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Research Article

REFERENCE RANGE OF HEART RATE VARIABILITY AND VALIDATION IN SUBJECTS WITH ASYMPTOMATIC ELEVATED LIVER FUNCTION ENZYMES

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ABSTRACT

The prevalence and severity of autonomic dysfunction appears to be related to the severity of liver disease (e. g. alcoholic cirrhosis) and is associated with an increase in mortality. This study aims to evaluate time domain parameters of heart rate variability in asymptomatic liver functions elevated healthy subjects and comparison of it with normal population reference range. The rationale of the study is that increasing severity of liver failure is associated with a reduction in total heart rate variability and regularity; therefore measurement of HRV offers a simple, noninvasive means of assessing the cardiovascular and autonomic effects of liver disease.

The finding of the current study shows that Heart rate variability of Liver functions elevated subjects are found to be higher than the normal population reference range. The reason for finding of higher variability was that subjects included in this study had bradycardia. Bradycardia is known to lead to higher heart rate variability.

Keywords: Heart rate variability, Autonomic nervous system, Liver Functions.

INTRODUCTION

The autonomic nervous system, through the sympathetic and parasympathetic pathways, supplies and influences every organ in the body. 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]. Fleisher L et, al investigated that chronic liver disease, both alcoholic and nonalcoholic has been shown to be associated with autonomic neuropathy, as well as other hemodynamic and circulatory disturbances. Increasing severity of liver failure is associated with a reduction in total heart rate variability and regularity. Measurement of HRV offers a simple, noninvasive means of assessing the cardiovascular and autonomic effects of liver disease; pNN50 was significantly reduced in all liver disease patients compared to that in controls [2].

Aim of the study

This study aims to evaluate time domain parameters of heart rate variability in asymptomatic liver functions elevated healthy subjects and comparison of it with normal population reference range.

Methods

The reference range of time domain parameters of heart rate variability was taken from the previous in house study conducted by same authors in Ranbaxy Clinical Pharmacology Unit (RCPU) [3].

Values were obtained by including seventy (70) healthy adult male subjects from volunteer bank of (RCPU). The subject age range was between 18-45 yrs with Mean ± SD 27.6 ± 6.7 yrs. Height ranged between 157-180 cms with Mean ± SD 165.5 ± 6.1 cms. 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 rests were nonvegetarian. A total of 14 subjects were smokers among all. A total of twenty (20) subjects with asymptomatic elevation of Liver Function enzymes (AST, ALT) were included in the study. 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 performed after taking subject consent on informed consent form. When subjects came to RCPU for normal screening, they asked for 10 minute relaxation then ECG was recorded for 30 minute by using Mortara H12+ Holter ECG Recorder. The subjects were monitored throughout the study period for any 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 [3].

Heart rate variability analysis after

complete recording for at least 30 minutes, the cards was scanned and subject electrocardiographic data was saved [3]. 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 of heart rate variability found in healthy adult male were RMSSD (35.3 ± 2.5) ms, SDRR-Magid (54.6 ±. 2.3) ms, SDRR-Kleiger (59.8 ± 2.4) ms and PRR50% (11.4 ±1.6). These values were obtained from the previous in house study at RCPU. The current study evaluate the time domain parameters of

HRV in liver functions elevated subjects as RMSSD (53.6 ± 5.8) ms, SDRR-Magid (68.8 ±. 5.4) ms, SDRR-Kleiger (76.4 ± 5.4) ms and PRR50% (26 ±4.4). The graphical representation of all the values between these two groups are shown in Figure 1.

The values of HRV parameters in these subjects found to be higher as comparison to normal reference range however, the mean values of heart rate in liver functions elevated subjects was found to be ± 65 b/min. which was lower than the mean of heart rate of normal healthy subjects' ± 85 b/min indicates occurrence of bradycardia in these subjects. All the values are compared shown in Table 1 while the statistical description of all the values is given in Table 2.

