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Appraisal of Relationship between Hypertension and Short-Term Heart Rate Variability Indices

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Abstract:
Background: Hypertension, the silent killer is as an important risk factor for cardiac arrest, stroke, kidney disease and increased mortality rates in adults. Heart Rate Variability (HRV) is a physiological phenomenon of variation in the time interval between heartbeats and is a gold-standard to assess the perpetually changing oscillations of a salubrious heart. Early detection of hypertension by a non-invasive tool as HRV can identify the autonomic regulation in hypertensive individuals at high risk for developing cardiovascular morbidities complications. The aim was to study the autonomic correlates of cardiovascular health in hypertension in terms of short term HRV and to analyse the association between HRV indices and elevated blood pressure.

Methods: It was a cross-sectional observational study carried out in Sports Physiology Laboratory in Department of Physiology of a rural medical college in central India. 25 known cases of hypertension (having Systolic BP >140 mmHg and diastolic BP >90 mmHg) in the age group of 35-60 yrs and 75 age matched normotensives as controls (Systolic BP < 120 mm of Hg and Diastolic BP < 80 mm Hg) were selected. ECG was recorded using Power lab data recording system, AD instruments and analysis was done by HRV Module of Lab chart software. The subjects performed an incremental ramp exercise test to the limit of tolerance on a motorized treadmill.

Results: The mean age of control males was 39.80±6.68 and mean age of control females was 37.05±2.75. Out of hypertensives, 17 were males (mean age 42.58 ± 6.94) and 8 were females (mean age 42.6±8.84). There was statistically significant difference observed in SDNN, RMSSD, HF%, HFnu between control and cases males but no significant relationship was observed among other parameters in males. On comparing the sympatho-vagal ratio (LF/HF), female cases were having high ratio than control females indicating a dominant sympathetic response. From Pearson's correlation analysis, a positive non-significant relationship was observed between systolic BP and Frequency domain indices in controls while in cases a negative correlation was found which was also statistically non-significant. A strong positive correlation was found between Systolic BP and SDNN (r=0.55) in hypertensives. The time domain parameters were also found to be negatively correlated with mean heart rate in both controls and cases.

Conclusions: This pioneering study analysed the association between heart rate variability indices and high blood pressure. The analysis of HRV can distinguish parasympathetic from sympathetic influences on the heart and provides important insights into the role of the autonomic nervous system in the pathogenesis of essential hypertension. HRV is reduced in men and women with systemic hypertension. Among normotensive men, lower HRV was associated with greater risk for developing hypertension. These findings clearly exhibit that autonomic dysregulation is present in the early stage of hypertension.

***Keywords*- hypertension, heart rate variability, frequency domain indices, time domain indices**

1. INTRODUCTION

Hypertension also known as high blood pressure, is a long-term medical condition in which the blood pressure in the arteries is persistently elevated. It can be primary or essential high blood pressure or secondary high blood pressure. It is expressed as systolic and diastolic blood pressures, which are the maximum and minimum pressures respectively. According to the **2020 International Society of Hypertension Global Hypertension Practice Guidelines**, Hypertension is said to be diagnosed when a person's systolic blood pressure (SBP) is ≥140 mm Hg and/or their diastolic blood pressure (DBP) is ≥90 mm Hg following repeated examination [1].

The World Health Organization (WHO) categorizes high blood pressure (BP) as the top risk factor for death rate, accounting for 13% of fatalities globally. Also, hypertension, or the 'silent killer' as it is also known, has been recognized as an important risk factor for cardiac arrest, stroke, kidney disease, and is major cause of premature death worldwide (WHO 2023) [2]. It has been well-established that one of the most important causes of coronary heart disease is hypertension, which creates a major economic burden in various countries throughout the world [3]. The prevalence of hypertension is a massive 30% in India [4].

