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A Comprehensive Study of Autonomic Dysfunction in Hypertension by Assessing Autonomic Function Tests and HRV

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***Abstract:** Aims: To study the variations of autonomic nervous system in hypertensive patients using a set of autonomic function tests and to correlate cardiac autonomic function with Heart rate variability in hypertensives. Background: The pathophysiological mechanism for the development of hypertension is the lack of balance between sympathetic and parasympathetic nervous system. Both Heart rate variability (HRV) and Autonomic function tests provide a tool to know the concept of autonomic modulation of heart. They also forms an index of cardiac autonomic regulation. Methods: The study included 50 hypertensive patients and 50 normotensive subjects. All the subjects underwent for the analysis of heart rate variability in time domain (TD) and frequency domain and a set of autonomic function tests were done to assess the autonomic functions. These results were compared with age and sex matched controls (normotensives). The subjects were selected based on exclusion-inclusion criteria. Results: Results showed that S: L ratio, Valsalva ratio & Heart rate response to deep breathing test values were decreased in Hypertensives as compared to Normotensives (p<0.05). Isometric handgrip exercise, BP response to standing and cold pressor tests shows that there was significant rise in the systolic and diastolic blood pressure in Hypertensives as compared to Normotensives which was statistically significant (p<0.05). Both the time domain and frequency domain values of HRV reduced significantly in hypertensives indicated that there is increased sympathetic activity and decreased parasympathetic activity. Conclusion: From this study, it is evident that Hypertension can alter the normal autonomic functions of the body and predisposes to autonomic neuropathy. Early and regular screening of these individuals is necessary to prevent any future complications.*

Keywords*:* Autonomic nervous system, Hypertension, Blood Pressure, Heart rate variability.

1. Introduction

Overall, approximately 20% of the world's adults are estimated to have hypertension and contributing to more than 7.1 million deaths per year[22]. Hypertension is defined as a sustained elevation of systemic arterial blood pressure. It is commonly due to increased peripheral resistance or increased cardiac output, but most commonly due to increased peripheral resistance. It can be produced secondary to many diseases or more commonly without any cause. Hypertension is the term used to describe high blood pressure. The major complications of hypertension are: Excess work load on the heart leads to heart failure and coronary heart disease, often leads to death due to heart attack, High pressure damages a major blood vessels in brain, it is a cerebral infarct clinically it is called stroke. A stroke can cause Paralysis, dementia and blindness; High pressure almost causes injury in kidneys leads to renal failure, uremia and death

The autonomic nervous system plays a crucial role in blood pressure (BP) and heart rate (HR) control and may thus be an important pathophysiological factor in the development of hypertension. Hypertension is one of the common non-communicable disease which is usually asymptomatic but readily detectable and treatable condition and often leads to lethal complications like coronary heart disease, stroke etc. if left untreated. It is probably the most important public health problem in all developed countries as they have achieved a successful control of much infectious and communicable disease.

The Autonomic Nervous System regulates the 'automatic' functions of the body such as blood pressure, heart rate, breathing, stomach and intestinal function, and bladder function. If it becomes unbalanced, a person may experience a variety of symptoms. Disorders of the autonomic nervous system can be identified through autonomic function testing and Heart rate variability. For these tests a person will be attached to a blood pressure machine which monitors the blood pressure continuously and an electrocardiograph which monitors the heart rhythm continuously. The present study was conducted to identify the changes in autonomic functions in hypertensive patients by evaluating the autonomic function tests and heart rate variability.

The integrity of autonomic modulation of heart rate is evaluated by analyzing heart rate variability (HRV) and autonomic function testing. Both Autonomic function testing and heart rate variability are useful noninvasive, an accurate, reliable, reproducible tools to assess cardiac autonomic function.

