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Autonomic Correlates of Cardiovasular Health

A Quantitative Probe into A Potential Non-Invasive Signature

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Abstract:-

- ***Background***

Hypertension, the silent killer has not only increased mortality rates in adults but also is an important risk factor for stroke, cardiac arrest, kidney disease etc. There is a massive 30% prevalence of hypertension in India. 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.

- ***Aim***

The purpose 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 in the age group of 35-60 yrs and 75 age matched normotensives as controls 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. 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 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 in hypertensives. The time domain parameters were also found to be negatively correlated with mean heart rate in both controls and cases.

- ***Conclusions***

This study analysed the association between heart rate variability indices and hypertension. 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 women along with men accompanied by 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, HRV, Frequency Domain Indices, Time Domain Indices.*

I. INTRODUCTION

Hypertension which in layman's term called as high blood pressure, is a long standing 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 American Heart Association (AHA) 2017 Guidelines, Hypertension is now defined as having Systolic BP ≥ 130 mmHg and Diastolic BP≥ 80 mmHg.(1).

High blood pressure (BP), which causes 13% of fatalities worldwide, is ranked as the top risk factor for mortality by the World Health Organization (WHO). Moreover, hypertension, sometimes known as the "silent killer," has been identified as a significant risk factor for cardiac arrest, stroke, renal illness, and higher adult death rates. (WHO 2014).(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. Our autonomic system can be linked to heart rate variability. The autonomic nervous system controls a number of vital bodily functions, such as heart rate, breathing rate, and digestion. There are parasympathetic (rest) and sympathetic (activity) branches of the autonomic nervous system. Heart rate variation is a sign that both branches are working properly. The sympathetic and parasympathetic pathways of the autonomic nervous system are primarily responsible for controlling the cardiovascular system. Reduced heart rate variability may be linked to worse cardiovascular health and outcomes, whereas a heart rate that is variable and sensitive to demands is thought to confer a survival benefit. (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.

The ability of decreased HRV to predict incident hypertension has not been well studied and there is not much evidence of whether hypertension leads to changes in HRV. 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.

- *Objective*

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

II. MATERIALS AND METHODS

- *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.

- *Study Participants:*

25 Known cases of hypertension (having Systolic BP >140mmHg 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.

- *Inclusion Criteria*

- *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.

- *Controls:*

Individuals who were normotensives and had given written informed consent for participation in the study.

- *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. Subjects had been asked not to consume caffeine within 8 hours prior to testing.

- *Statistical Analysis*

Statistical analysis was done using unpaired t test and Microsoft excel was used. P value <0.05 was considered as statistically significant.

- *Ethics Consideration*

We obtained a signed written informed consent 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, benefits, risks and possible discomforts of the study.

- *Equipments*

- *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. LabChart recordings of the ECG or arterial pulse signal were analysed with the aid of the Heart Rate Variability (HRV) Module (Windows). HRV operates online, processing computations and showing outcomes while data was being recorded. Moreover, HRV included features that made it possible to analyse data offline. The HRV module expanded LabChart's capability by enabling analysis and presentation of RR interval fluctuation. It did this by analysing beat-to-beat interval variation in ECG data. The R component was extracted from each raw ECG waveform using a threshold detector to provide RR Interval data. The programme automatically identified beats and divided them into three categories: normal, ectopic, and artefact. 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).

- *Motorised Treadmill Aerofit AF 101*

➢ *Procedure*

- Relevant history was recorded followed by anthropometry and clinical examination. Resting pulse rate and blood pressure, resting respiratory rate was measured.
- The height and weight were recorded.
- All subjects were recruited by word of mouth.
- After familiarization with the laboratory and procedures the subjects 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.

➢ *HRV Parameters*

For scientific and medical purposes, short-term HRV monitoring was done. Two approaches to the analysis of HRV data were taken into consideration: time-domain and frequency-domain analysis, in accordance with the guidelines established by the Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology in 1996. The interbeat intervals were correctly estimated using either approach. (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.