Heart Rate Variability (HRV) is the physiological phenomenon of variation in the time interval between heartbeats. It is measured by the variation in the beat-to-beat interval. It is also called as cycle length variability or RR variability. Heart rate variability can be tracked back to our autonomic system. The autonomic nervous system regulates very important systems in our body, including heart and respiration rate and digestion. The autonomic nervous system has a parasympathetic (rest) and a sympathetic (activation) branch. Heart rate variability is an indicator that both branches are functioning. The cardiovascular system is mostly controlled by autonomic regulation through activity of sympathetic and parasympathetic pathways of autonomic nervous system. A heart rate that is variable and responsive to demands is believed to bestow a survival advantage, whereas reduced heart rate variability may be associated with poorer cardiovascular health and outcomes (5). Sympathetic nervous system has an important role in resistant hypertension. Heart rate is a marker of sympathetic activity. HRV measures fluctuations in autonomic inputs to the heart rather than mean level of autonomic inputs and is a non-invasive tool to quantitatively estimate cardiac autonomic activity. Measures of HRV in both the time and frequency domains have been used successfully to index cardiovascular autonomic nervous function activity. Despite a few previous researches (6-8), there is insufficient evidence of whether hypertension leads to changes in HRV and whether decreased HRV can predict incident hypertension is still unclear. The non-invasiveness and easy detection of the HRV measurement make it more practical and widely studied. It is one of the promising markers for cardiac autonomic nerve function.

The purpose of the study was to evaluate the autonomic correlates of cardiovascular health in hypertension in terms of short term HRV indices and to analyse the association between HRV indices and blood pressure.

2. MATERIAL AND METHODS

2.1 Study setting and design

It was a cross-sectional observational study carried out in Sports Physiology Laboratory in Department of Physiology of a rural medical college in central India.

2.2 Study Participants

25 Known cases of hypertension (having Systolic BP >140 mmHg and diastolic BP >90 mmHg) in the age group of 35-60 yrs and 75 age matched (Age of the hypertensive ± 5 years) controls (Systolic BP < 120 mm of Hg and Diastolic BP < 80 mm Hg) were selected.

2.3 Inclusion Criteria

2.3.1 Cases: All individuals who were known cases of hypertension as diagnosed by consultant physician of Department of Medicine of a rural hospital were included in the study. All the participants had given written informed consent and had fulfilled the above criteria.

2.3.2 Controls: Individuals who were normotensives when they were screened for borderline hypertension and had given written informed consent for participation in the study.

2.4 Exclusion Criteria

Individual having any history of cardiac problems other than hypertension, respiratory or psychiatric diseases; any other significant co- morbidities. Individuals who consume any drug like beta blockers affecting HRV. History regarding medications for diseases such as ischemic heart disease (within last one year), cardiac arrhythmias, retinopathy (Grade III Hypertensive Retinopathy/ clinically significant macular edema (CSME), nephropathy (Serum Creatinine > 1.4 mg%), were noted and taken into account. Subjects had been asked not to consume caffeine within 8 hours prior to testing.

2.5 Statistical Analysis
Statistical analyses were performed using GraphPad Prism 6.01 (GraphPad Software, CA, USA). Mean values of HRV indices were compared using unpaired t test. P value <0.05 was considered as statistically significant. Multiple comparisons were handled by ANOVA.

2.6 Ethics Consideration
The study was approved by Institutional Ethics committee vide reference MGIMS/IEC/PHY/1412019 dated 05/01/2019. A signed written informed consent was obtained from all the study participants prior to the beginning of the study. We ensured that consent was (a) given voluntarily, (b)fully informed, (c)and was obtained from the persons who were competent to do so. Each subject had been notified of commitment, befits, risks and possible discomforts of the study.