2. Methods

This study was undertaken by me on behalf of Department of Physiology, Narayana Medical College. The approval of Department of Cardiology and Medical ethics committee of Narayana Medical College, Nellore was taken for this "A Comprehensive Study of Autonomic Dysfunction in Hypertension by Assessing Autonomic Function Tests and HRV". Subjects were selected from Narayana General

Hospital attending Cardiology outpatient department for master health checkup, aged between 30 to 65 years, who volunteered to take part in the study. The procedure was explained and written consent was obtained from the subjects. All the subjects underwent a detailed clinical examination regarding anthrological measurement & physiological measurement before being included in the study as per the study protocol. The subject selection was based on the predetermined exclusion-inclusion criteria.

Inclusion criteria:

Study group:

Controlled Hypertension for more than 2 years
Males and females aged 30-65 years
Normal Cardiovascular and Respiratory system on clinical examination
No history of Diabetes mellitus
No history of any acute infectious diseases
No history of any chronic diseases

Control group:

Normotensive population
Males and females aged 25-65 years
Normal body mass index (BMI: 19-25 Kg/m^2)
Normal Cardiovascular and Respiratory system on clinical examination
No history of Diabetes mellitus
No history of any acute infectious diseases
No history of any chronic diseases

Exclusion Criteria:

< 25 years and > 75 years of age
History of Diabetes mellitus
History of Connective tissue disorders
History of Congenital heart diseases
History of Coronary artery disease
History of pericardial disease
History of valvular heart disease
History of cardiac arrhythmias
Patients where it was technically difficult to perform echocardiography
Abnormal Cardiovascular and Respiratory system on clinical examination

Cardiovascular Autonomic function tests were carried out in the morning in the department between 10 AM to 12 Pm after 2 hours of light breakfast, after intimate testing procedures with the subjects.

The Autonomic function tests which were performed to assess the cardiovascular sympathetic functional status:

1) **Cold Pressor test (cold pressure test):** Subject was instructed regarding the test. Blood pressure was recorded under basal conditions. Cold water was taken in a container. Subject was asked to submerge one of his upper limbs in cold water for 60 seconds. Blood pressure was recorded at the end of 60 seconds of submersion of the limb. Submersion of the limb in ice cold water increases systolic blood pressure by about 10-20 mm of Hg and diastolic blood pressure by about 10 mm of Hg.
2) **Hand Grip Test:** In the hand grip test, there is a rise in heart rate and blood pressure. The blood pressure rise is due to increased sympathetic activity and heart rate rise is due to decreased parasympathetic activity. Subject was made to lie down in semi recumbent position. ECG electrodes were connected for lead II recording of ECG and sphygmomanometer for blood pressure measurement. Basal heart rate and blood pressure were recorded. Subject was asked to maintain a pressure of 30% of the maximum activity in the hand grip dynamometer for about 5 minutes. Heart rate and change in SBP, DBP were recorded.
3) **Blood pressure response to standing:** Patient is again allowed to assume a supine position, and a recording of blood pressure is done in the supine position. Patient is then asked to stand up and blood pressure is recorded at 0 and 1 minute intervals.

The Autonomic function tests which were performed to assess the cardiovascular parasympathetic functional status:

1) **Deep breathing test -** This test is used to assess the parasympathetic activity. Subject was instructed to maintain deep breathing at a rate of six breaths per minute and was made to lie down comfortably in supine position with head elevated to 30^0. ECG electrodes were connected for recording Lead II ECG. While subject was breathing deeply at a rate of 6 breaths per minute (allowing 5 seconds each for inspiration and expiration) maximum and minimum heart rates were recorded with each respiratory cycle. Expiration to inspiration ratio was determined by using the formula.
2) **Valsalva Manoeuver -** The valsalva ratio is a measure of parasympathetic and sympathetic functions. Subject was made to lie down in a semi recumbent or sitting position. Nostrils were closed manually. Mouth piece was put into the mouth of the subject and the Mercury manometer was connected to the mouth piece. ECG machine was switched on for continuous recording. Subject was asked to exhale forcefully into the mercury manometer and asked to maintain the expiratory pressure at 40 mm of Hg for 10 – 15 seconds. ECG changes were recorded throughout the procedure, 30 seconds before and after the procedure. Valsalva ratio were calculated by using the formula.
3) **Heart rate response to standing:** On changing the posture from supine to standing heart rate increases immediately by 10-20 beats per minute. This response is detected by recording ECG in supine and standing postures. Subject was made to lie down in supine posture. ECG electrodes were connected from the subject to the cardiowin system. Subject was asked to relax completely for a minimum period of 10 minutes. Basal heart rate was recorded by using cardiowin system. Subject was asked to stand up immediately and change in heart rate is noted from the monitoring screen of cardiowin. Heart rate response to standing was determined by using the formula heart rate in standing position – heart rate in supine position.

