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Research Article

REFERENCE RANGES FOR TIME DOMAIN PARAMETERS OF HEART RATE VARIABILITY IN INDIAN POPULATION AND VALIDATION IN HYPERTENSIVE SUBJECTS AND SMOKERS

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ABSTRACT

Dysregulation of autonomic nervous system has been implicated in development of hypertension and cigarette smoking enhances the adrenergic activity and thus may be associated with hemodynamic changes in the cardiovascular system. In this study heart rate variability was analyzed in hypertensive subjects and smokers. Hundred healthy subjects (100), seventeen hypertensive subjects (17) and twelve smokers (12) were included in the study. Time domain parameters SDRR (standard deviation of R-R interval), RMSSD (root mean square of successive R-R interval) and pRR 50%were obtained from all participants after 30 minute ECG recording. All these parameters were significantly reduced in case of hypertensive subjects and smokers as compared to normal healthy population data. The base line values of time domain parameters of smokers are lower than normal population range and even all the parameters significantly reduced post smoking.

Keywords: ANS (autonomic nervous system), HRV (heart rate variability), Indian Population

INTRODUCTION

The autonomic nervous system, through the sympathetic and parasympathetic pathways, supplies and influences every organ in the body. It closely integrates vital processes such as heart rate, BP, myocardial contractility and body temperature and consequently plays a pivotal role in the regulation of the CV system. The sympathetic (SNS) and parasympathetic (PNS) branches of the autonomic nervous system (ANS) antagonistically influence the lengths of time between consecutive heartbeats. Faster heart rates, which can be due to increased SNS and/or lower PNS activity, correspond to a shorter interbeat interval while slower heart rates have a longer interbeat interval, which can be attributed to increase PNS and/or decrease SNS activity[1]. Heart rate variability (HRV) is a physiological marker used to assess the autonomic nervous system (ANS) and is significantly associated with a variety of pathologies, such as cardiovascular disease and diabetes mellitus. The HRV can be assessed over the short (usually 5-15) or long (24 hours) term[2]. Low HRV value indicates elevated sympathetic myocardial activity and increase risk of malignant dysarrythmias, particularly in patient with heart disease[3].Although the pathogenesis of most hypertension is unclear, dysregulation of the autonomic nervous system has been implicated in its development. Heart rate variability (HRV) has emerged as a practical, noninvasive tool to quantitatively investigate cardiac autonomic dysregulation in hypertension. Studies have reported decreased HRV among hypertensives1–12 and that the relation between blood pressure and HRV is present across a wide range of blood pressures. Data from the Framingham cohort and a subset of the Atherosclerosis Risk in Communities (ARIC) cohort suggest that individuals with decreased HRV have an increased risk of developing hypertension[4].

METHOD

Hundred (100) healthy adult male subjects from volunteer bank of Ranbaxy Clinical Pharmacology Unit were included in the study. Age of the subject range between 18-45 yrs with Mean ± SD 27.6 ± 6.7 yrs. Height ranged between 157-180cms with Mean ± SD 165.5 ± 6.1cms.Weights varied from 47-67 kg with Mean ± SD 57.9 ± 9.5 kg. They were neither underweight nor overweight as per height/weight chart of LIC India. Out of total subjects 15 subjects were having vegetarian diet and 85 were nonvegetarian. A total of 14 subjects were smokers among all. In addition to it seventeen (17) Borderline hypertensive volunteer from special population bank and twelve (12) smokers were included for the measurement & comparison of HRV parameters with the normal population. All the subjects were Male & Asian.