- *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. Time domain indices measured:

- ✓ Mean R-R interval (measured in seconds)
- ✓ Standard deviation of N-N interval (SDNN)
- ✓ Square root of mean squared difference of N-N intervals (RMSSD):It is the root mean square of successive differences between normal heartbeats .
- ✓ The NN-intervals refer to the intervals between normal R-peaks. The NN50 was the adjacent NN intervals that differ from each other by more than 50 ms.
- ✓ pNN50 is the percentage of NN50. RMSSD and pNN50% were used to estimate the parasympathetically mediated changes reflected in HRV. 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.

- *Calculation of Frequency Domain Indices*

After excluding the artefacts and ectopic beats from the RR interval series by the Polar transmitter, a five minute RR interval series was chosen from the recording of exercise and analysed with Labchart software for HRV which gives the frequency spectrum components using Fast Fourier transformation:

HRV Components	Analysis of Short Term Recording	Frequency Range
Total Power (5mins)	Variance of N-N intervals over the temporal segment	Approx. ≤0.4Hz
VLF	Power in very low frequency range	0-0.04Hz
LF	Power in low frequency range **[SYMPATHETIC]**	0.04-0.15Hz
LF norm	LF power in normalized units LF/(total power-VLF)*100	
HF	Power in high frequency range **[PARASYMPATHETIC]**	0.15-0.4Hz
HF norm	HF power in normalized units HF/(total power-VLF)*100	
LF/HF	Ratio LF/HF [**SYMPATHO-VAGAL BALANCE]**	

The HF power, LF power and LF/HF ratio were considered to represent parasympathetic activity, sympathetic activity and sympatho-vagal balance, respectively. The analysis of HRV indices as evaluated by Lab Chart software is represented in Figure 1.

Fig 1 Lab Chart View of HRV

The assumptions underlying the LF/HF ratio is that LF power may be generated by the SNS while HF power is produced by the PNS. A low LF/HF ratio reflects parasympathetic dominance. This is seen when we conserve energy and engage in tend-and-befriend behaviours. In contrast, a high LF/HF ratio indicates sympathetic dominance, which occurs when we engage in fight-or-flight behaviours or parasympathetic withdrawal (14). A high frequency component in the RR tachogram is considered to be due to resting parasympathetic activity and low frequency component is considered mainly due to resting sympathetic activity. The total power provides the overall heart rate variability observed in the recording. Resting parasympathetic activity is the major contributor for HF power, HFnu, SDNN, RMSSD and NN50. While LFnu reflects sympathetic activity, LF component is predominantly due to resting sympathetic activity with some influence from resting parasympathetic activity. Physiological explanation for VLF component is ill defined and it cannot be interpreted based on short term HRV recordings and so is not discussed further. LFnu and HFnu represent controlled and balanced resting activity of sympathetic and parasympathetic nervous system.

III. RESULTS

The study population consist of 75 controls and 25 hypertensives including both males and females in the age range of 35-60yrs. 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 Tables1 and 2 respectively.

Table 1 Baseline Demographic Parameters of Males

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, weight, waist circumference, heart rate in control and case male subjects while a significant relationship was observed in blood pressure.

Table 2 Baseline Demographic Parameters of Females

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 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 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.