2.7 Equipment required for ECG recordings to derive HRV
ECG was recorded using Power lab data recording system, AD instruments and analysis was done by lab chart software. The Heart Rate Variability (HRV) Module (Windows) helped to analyze LabChart recordings of ECG or arterial pulse signal. HRV works online, performing calculations and displaying results as data was recording. HRV also had additional functionality to allow for offline data analysis. The HRV module analyzed beat-to-beat interval variation in ECG recordings, it extended LabChart functionality to allow analysis and display of RR interval variation. After obtaining baseline characteristics and resting BP and Heart rate measurements in supine posture, the subject was asked to wear the Equivital EQ-02-B3 ECG sensor belt and along with a Polar transmitter SPO180 (having chest strap) which was a Wireless Heart Rate Kit (PTK25). This Kit contained a Polar Receiver Interface Cable (3m). The Polar Transmitter transmits at a range of 1.2 m (4 ft).

2.8 Procedure
Relevant history was recorded followed by anthropometry and clinical examination. Resting pulse, blood pressure, and respiratory rate were measured. The height and weight were recorded using Electronic BMI Machine. The participants performed an incremental ramp exercise test to the limit of tolerance on a motorized treadmill in the presence of a senior resident from Medicine department. Motorised Treadmill Aerofit AF 101 was employed for the purpose of exercise.

2.9 HRV Parameters
Short-term HRV recording was performed for research and clinical investigations. According to the standards set forth by the Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology in 1996, two methods of analysis of HRV data were considered: time-domain and frequency-domain analysis. In either method, the interbeat intervals was properly calculated (12). On completion of paperwork, subject was oriented to equipments and procedures. Before that initial blood pressure was taken and recorded.
Heart rate and its fluctuations on a beat-to-beat basis (using RR-interval based on ECG) was used to monitor autonomic influx and withdrawal. Beat-to-beat variation in SA node discharge as recorded by ECG was been computed and analyzed by the software to determine the spectral indices of HRV. ECG signals was acquired at rate of 1000 samples/second using data acquisitions(raw ECG signal and RR-intervals was acquired on moving time base) and data been transferred to windows based laptop loaded with software for HRV analysis.

2.9.1 Calculation of time domain indices
Time domain indices are the simplest parameters to be calculated. Each QRS is extracted and N-N intervals are determined. The following time domain variables were determined: the Mean R-R interval (measured in seconds), the Standard deviation of N-N interval (SDNN), RMSSD (root mean square of successive differences between normal), NN50 (adjacent NN intervals differing from each other by more than 50 ms), and pNN50 (percentage of NN50). The time-domain parameters were associated mostly with overall variability of HR over the time of recording, except RMS-SD, which was associated with fast (parasympathetic) variability.

2.9.2 Calculation of Frequency Domain Indices
Labchart software for HRV provides the frequency spectrum components as: Total Power (5mins) which represents the variance of N-N intervals over the temporal segment (≤ 0.4Hz), VLF (power in a very low frequency range, i.e., 0.04Hz), LF (power in the low frequency range, i.e., 0.04-0.15Hz), LF norm (LF power in normalized units), LF/ (total power – VLF) ×100, HF (power in the high-frequency range, i.e., 0.15-0.4Hz), HF norm (HF power in normalized units), HF/ (total power-VLF) ×100, and LF/HF ratio. The HF power, LF power and LF/HF ratio were considered to represent parasympathetic activity, sympathetic activity and sympatho-vagal balance, respectively.

3. RESULTS

The study population consist of 75 controls and 25 hypertensives including both males and females in the age range of 35-60 years. Out of 75 controls, there were a total of 56 male subjects and 19 female subjects. The mean age of control males was 39.80±6.68 and mean age of control females was 37.05±2.75. Out of 25 hypertensives, 17 were males (mean age: 42.58 ± 6.94) and 8 were females (mean age: 42.6±8.84). There was no statistically significant difference between hypertensive patients and controls for age and height. Various demographic parameters of the study subjects of both controls and cases are represented in Tables 1 and 2 respectively.