The study subjects were judged to be medically healthy based on the demographic data (including age, sex, history of smoking and alcohol consumption, body weight and height), vital signs and physical examination, ECG, chest X-ray and clinical laboratory tests (including disease markers of syphilis, HIV and hepatitis B and C) and urinary drug screening. Chest X-rays were performed at the Department of Radio Diagnosis and Imaging of Fortis Hospital. A brief clinical examination of the subjects, which included general physical examination cardiovascular, respiratory system, abdominal and CNS examinations was conducted by a qualified medical designate

Study design

This study was initiated after the protocol and informed consent form (ICF) were reviewed by the Fortis Hospital Institutional Review Board (FH-IRB). Study was conducted when subjects came to CPU for normal screening. Holter ECG recording was done using the Mortara Portrait Electrocardiograph Holter H-12 Recorder. Holter was applied on subjects when they were completely relaxed, and 30 minute ECG was recorded. The subjects were monitored throughout the study period for adverse events. They were specifically asked about any adverse event after holter application, none of the subjects developed any significant abnormal clinical findings during the conduct of the study.

HRV analysis

After complete recording for 30 minutes, the cards were scanned and subject electrocardiographic data was saved. HRV analysis was performed using heart rate variability software H- Scribe Software. Time domain analysis was performed, for the time domain, the standard deviation of R-R interval (SDRR), the root mean square of successive R-R interval difference (RMSSD), pRR50% were measured. All records were visually examined and manually over read to verify beat classification.

Statistical analysis

All data were presented as the Mean ± SEM. All time domain parameters were calculated using one way ANOVA technique with the help of instat graph pad which is easily available online software. p value less than 0.05 was considered as significant and the confidence interval were calculated to establish population reference range.

RESULTS

The values of time domain parameters in healthy adult male India population are RMSSD (36.8 ± 2.8) ms, SDRR-Magid (56.3 ± 2.0) ms,

SDRR-Kleiger (62.2 ± 2.1) ms and pRR50 %(13.1 ± 1.4) which are in concurrence with the previous population based studies[4, 7, 8, and 9] However further studies with preferably large sample size are required to further validate the result of this study. Our study may further help in evaluating clinical utility of heart rate variability in Indian population.

This study also evaluates the time domain parameters of HRV in smoking and borderline hypertensive volunteers. The time domain parameters of hypertensive subjects are RMSSD (26.0 ± 2.6) ms, SDRR-Magid (44.4 ± 3.8) ms, SDRR-Kleiger (50.1 ± 3.8) ms and pRR50% (6.5 ± 1.5) [Table1] which are significantly lower than normal population range. Graphical comparison of these parameters given in [Fig.1]