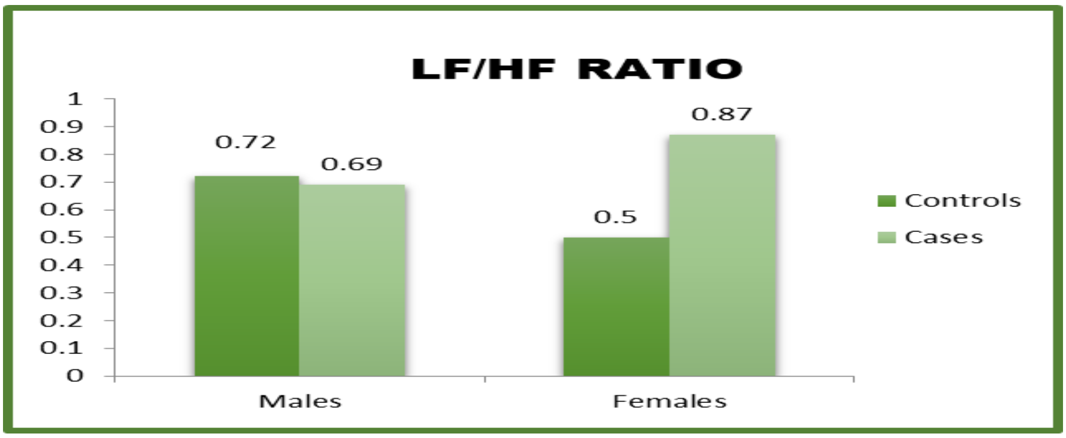

Fig 2 Graphical Representation of LF/HF Ratio in the Study Groups

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

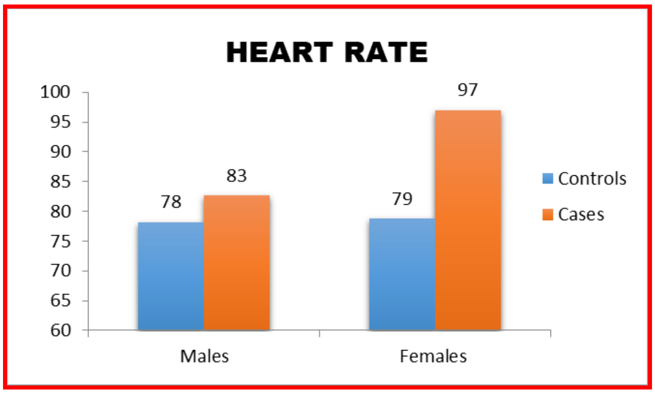

Fig 3 Graphical representation of Heart rate in Controls and cases

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

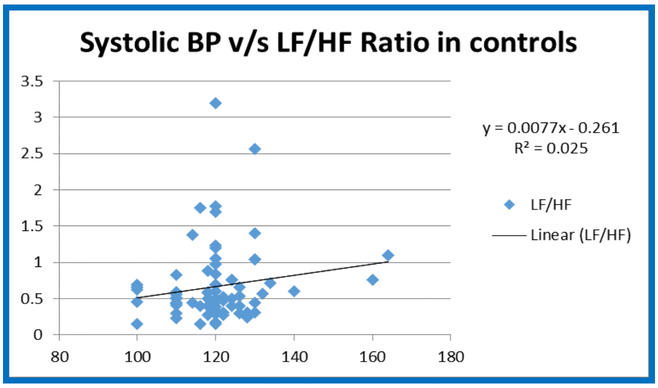

Fig 4 Scatter Diagram for Systolic BP and LF/HF Ratio in Controls

From Pearson's corelation 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 stastically non significant.

A strong positive corelation was found between Systolic BP and SDNN (r=0.55) in hypertensives which is represented in the scatter diagram (Figure 5)

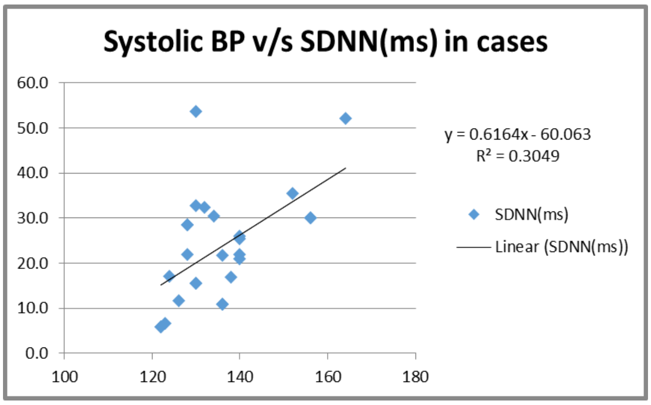

Fig 5 Scatter Diagram for Systolic BP and SDNN in Cases

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.