Table 1: Demographic Parameters of Males

S. No	Parameters	Control males (n=56) Mean ± SD	Cases males (n=17) Mean ± SD	*P Value
1	Age(years)	39.80±6.68	42.58 ±6.94	0.14 (NS)
2	Height(cms)	168.09±6.59	170.1±7.59	0.29 (NS)
3	Weight(kgs)	65.30±10.63	69.83±9.43	0.11 (NS)
4	Waist Circumference(cms)	86.59±7.40	89.41± 8.72	0.19 (NS)
5	Heart Rate	80.06±10.87	82.66±11.08	0.39(NS)
6	Systolic BP(mmHg)	121.65±11.37	140.33±13.12	0.0001 (S)
7	Diastolic BP(mmHg)	80.18±8.01	91.83±11.73	0.0001 (S)

*All the p values reported are based on unpaired t test between controls & cases.(S)-Significant, (NS)-Non Significant

There was no statistically significant difference in the mean age, height, weight, waist circumference, heart rate in control and case male subjects while a significant relationship was observed in blood pressure

Table 2: Demographic Parameters of Females

S.No.	Parameters	Control females (n=19) Mean ± SD	Cases females (n=8) Mean ± SD	*P Value
1	Age(years)	39.05±2.76	42.6±8.84	0.1199(NS)
2	Height(cms)	158.26±3.59	160.4±7.23	0.3091(NS)
3	Weight(kgs)	59.79±10.10	72.4±1.67	0.0019(S)
4	Waist Circumference(cms)	88.42±9.79	106.4±2.19	0.0001(S)
5	Heart Rate	89.50±10.75	97± 7.34	0.08(NS)
6	Systolic BP(mmHg)	116.31±6.94	125.6±4.09	0.0017(S)
7	Diastolic BP(mmHg)	79.90±4.50	84±5.47	0.0531(NS)

*All the p values reported are based on unpaired t test between controls & cases.(S)-Significant, (NS)-Non Significant
There was no statistically significant difference in the mean age, height and heart beat in control and cases female subjects but it was observed that statistically significant difference occurs in weight, waist circumference and systolic blood pressure.

Data of Time Domain and Frequency Domain indices of males and females of both the study groups as measured on treadmill are expressed as mean ± standard deviation and is given in Table 3 and 4 respectively.

Table 3: HRV indices in males measured on treadmill

S.No.	Parameters	Control Males (N=58) Mean ± SD	Case Males (N=17) Mean ± SD	*p Value
1	SDNN	136.66±30.54	112.02±13.16	0.0019(S)
2	RMSSD	92.80±28.82	45.54±2.88	0.0001(S)
3	PNN50	1.96±2.27	0.9±0.17	0.05(NS)
4	LF%	47.40±28.22	37.65±43.93	0.27(NS)
5	HF%	65.80±2.84	32.2±8.92	0.0001(S)
6	LF NU	30.13±16.16	22.67±18.38	0.10(NS)
7	HF NU	47.60±18.56	31.24±17.48	0.0018(S)
8	LF/HF	0.72±0.56	0.69±0.36	0.83(NS)
9	Total Power	879.36±1359.55	633.12±637.87	0.47(NS)

There is statistically significant difference observed in SDNN, RMSSD, HF%, HFnu between control and cases males but no significant relationship was observed among other parameters in male.

Table 4: HRV Indices in Females measured on Treadmill

S.No.	Parameters	Control Females (N=19) Mean±SD	Case Females (N=8) Mean±SD	*p Value
1	SDNN	134.42±25.75	110.98±5.57	0.018(S)
2	RMSSD	14.60±17.52	4.87±0.61	0.13(NS)
3	PNN50	1.84±3.11	0.9±0.54	0.40(NS)
4	LF%	32.56±30.10	16.79±3.11	0.15(NS)
5	HF%	101.57±162.61	13.57±13.16	0.0006(S)
6	LF NU	15.42±8.82	8.46±8.18	0.06(S)
7	HF NU	35.78±19.39	10.61±7.91	0.0017(S)
8	LF/HF	0.51±0.35	0.87±0.57	0.042(S)
9	Total Power	1063.65±1745.19	202.48±165.67	0.18(NS)

Statistically significant correlation was observed in SDNN, HF%, LF NU, HF NU, LF/HF ratio between study groups.