Heart rate variability test: HRV was done between 9 am to12 pm to minimize the effect of diurnal variation. Subjects were informed to fast atleast before 12 hours to abort effect of food on HRV. Subject was asked to lie down comfortably on supine position for 5 minute before recording of HRV to avoid wrong results. Subjects were instructed to breathe quietly and avoid movement and not to talk while procedure as it can make artifact in recordings. The HRV was analyzed both by the time domain and the frequency domain methods during normal breathing by using PowerLab and LabChart data acqusition software which Record, measure and analyze beat-to-beat interval variation. After complete recording for 15 minutes, the frequency domain and time-domain indices which were reported from the HRV recordings includes:

Time domain

Mean heart rate (Mean RR)
SDNN - Standard deviation of all R-R intervals (ms)
RMSSD - Square root of the mean of the successive differences between R-R intervals (ms)
NN50 - number of interval differences of successive NN intervals greater than 50 ms
PNN50 - Percentage of successive differences between R-R intervals greater than 50 ms (%)

Frequency domain

TF - Total power (μs^2)
VLF – Very Low frequency spectrum (μs^2) (Between 0 and 0.04 Hz)
LF - Low frequency spectrum (μs^2) (Between 0.04 and 0.15 Hz)
HF - High frequency spectrum (μs^2) (Between 0.15 and 0.45 Hz)
LF/HF - LF/HF ratio

3. Results

Results were analyzed by SPSS version 17.0 and Graph pad prism. ANOVA and Student't' test was used to compare the data of hypertensive and normotensive subjects. Data presented are mean+SD. The P values < 0.05 was statistically considered significant.

Data presented in Table 1 shows Age, anthropometric and basal cardiovascular parameters of normotensive and hypertensive subjects.

Data presented in Table 2 shows that there was significant rise in the systolic and diastolic blood pressure in Hypertensives as compared to Normotensives during the application of isometric handgrip exercise and cold pressor tests (p<0.05) and the increase was statistically significant (p<0.05). Both the SBP and DBP reponses to standing are also significantly higher in Hypertensives when compared to normotensives (p<0.01).

Table 1: Mean ± SD values of Anthropometric and Physiological variables

Variables	Hypertensives (n=50)	Normotensives (n=50)
Age(yrs)	49.47±4.8	46.0±4.9
Height (cms)	162.77±10.64	165.70 ± 9.56
Weight(kgs)	76.13±4.9	68.11±4.3
BMI (kg/m^2)	27.6±3.8	25.9±3.6
Heart rate (bpm)	75.7±9.3	69.2±9.0
Blood Pressure(mm of Hg)	SBP-159.83±10.2 DBP-100.23±5.2	SBP-124.63±10.2 DBP-78.43±5.2

Table 2: Statistical analysis of sympathetic function tests in Group I and Group II

Variables	*Hypertensives (n=50)*	*Normotensives (n=50)*	*P value*
Isometric Handgrip SBP	12.2±1.2	8.3±1.3	<0.05*
Isometric Handgrip DBP	12.1±1.4	8.1±1.2	<0.05*
Cold Pressor Test SBP	12.2±1.6	8.2±1.4	<0.05*
Cold Pressor Test DBP	13.1±1.8	9.1±1.4	<0.05*
BP Response to standing SBP change	7.0 ± 1.22	5.43±0.66	<0.01**
BP Response to standing DBP change	2.9 ± 0.41	2.2±0.43	<0.01**

Data presented in Table 3 shows that there was significant increase in the Heart rate response to standing values in hypertensives when compared to normotensives (p<0.05). Valsalva ratio & Heart rate response to deep breathing (HRDB) was decreased in Hypertensives as compared to Normotensives (p<0.05). S: L ratio also decreased, and the decrease was statistically significant (p<0.05).