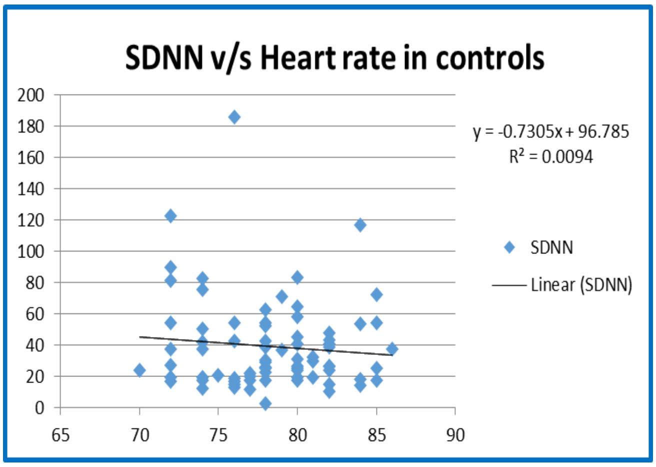

Fig 6 Scatter Diagram for SDNN and Heart Rate in Controls

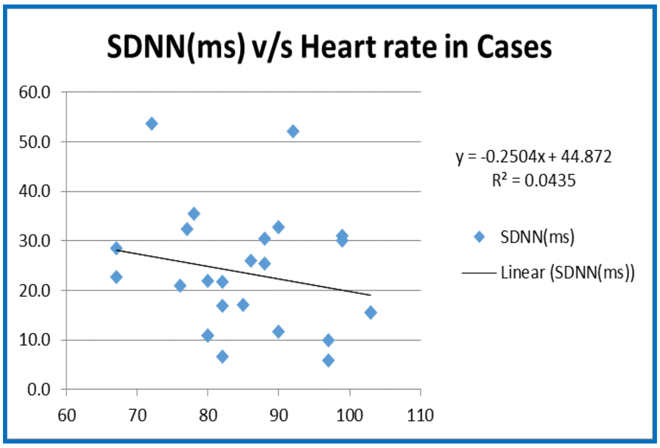

Fig 7 Scatter Diagram for SDNN and Heart Rate in Cases

IV. DISCUSSION

Worldwide, the prevalence of hypertension and the related morbidities is rising. When heart rate is analysed on a beat-by-beat basis, the irregular heartbeat is easily visible; nevertheless, this irregularity is missed when a mean value across time is obtained. These heart rate variations are the consequence of intricate, nonlinear interactions between several physiological systems. A measure of neuro-cardiac activity, HRV is thought to represent the dynamics of the autonomic nervous system and heart-brain communication.. It is one of the promising marker. 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 **c**omparison of frequency domain indices of HRV, between the two study groups controls and hypertensives, in the age range of 35-60 yrs, LF, HF, LF(nu),(HF(nu) was found to be reduced in cases and in females the reduction was statistically significant. Total power (ms^2) 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 indicates 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)

➢ *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.

V. CONCLUSION

Both men and women with systemic hypertension have lower HRV. Lower HRV was linked to a higher risk of developing hypertension in normotensive males. Above and above what can be determined from measures of baseline systolic and diastolic blood pressures, body mass index, and age, estimation of LF using spectral analysis of ambulatory ECG recordings increases the prediction of risk of hypertension in males. These results support the idea that autonomic dysfunction exists in the first stages of hypertension.

➢ *Clinical Implications*

The current study broadens the clinical relevance of HRV beyond its use in monitoring diabetes and myocardial infarction patients. It has been demonstrated that a decline in HRV can predict the likelihood of cardiac events as well as overall mortality and is linked to an increased risk of cardiac mortality. Whether decreased HRV is a factor in the elevated cardiac mortality in hypertension, more investigation is required. The choice of anti-hypertensive treatment may be influenced by an evaluation of HRV.

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