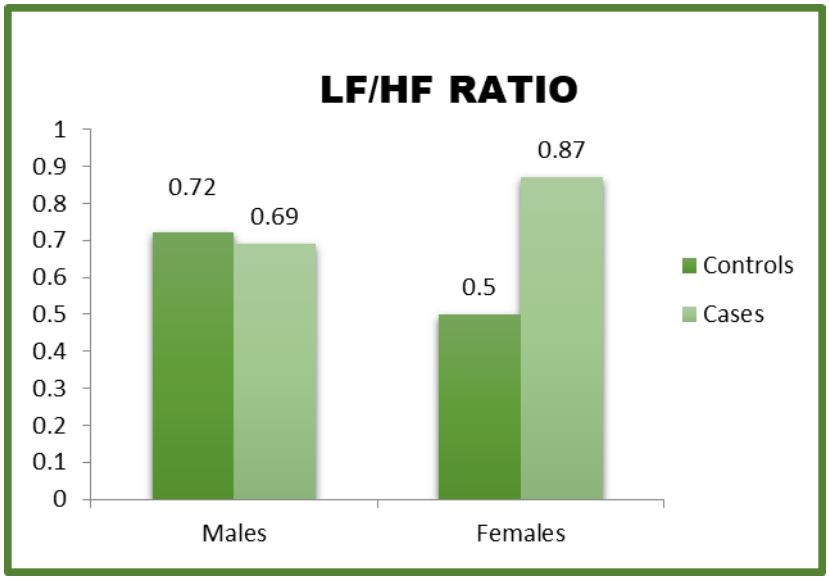

Figure 2: Graphical representation of LF/HF ratio in the study groups

On comparing the sympatho-vagal ratio (LF/HF), female cases where having high ratio than control females indicating a dominant sympathetic response.

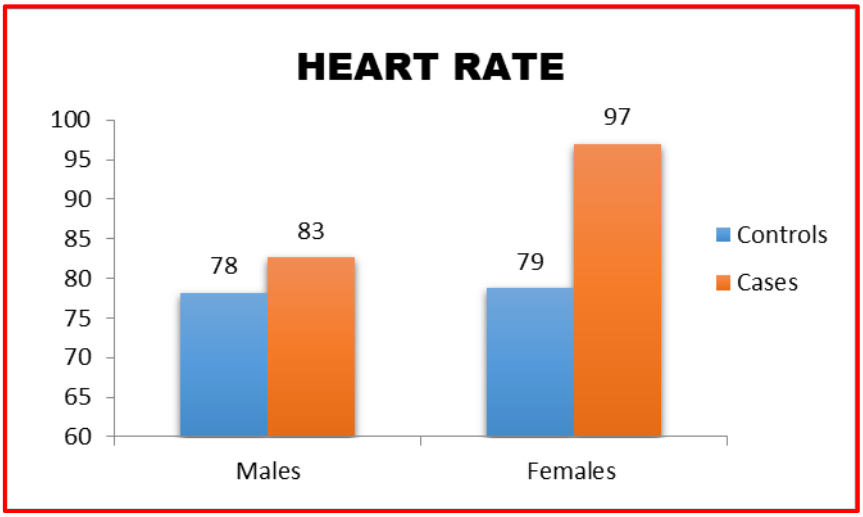

Figure 3: Graphical representation of Heart rate in Controls and cases

From the above graph, it is interpreted that heart rate is higher in cases when compared to controls in both sexes.