Table 3: Parasympathetic function tests in Group I and Group II

Variables	*Hypertensives (n=50)*	*Normotensives (n=50)*	*P value*
HR response to standing 30:15 Ratio	1.33±0.03	1.11±0.02	<0.05*
Valsalva ratio	1.45±0.11	1.65±0.28	<0.05*
HR response to deep breathing	1.12±0.16	1.27±0.20	<0.05*

Data presented in Table 4 shows that there was significant decrease in time domain indices of HRV in hypertensives as compared to normotensives. The value of SDNN in hypertensives was decreased as compared to the value in normotensives (38.9±1.4ms vs 56.7±3.1; p<0.0001). RMSSD, NN50 and pNN50% were also decreased in hypertensives when compared with normotensives and these values also significant statistically.

Data presented in Table 5 shows that there was the frequency domain indices of HRV in hypertensives and normotensives. It shows that total power, VLF, LF and HF has distinctly declined in hypertensives when compared with normotensives. The decrease in frequency domain parameters in hypertensives was found statistically significant (p <0.0001) by student's t-test.

Table 4: Time Domain Analysis of HRV between Hypertensives and Normotensives

Variables	**Hypertensives (n=50)**	**Normotensives (n=50)**	**P value**
Mean RR (s)	0.842±0.132	0.978±0.141	0.0001**
SDNN (ms)	38.9±1.4	56.7±3.1	0.0001**
RMSSD	24.06±10.08	49.90 ± 21.86	0.0001**
NN50	17.87±8.75	24.42±12.16	0.0026*
PNN50 %	6.02±2.18	8.15±3.05	0.0001**

Table 5: Frequency Domain Analysis of HRV between Hypertensives and Normotensives

Variables	**Hypertensives (n=50)**	**Normotensives (n=50)**	**P value**
TP (μs^2)	1563.6±138.5	2477.4±364.1	0.0001**

VLF (μs^2)	832.6±79.1	1424.9±254.9	0.0001**
LF (μs^2)	487.8±54.2	1016.8±130.7	0.0001**
HF (μs^2)	222.8±29.1	511.6±90.5	0.0001**
LF/HF ratio	326.6±20.6	303.7±35.8	0.0002**

4. Discussion

The results of the present study showed that the valsalva ratio and heart rate response to deep breathing in hypertensives were significantly lower as compared to the control group, it indicates base line levels of vagal cardiac nerve activity and vagally mediated arterial baroreceptor cardiac reflex responses are decreased in hypertensive subjects. This decreased parasympathetic activity leads to decreased heart rate variability with respiration, which is reflected in our study as decreased E: I and Valsalva ratio values in Hypertensives. The findings in our study correlated with the study conducted by Knut severe et al[9]. The results for the above mentioned tests are statistically significant.

When a subject assumes an erect posture from supine posture, gravity causes pooling of blood in the lower limbs. As a result venous return, cardiac output and arterial BP decreases. This leads to decrease stretch of baroreceptors and activation of vasomotor center. This in turn leads to increased sympathetic discharge, decreased vagal tone and an instantaneous increase in HR and BP. In our study, Heart rate and BP response to standing values were increased in all the subjects but these values were significantly increased in hypertensive group when compared to the normotensive group. This finding indicates possible dysfunction of sympathetic and parasympathetic component of autonomic nervous system. The findings in our study correlated with the study conducted by WW McCrory, AA Klein et.al[11].

