57 ± 10.73	114.57 ± 7.18
DBP (mmHg)	73.67 ± 7.68	75.20 ± 6.76
CO (lt/m)	4.43 ± 0.82	4.38 ± 0.96
SV (ml/beat)	55.44 ± 11.60	56.02 ± 14.59
HR (bpm)	81.07 ± 10.27	79.47 ± 9.99
SVR (dyne.sec/cm^5)	1648.47± 313.85	1687.60±374.63
BFI (%)	0.99 ± 0.17	0.93 ± 0.20
PAT (ms)	187.33 ± 25.45	188.33 ± 24.51
PTT (ms)	356.33 ± 52.19	329.33 ± 57.50

Values are mean ± SD, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CO: Cardiac output, SV: Stoke volume, HR: Heart rate, SVR: Systemic vascular resistance, BFI: Blood flow index, PAT: Pulse arrival time, PTT: Pulse termination time

Comparison of Heart rate variability components between the study groups were demonstrated in Table 2. Total power, amplitude of LF power, amplitude of HF power, LF power in absolute units (LF ms^2) and HF power in absolute units (HF ms^2) in subjects with FH^+ and FH^- showed no significant differences. In contrast, the LF nu (49.81 ± 21.98) was significantly higher (P<0.05) and the HF nu (50.19 ± 21.98) was significantly lower (P<0.05) in subjects with FH^+ as opposed to the subjects with FH^- (LFnu=38.39 ± 16.49; HFnu=61.61 ± 16.49). The LF/HF ratio was significantly higher (P<0.01) in subjects with FH^+ (1.55 ± 1.46) as compared to the subjects with FH^- (0.75 ± 0.52).

Table 2: Comparison of heart rate variability components between the study groups

HRV Components	Nomotensive subjects with FH^+ (n=30)	Nomotensive subjects with FH^- (n=30)	p value
Total power (ms^2) (0.0 – 0.4 Hz)	1877.57 ± 2369.69	1123.42 ± 841.14	0.1059
Amplitude of LF power (ms)	4.48 ± 2.35	3.19 ± 1.58	0.0156
Amplitude of HF power (ms)	3.50 ± 2.98	4.80 ± 2.98	0.0988
LF power in absolute units (LF ms^2) (0.04 – 0.15 Hz)	478.65 ± 486.99	278.38 ± 314.40	0.0634
HF power in absolute units (HF ms^2) (0.15 – 0.4 Hz)	754.15 ± 1251.20	489.02 ± 451.59	0.2795
LF power in normalized units (LF nu)	49.81 ± 21.98	38.39 ± 16.49	0.0265*
HF power in normalized units (HF nu)	50.19 ± 21.98	61.61 ± 16.49	0.0265*
LF/HF ratio	1.55 ± 1.46	0.75 ± 0.52	0.0065**

Values are mean ± SD, *p<0.05, **p<0.01, HRV: Heart rate variability, LF: Low frequency, HF: High frequency, FH^+: Subjects with parental history of essential hypertension, FH^-: Subjects without parental history of essential hypertension

Discussion: Autonomic functions were assessed by measurement of the variation in resting heart rate using frequency spectrum analysis of HRV. High frequency spectral power reflects parasympathetic modulation of RR intervals at respiratory frequency[10]. LF power in absolute units of power quantifies baroreflex mediated modulation of RR intervals in the 0.04-0.15 Hz range changes in sympathetic as well as vagal nerve traffic to heart are thought to contribute to LF power[11]. Total power calculated as the sum of LF and HF powers is also an index of overall HRV. The representation of LF and HF in normalized units emphasizes the controlled and balanced behaviour of the two branches of autonomic nervous system[4].

The amplitude of LF or HF power is a measure of autonomic nervous system modulation of sinus node firing, and not a measure of global sympathetic and parasympathetic nervous system tone. However, the LF/HF ratio is used as an index of sympathetic-parasympathetic balance[12]. Hemodynamic variables were assessed on the principle of Impedance plethysmography (IPG). IPG was used for measuring changes in blood volume or blood flow in neck and lower extremities. The amplitude normalized dZ/dt (rate of change of impedance) waveform is a gross indicator of blood flow. Thus maximum amplitude of NdZ/dt (normalized dZ/dt) wave form will be taken as an index of blood flow in the limb and termed as Blood flow index (BFI). BFI represents arterial blood flow[5]. While travelling toward the periphery, the arrival time of a pressure pulse at two different sites of the arterial tree are commonly referred to as pulse arrival time[13].

Present study examined the autonomic responsiveness and hemodynamic variables in subjects with and without parental history of essential hypertension. We observed a significant higher LF nu (p<0.05), reduced HF nu (p<0.05) and higher LF/HF ratio in subjects with FH^+ as opposed to subjects with FH^- [Table 2], consistent with the study of Sowmya et al, (2009)[14].

Consistent with present reports, Piccirillo et al, (2000) and Maver et al,(2004). Piccirillo et al, (2000) also reported that higher spectral densities of low frequency in normalized units also had a greater ratio of low-frequency to high-frequency powers (LF/HF) of R-R interval variability in normotensive persons with a positive family history of arterial hypertension compared to the persons with a negative history[15]. However, Maver et al in 2004 observed decreased high-frequency power of the heart rate variability spectrum. They concluded that normotensives with a family history of hypertension exhibit altered sympathovagal balance with decreased parasympathetic activity at the cardiac level[16].

Contrary to the above studies, Shang Wu et al, (2008) found that FH^+ subjects had lower HF power than that of FH^- subjects but there was no difference in the square roots of LF/HF ratios between FH^+ and FH^-[17].

The above studies had shown that normotensive subjects with parental history of essential hypertension exhibit exaggerated sympathetic activity and reduced parasympathetic activity indicating altered sympathovagal balance as evidenced by increased LF (nu), LF/HF ratio and decreased HF (nu). Thus, the altered sympathovagal balance may be an early marker of cardiovascular changes in subjects with a genetic predisposition to hypertension. Autonomic imbalance could also be the direct consequence of genetic defects or a result of the cardiac structural and functional abnormalities found in the offspring of hypertensive families[18].

Conclusion: The normotensives with a family history of hypertension exhibit altered sympathovagal balance with decreased parasympathetic activity at the cardiac level, suggesting that early diagnosis and treatment does have significant effect on cardiovascular autonomic activity. The ability to detect cardiovascular autonomic changes in younger age group may help to identify those persons who are prone to develop hypertension later in their future life.

Limitation: The future studies should include more methods of assessment of autonomic activity such as sympathetic activity by estimation of plasma catecholamine or metabolites of catecholamine in urine like Vanillylmandelic acid (VMA), Metanephrine and Normetanephrine together with HRV analysis to validate the present findings.

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