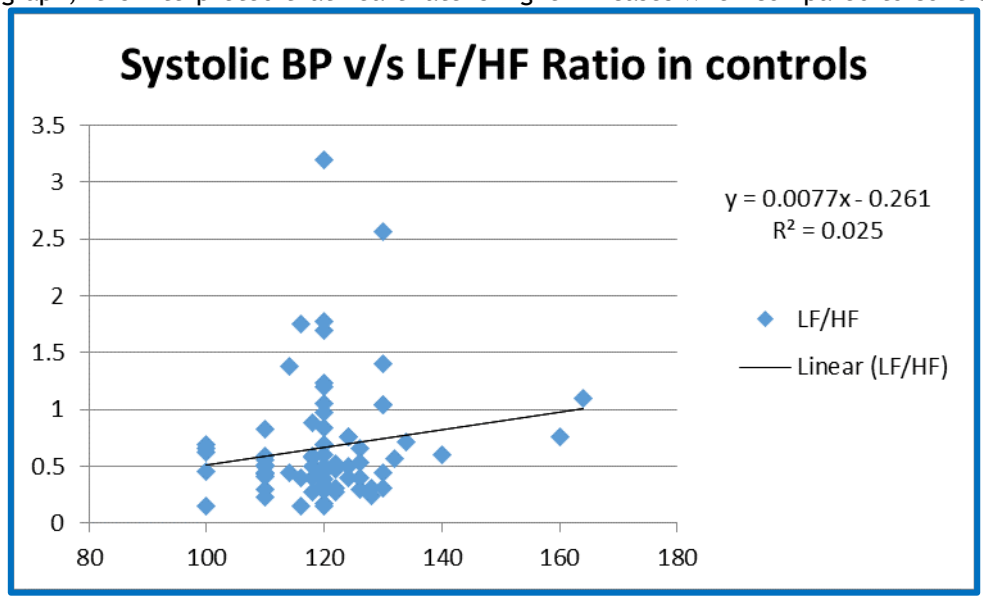

Figure 4. Scatter diagram for Systolic BP and LF/HF Ratio in controls

From Pearson's correlation analysis, a positive non-significant relationship was observed between systolic BP and Frequency domain indices in controls while in cases a negative correlation was found which was also statistically non-significant. A strong positive significant correlation was found between Systolic BP and SDNN (r=0.55) in hypertensives which is represented in the scatter diagram (Figure 5)

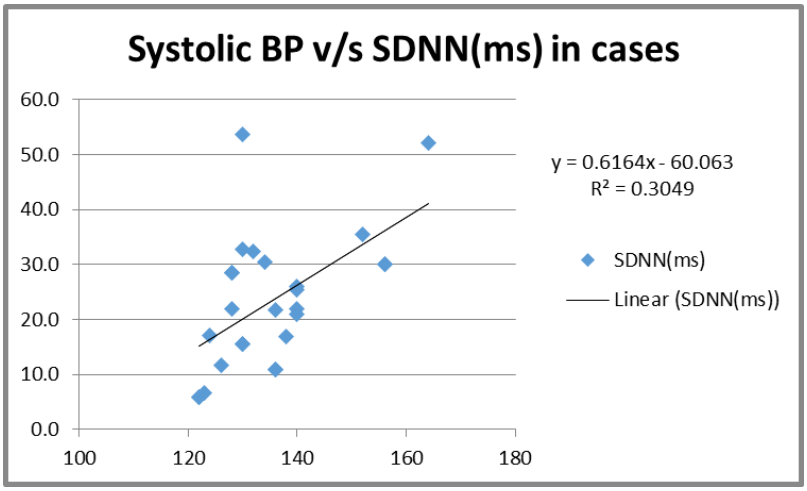

Figure 5. Scatter diagram for Systolic BP and SDNN in Cases

However RMSSD was found to be negatively correlated with Systolic BP statistically not significant. The time domain parameters were also found to be negatively correlated with mean heart rate in both controls and cases depicted in Figure 6 and Figure 7 respectively.