There was an increased blood pressure response to cold pressor test in the hypertensives in contrast to the control group. The afferent fibers for this response are the pain fibers which are stimulated by placing the hand in cold water and the efferent fibers are the sympathetic fibers. An increase in the blood pressure after the cold water immersion points towards sympathetic hyperactivity in hypertensives. Hypertension impairs autonomic control of heart rate and blood pressure. In our study there is significant rise in both systolic blood pressure and diastolic blood pressure in hypertensive group. The pattern of rise of blood pressure was within 30 seconds reaching its peak at around 60 seconds and the basal blood pressure was achieved within 2 minutes in normotensive subjects and prolonged pressor response was found in hypertensive patients. Generally, Cold pressor test is largely related to great sympathetic efferent discharge causing arterial vasoconstriction. Hypertensive subjects respond to cold pressor stimulus with a predominant rise in total peripheral resistance and also there were higher levels of plasma norepinephrine. The findings in our study correlated with the study conducted by Benetos A. and Douglas L. et.al[12, 13].

Isometric exercise produces a significant increase in blood pressure and heart rate, which can easily be elicited by using sustained hand grip. In hand grip test, increase in blood pressure is due to increased sympathetic activity mediated by the alpha adrenergic receptors of the autonomic nervous system. An increase in heart rate in response to handgrip is due to impulses from the Limbic cortex, motor cortex and the proprioceptors within small hand joints acting as afferent inputs into the medullary cardiac centres causing inhibition of cardiac inhibitory centre, decrease in vagal tone and increase in heart rate. The results of the present investigation have demonstrated that sustained handgrip causes significant increase in arterial pressure in hypertensive patients. The findings in our study correlated with the study conducted by S.G. Chrysant et.al[10].

The current study also demonstrated that heart rate variability both in time and frequency domains, is diffusely decreased in hypertensives as compared with normotensives. This reduction reflects the degree of cardiac autonomic activity determined by the baroreceptor reflexes, which are impaired in hypertensives. The significant decrease in VLF, LF, HF (ms^2) (Frequency Domain Parameters) in hypertensives indicates sympathetic over-activity, reduced parasympathetic activity and sympathovagal imbalance in hypertension. Increased LF / HF ratio in hypertensives also indicating sympathetic overdrive and sympathovagal balance. All time domain parameters like SDNN, RMSSD, NN50, Pnn50% were reduced in hypertensives as compare to normal subjects reflects both sympathetic and parasympathetic activity which predict increased risk for subsequent cardiac events in hypertensives. The findings in our study correlated with the previous studies [16, 17, 18, 19].

5. Acknowledgment

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***Conflict of Interest**:* Nil

6. Conclusion

Hypertension is associated with both sympathetic and parasympathetic nervous system dysfunction which may result in various cardiovascular complications. From present study it indicates that hypertensives had markedly depressed HRV and abnormal autonomic reflexes which reflects sympathovagal imbalance. So, if this dysfunction is diagnosed early by doing various autonomic function tests and HRV, it will be of great help in identification of those which are prone to risk of various cardiovascular complications.