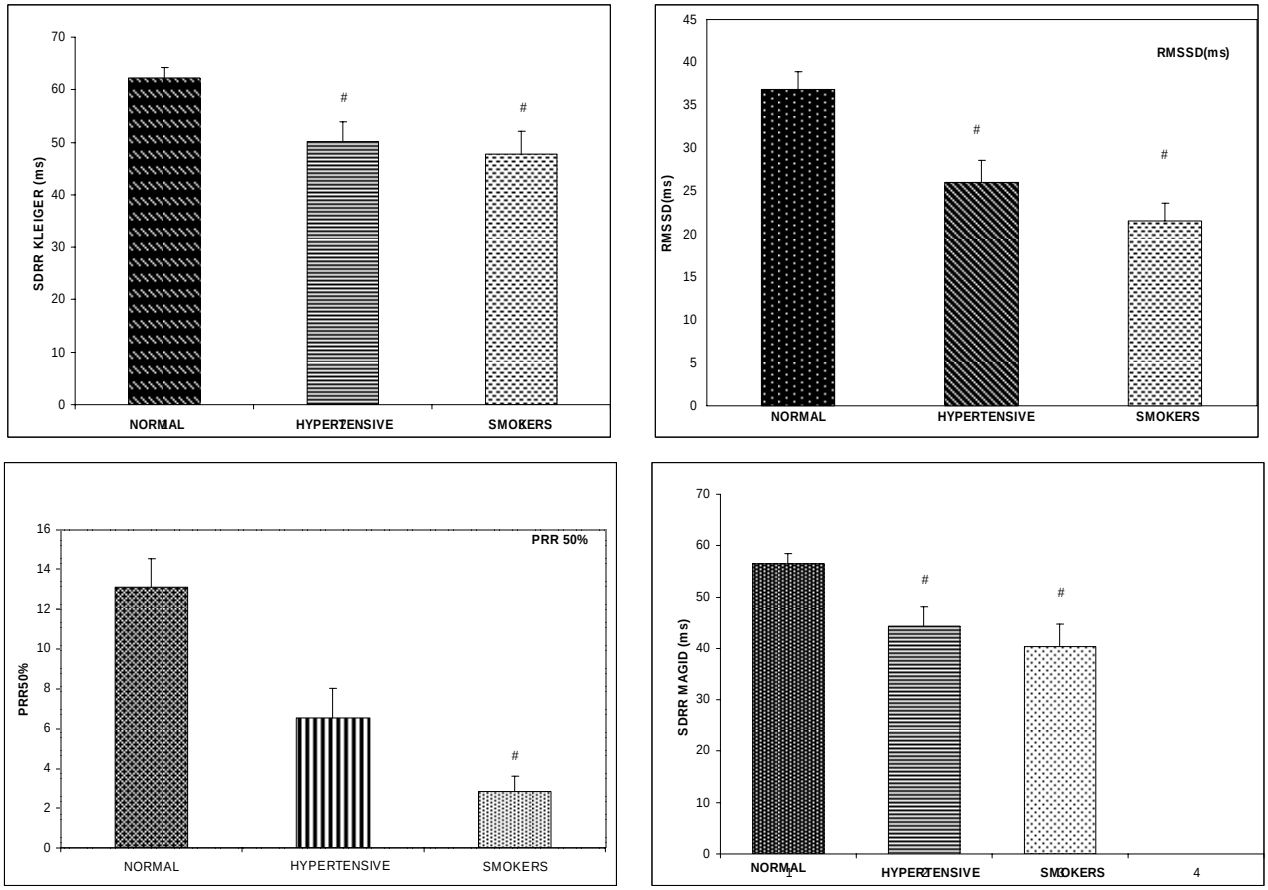

Fig. 1: It shows the comparison of heart rate variability among normal borderline hypertensive subjects and smokers

indicate P value < 0.05

The base line values of time domain parameters of smokers are RMSSD (29.4 ± 2.1) ms, SDRR-Magid (53.5 ± 3.0) ms, SDRR-Kleiger (61.0 ± 3.64) ms and pRR50% (6.17 ± 1.3) [Table2] lower than normal population range and even all the parameters significantly reduced post smoking, RMSSD (21.5 ± 2.1)ms, SDRR-Magid(40.3 ± 4.4)ms, SDRR-Kleiger(47.7 ± 4.5) ms and pRR50%(2.83 ± 0.8).

DISCUSSION

The finding of our study that time domain parameters of heart rate variability were significantly reduced in case of hypertensive subjects and smokers. The base line values of time domain parameters of smokers are lower than normal population range and even all the parameters significantly reduced post smoking. These finding are in concurrence with previous population studies. Several previous studies had established population reference range of time domain parameters of HRV. In a study conducted by Sevre.K et al[5]in Norway, and the University Hospital of Groningen, Netherlands the values of these parameters evaluated were pRR50% (9.8 ± 1.5) , RMSSD (35.7 ± 3.0) ms .Karakaya .O et al[6] conducted HRV analysis in population of Turkey observed the values of these parameters as SDRR (61 ± 19) ms, RMSSD (61 ± 37) ms and the values of time domain parameters evaluated by Schroeder et al[4] in North Carolina were SDRR (37.3 ± 0.4) ms, RMSSD (28.6 ± 0.4) ms[Fig 2]. In current study the values of these parameters in healthy adult male India population evaluated were SDRR-Magid (56.3 ± 2.0) ms, SDRR-Kleiger (62.2 ± 2.1) ms pRR50 %(13.1 ± 1.4) and RMSSD (36.8 ± 2.8) ms, which are in concurrence with the previous population based studies [4, 7, 8, and 9]. However further studies with preferably large sample size are required to further validate the result of this study. These reference ranges may help in evaluating clinical utility of heart rate variability in Indian population.