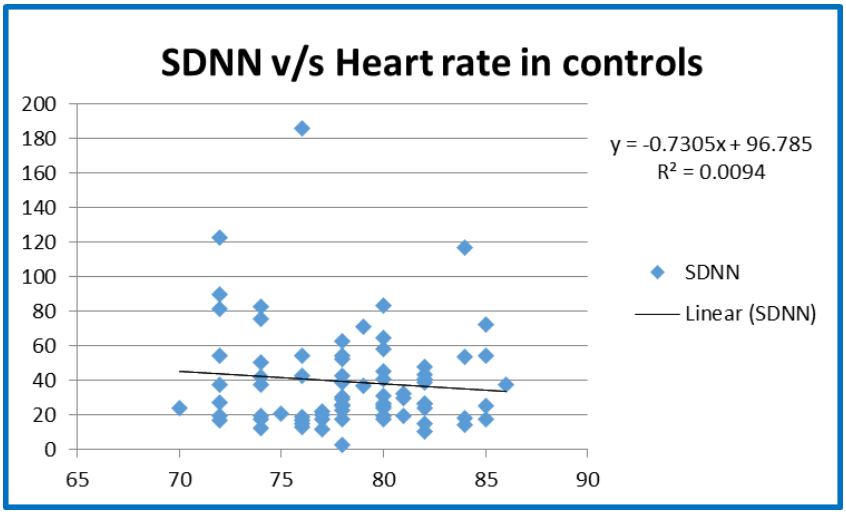

Figure 6. Scatter diagram for SDNN and Heart Rate in controls

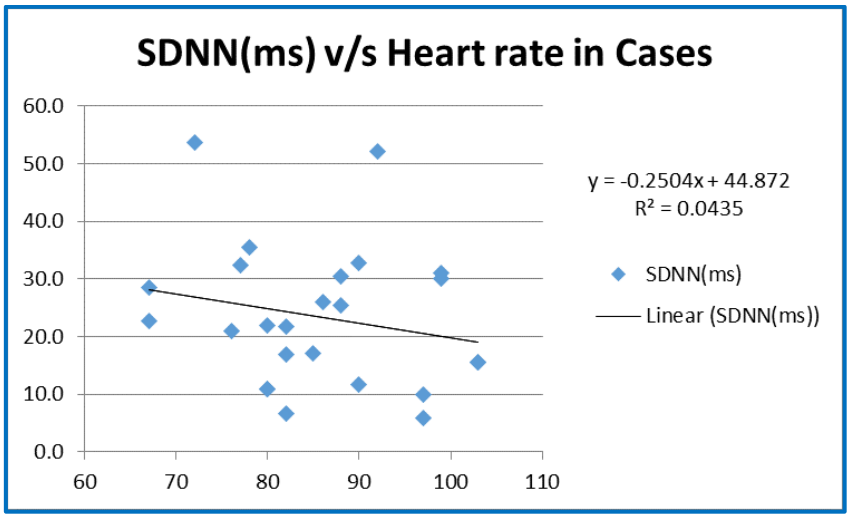

Figure 7. Scatter diagram for SDNN and Heart rate in cases

4. Discussion and Conclusion

The incidence of hypertension is increasing worldwide and its associated morbidities. The irregular behavior of heart beat is readily apparent when heart rate is examined on a beat-to-beat basis, but is overlooked when a mean value over time is calculated. These fluctuations in heart rate result from complex, non-linear interaction among a number of physiological systems. HRV is considered a measure of neuro-cardiac function that reflects heart-brain interaction and autonomic nervous system dynamics. It is one of the promising markers. Any distress is preceded by reduction in HRV before any changes occur in heart rate itself. Among normotensives, lower HRV is associated with greater risk of developing hypertension. Low HRV contributes to the increased cardiovascular morbidity and mortality. In the early stage of hypertension autonomic regulation will be present, which can be identified by HRV and control measures can be taken.