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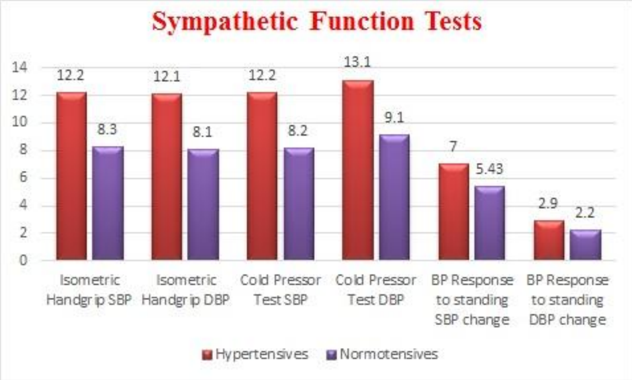
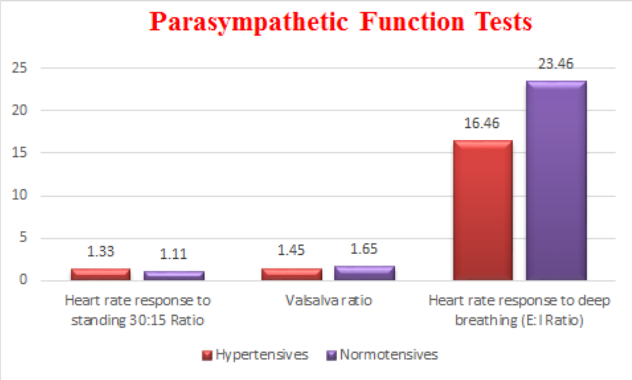
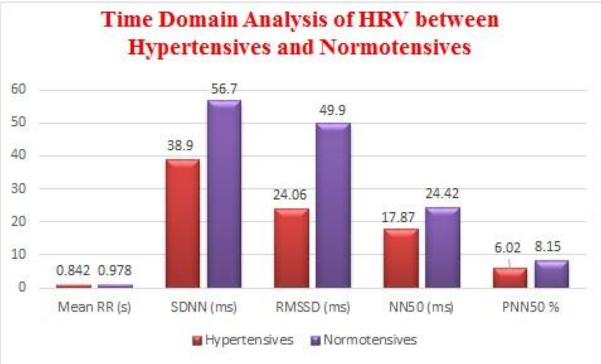
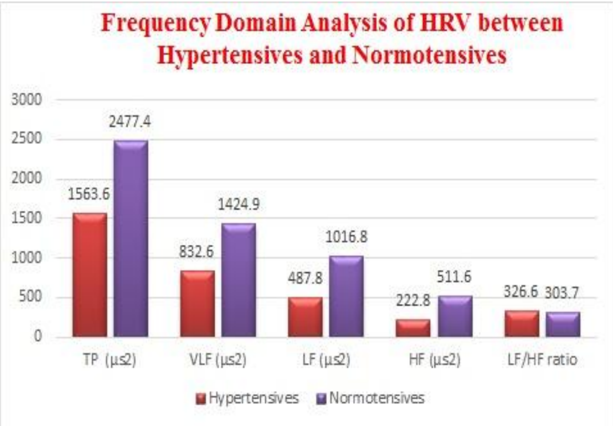
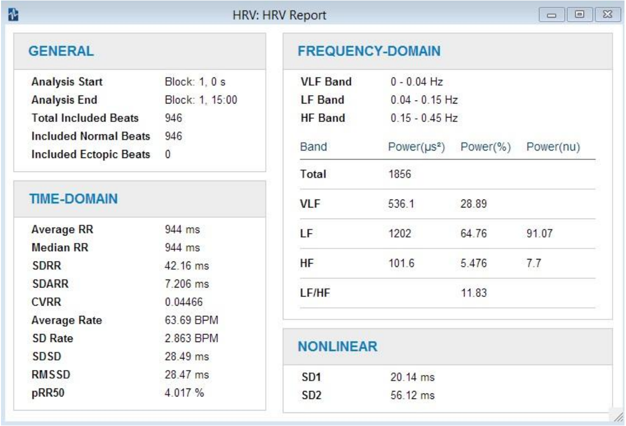
Graphs & Figures











HRV: HRV Report

GENERAL

Analysis Start	Block: 1, 0 s
Analysis End	Block: 1, 15:00
Total Included Beats	946
Included Normal Beats	946
Included Ectopic Beats	0

TIME-DOMAIN

Average RR	944 ms
Median RR	944 ms
SDRR	42.16 ms
SDARR	7.206 ms
CVRR	0.04466
Average Rate	63.69 BPM
SD Rate	2.863 BPM
SDSD	28.49 ms
RMSSD	28.47 ms
pRR50	4.017 %

FREQUENCY-DOMAIN

VLF Band	0 - 0.04 Hz
LF Band	0.04 - 0.15 Hz
HF Band	0.15 - 0.45 Hz

Band	Power(μs²)	Power(%)	Power(nu)
Total	1856		
VLF	536.1	28.89	
LF	1202	64.76	91.07
HF	101.6	5.476	7.7
LF/HF		11.83	

NONLINEAR

SD1	20.14 ms
SD2	56.12 ms

Author Profile

Chiranjeevi Kumar Endukuru received the B.Sc. degree in Medical lab technology and M.Sc. degree in Medical physiology from Narayana Medical College, Nellore, Andhra Pradesh, India in 2009 and 2012, respectively. Currently working as a Tutor/Demonstrator in the Department of physiology, AIIMS Bhopal.