Current study also evaluated time domain parameters of heart rate variability in borderline hypertensive subjects. Schroeder et al[4] investigated the temporal sequence linking hypertension, blood pressure, and heart rate variability in a population-based cohort of 11061 individuals aged 45 to 54 years at baseline. Individuals with hypertension had decreased heart rate variability at baseline, and this association was present across the full blood pressure range. Schroeder et al suggested that Heart rate variability is uniformly reduced in mild to moderate untreated hypertension. Time domain measure like SDRR, RMSSD and SDRR will all decrease. Higher heart

rate, advancing age, higher blood pressure, and female gender are independent determinants of reduced heart rate variability[4]. Jagmeet P. Singh, et al[7] compares measures of HRV between hypertensive and Normotensive subjects and examines the role of HRV as a predictor of new-onset hypertension. The first 2 hours of ambulatory ECG recordings obtained from 931 men and 1111 women attending a routine examination at the Framingham Heart Study were processed for HRV. Three time-domains were studied: standard deviation of normal RR intervals (SDNN), Percentage of differences between adjacent normal RR intervals exceeding 50 milliseconds, square root of the mean of squared differences between adjacent normal RR intervals. On cross-sectional analysis, HRV was significantly lower in hypertensive men and women[7]. Sevre.K et al[5] suggest that HRV, which estimates the tonic HR control, is generally reduced (standard deviation of all R-R intervals [SDNN] and total power [energy in the heart period spectrum between 0.0033 and 0.40 Hz] [TP]) in hypertensive patients[5].

Our study evaluated the time domain parameters of HRV in borderline hypertensive volunteers. The time domain parameters of hypertensive subjects evaluated were RMSSD (26.0 ± 2.6) ms, SDRR-Magid (44.4 ± 3.8) ms, SDRR-Kleiger (50.1 ± 3.8) ms and pRR50% (6.5 ± 1.5) [Table 1] were significantly lower than normal population range. The results are in concurrence with the previous population based studies. Blood pressure elevation, increased sympathetic activity, and decreased parasympathetic activity lead to a normalization of cardiac output, an increase in vascular resistance and parasympathetic tone, and a decrease in sympathetic tone[4].

Table 1: heart rate variability parameters of borderline hypertensive subjects

S. No	Ref. No	Mean Rate	pRR50%	RR50 count	RMSSD (ms)	SDRR (ms) M	SDRR (ms) K	BP (mmHg)
1	8039	74	2	1.48	25	65	70	136/102
2	8097	76	11	8.36	34	61	69	137/91
3	10450	81	13	10.53	37	51	57	132/96
4	5800	103	0	1.03	10	22	25	132/97
5	6590	80	24	19.2	44	58	61	146/101
6	7200	69	4	2.76	27	53	52	137/99
7	4320	79	10	7.9	40	65	70	136/94
8	6979	87	1	0.87	19	31	41	134/91
9	11904	85	8	6.8	31	52	55	145/98
10	11707	79	15	11.85	41	64	70	131/100
11	12228	86	2	1.72	21	34	41	149/106
12	10866	89	0	0.89	11	22	31	145/103
13	8823	82	6	4.92	31	53	66	147/92
14	4766	86	8	6.88	22	37	40	140/97
15	7266	80	1	0.8	17	26	32	138/92
16	5362	85	3	2.52	11	27	30	140/92
17	2376	82	3	2.46	22	35	42	138/94
	Mean	82.5	6.5	5.35	26.0	44.47	50.11	
	Max	103	24	5.35	44	65	70	
	Min	69	0	19.2	10	22	25	
	SD	8.0	6.8	0.8	10.9	15.77	15.9	

SDRR (standard deviation of R-R interval)
RMSSD (root mean square of successive R-R interval)
RR 50 count (Number of RR interval with value more than 50 ms)