Although previous studies (6-11) have identified abnormal HRV in systemic hypertension, there is a paucity of data examining the association between HRV and blood pressure. This pioneering study had analysed the association between heart rate variability indices and blood pressure. The analysis of HRV can distinguish parasympathetic from sympathetic influences on the heart and may provide important insights into the role of the autonomic nervous system in the pathogenesis of essential hypertension.
On comparison of frequency domain indices of HRV, between the two study groups controls and hypertensives, in the age range of 35-60 years, LF, HF, LF(nu),(HF(nu) was found to be reduced in cases and in females the reduction was statistically significant. Total power (ms2) in controls was seen higher than cases indicating a lower Heart rate variability in cases and in female cases the total power value was lower than male cases. The presence of reduced HRV in hypertensive subjects are consistent with the hypothesis that dysregulation of the autonomic nervous system plays a role in the pathogenesis of hypertension.
Because changes in blood pressure affect autonomic tone and vice versa, HRV measures differ in hypertensive subjects when compared with those with normal blood pressure. Our findings of reduced SDNN in systemic hypertension concur with results from 3 population-based studies. (6,7,11) These studies were either restricted to men (7) or examined HRV in men and women pooled together(6,11) and included subjects on a variety of cardioactive medications.(6,7) We examined the association between HRV and blood pressure separately in healthy middle-aged men and women free from the confounding effects of cardio-active medications.

In a cohort study of 2061 examinees from the Atherosclerosis Risk In Communities (ARIC), the cardiac autonomic function and HRV was related with prevalent and incident hypertension. The findings were reduced vagal function and the imbalance of sympatho-vagal function was associated with the risk of developing hypertension (13).
In a previous study on 80 elderly population, it was concluded that hypertensive patients had decreased HRV and decreased parasympathetic modulation when compared to normotensive elderly (14).

The absence of a difference in the LF/HF ratio between normotensive and hypertensive male individuals in our study could be explained by variable responsiveness of the neural regulatory mechanisms between individuals and the fact that the LF/HF ratio in males correlated poorly with other HRV measures except SDNN, RMSSD, HF%, HF-NU where significant differences were obtained. The weak relation observed between HRV and diastolic blood pressure as opposed to systolic blood pressure could be a reflection of the low incidence of diastolic hypertension which corroborates with the similar finding of the middle-aged Framingham Heart Study population (9).
The time domain parameters which indicate parasympathetic tone was negatively correlated with heart rate in both cases and controls. SDNN and RMSSD has a positive correlation with total power. These findings are in accordance with the results of Kirthana et al, who investigated HRV in 291 individuals of South India (15).

4.1 Strengths and limitations of the study

An important strength of this study is the well-characterized study sample which allowed us to select subjects who were free of clinically apparent cardiovascular disease, which can alter autonomic function and HRV measurements. The recordings were obtained when subjects underwent an exercise and are not representative of basal resting conditions. Such activity can precipitate short-term changes in the autonomic tone that can confound the relation of autonomic tone to resting blood pressure measurements. So the lack of resting-state HRV data is a shortcoming which remains to be addressed in future studies. The small sample size (especially for hypertensive females) was another limitation which was probably due to low female patient inflow to the outpatient department.

4.2 Conclusion

HRV is reduced in men and women with systemic hypertension. Among normotensive men, lower HRV was associated with greater risk for developing hypertension. Estimation of LF using spectral analysis of ambulatory ECG recordings improves the prediction of risk of hypertension in men above that which can be obtained from measurements of baseline systolic and diastolic blood pressures, body mass index, and age. These findings are consistent with the hypothesis that autonomic dysregulation is present in the early stage of hypertension.

4.3 Clinical Implications

The present study extends the clinical utility of HRV beyond its role in the surveillance of diabetics and patients after myocardial infarction. A reduction in HRV is associated with an increased risk of cardiac mortality and has been shown to predict risk for cardiac events and overall mortality. Additional research is needed to determine whether reduced HRV contributes to the increased cardiac mortality in hypertension. It is possible that an assessment of HRV may help guide the selection of anti-hypertensive therapy.

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7. Conflicts of Interest

The authors declare that there are no conflicts of interest.

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