Current study also evaluated time domain parameters of heart rate variability in smokers in presmoke, during smoke and postsmoke condition. Twelve smokers were selected from the special population bank of CPU their HRV was obtained by measuring 30 minute holter ECG. Previous study conducted by Kupari et al[10] observed that HRV was lower in people who smoke at least 10 cigarettes as compared to nonsmoker group or people who smoke fewer than 10 cigarettes per day. Eryonucu et al[9] showed that time domain parameters of HRV were significantly lower in smokers than nonsmokers. Also, Hayano et al[11]measured HRV in heavy smokers, moderate smokers, and normal subjects, performing controlled breathing for 5 minutes while supine and for 5 minutes while standing, and concluded that heavy smoking causes long-term reduction in vagal cardiac control in young people and blunted postural responses in autonomic cardiac regulation. Levin et al found a trend to increased heart rate and decreased HRV among smokers, as measured by SDNN over 5 minutes recording.

In current study the base line values of time domain parameters of smokers were SDRR-Magid (53.5 ± 3.0) ms, SDRR-Kleiger (61.0 ± 3.64) ms, pRR50% (6.17 ± 1.3) and RMSSD (29.4 ± 2.1) ms, lower than normal population range and even all the parameters significantly reduced post smoking, RMSSD (21.5 ± 2.1) ms, SDRR-Magid(40.3 ± 4.4) ms, SDRR-Kleiger(47.7 ± 4.5) ms and pRR50%(2.83 ± 0.8) [Table 2]. Again all results are in concurrence with the previous population based studies. The mechanism of acute smoking-induced changes in HRV is probably complex; however, most of the acute effects of smoking on neurocardiovascular regulation have been mainly attributed to nicotine, which is the main constituent of cigarette. Nicotine has well-known acute and chronic cardiovascular effects, mainly through sympathetic activation as a consequence of enhanced release of catecholamine. Indeed, nicotine is implicated in a wide spectrum of cardiac rhythm disorders, including transient sinus arrest and/or bradycardia, sinus tachycardia, atrial fibrillation, sinoatrial block, atrio-ventricular block, and ventricular tachyarrhythmia's therefore, nicotine may in part be associated with the changes in HRV observed after smoking a cigarette[12].

Table 2: heart rate variability parameters of smokers

S. No	pRR50%	RMSSD(ms)	SDRR (MAGID)	SDRR (Kleiger)
1	0	12	22	28
2	4	33	33	55
3	5	26	56	61
4	10	34	72	82
5	4	25	49	55
6	1	21	33	37
7	1	18	42	45
8	3	22	53	58
9	0	12	18	32
10	3	24	44	50
11	1	14	33	38
12	2	17	29	32
MEAN	2.83	21.50	40.33	47.75
SD	2.79	7.37	15.45	15.57
SEM	0.81	2.13	4.46	4.50

Table 3: Comparison of heart rate variability parameters between Normal, borderline hypertensive subjects and smokers (Mean ± SEM)

Parameters	Normal subjects	Hypertensive	Smokers
pRR50%	13.1 ± 1.4	6.5 ± 1.5	2.8 ± 0.8
RMSSD	36.8 ± 2.8	26.0 ± 2.6	21.5 ± 2.1
SDRR Magid	56.39 ± 2.0	44.4 ± 3.8	40.3 ± 4.4
SDRR Kleiger	62.2 ± 2.1	50.1 ± 3.8	47.7 ± 4.4

SDRR (standard deviation of R-R interval)
RMSSD (root mean square of successive R-R interval)
RR 50 count (Number of RR interval with value more than 50 ms)

CONCLUSION

During short term analysis of heart rate variability we observed that time domain parameters of heart rate variability were significantly reduced in case of hypertensive subjects and smokers as compared to normal population reference range. The base line values of time domain parameters of smokers are lower than normal population range and even all the parameters significantly reduced post smoking

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