DISCUSSION

The normal value of time domain parameters of heart rate variability found in previous in-house study 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, This study measured the 30 minute HRV of normal healthy adult male subjects. The study was conducted in Ranbaxy clinical pharmacology unit Noida. Time domain parameters of liver functions elevated subjects found in current study are pRR50% 26 ±4.4, SDRR (M) 68.8 ±. 5.4 ms, SDRR (K) 76.4 ± 5.4 ms and RMSSD 53.6 ± 5.8 ms, the result of this study shows that HRV of these subjects found to be higher than the normal population reference range. The mean heart rate in these subjects was found to be 65 which were lower than the mean heart rate of normal healthy subjects 85 elevated in this study. This indicates that Liver functions elevated subjects in this study had bradycardia. The time domain parameters of HRV found to be higher in liver functions elevated subjects i. e. bradycardia leads to higher HRV. Sinus bradycardia is associated with advance liver disease, it occurs during episodes of hypervagotonia (vasovagal syncope) [4]. A study conducted by CHEN KY et al demonstrated a change in cardiac vagal tone associated with acute hepatitis by analysis of HRV, and such alteration is less pronounced later during the clinical course of acute hepatitis. They evaluated the heart rate variability (HRV) of 10 patients with acute hepatitis (6 males, 4 females; mean age, 44.0 y; range, 20-69 y). Frequency-domain analysis of short-term and stationary R-R intervals was performed on the first day of admission to detect low-frequency power (LF; 0.04-0.15 Hz), high-frequency power (HF, 0.15-0.40 Hz), the ratio of LF to HF (LF/HF), and LF in normalized units (LF %). The same measurement was repeated on the 7th day of admission. They found that there was a significant increase of HF as well as variance of the R-R interval on the 7th day after admission ($P < 0.05$) [5].

Stuart C. Gordonet al found that cardiovascular complications of viral hepatitis are not widely recognized. Profound hypotension and a variety of dysrhythmias, including sinus arrest, have been reported in association with viral hepatitis, but most of these cases were described before the advent of specific viral serologic markers. Furthermore, previous instances of cardiovascular complications occurred during the course of an established viral syndrome. They report the cases of two previously healthy women who presented with unexplained hypotension and bradycardia as the initial manifestations of acute icteric hepatitis A. This phenomenon appears to represent a variant clinical presentation of a common viral entity [6].

Table 1: Statistical data of normal healthy and liver functions elevated subjects

HEALTHY/NONSMOKERS **RMSSD**		**AST/ALT SUBJECTS**
SAMPLE SIZE (70)		**SAMPLE SIZE (20)**
MEAN	35.3	53.6
SD	20.7	26.2
SEM	2.5	5.8
LOWER 95%CI	30.2	41.3
UPPER95%CI	40.3	65.8
MIN	10	19
MAX	119	113
P value- 0.016 (Considered very significant)		
SDRR (M)		
MEAN	54.6	68.8
SD	19.5	24.5
SEM	2.3	5.4
LOWER 95%CI	49.8	57.3
UPPER95%CI	59.4	80.3
MIN	26	29
MAX	137	131
P value- 0.0088 (Considered very significant)		
SDRR (K)		
MEAN	59.8	76.4
SD	19.9	24.1
SEM	2.4	5.4
LOWER 95%CI	55	65.1
UPPER95%CI	64.7	87.7
MIN	30	33
MAX	142	139
P value- 0.0026 (Considered very significant)		
pRR50%		
MEAN	11.4	26
SD	13.5	20.1
SEM	1.6	4.4
LOWER 95%CI	8.1	17.5
UPPER95%CI	14.7	36.3
MIN	0	0
MAX	66	66

P value- 0.0001 (Considered extremely significant)

Table 2: Comparison of hrv parameters between normal healthy and liver functions elevated subjects (mean ±sem)

HRV Parameters	Normal subjects	Subjects with liver functions Elevation
pRR50%	11.4 ± 1.6	26 ± 4.4*
RMSSD	35.3 ± 2.5	53.6 ± 5.8*
SDRR Magid	54.6 ± 2.3	68.8 ± 5.4*
SDRR Kleiger	59.8 ± 2.4	76.4 ± 5.4*

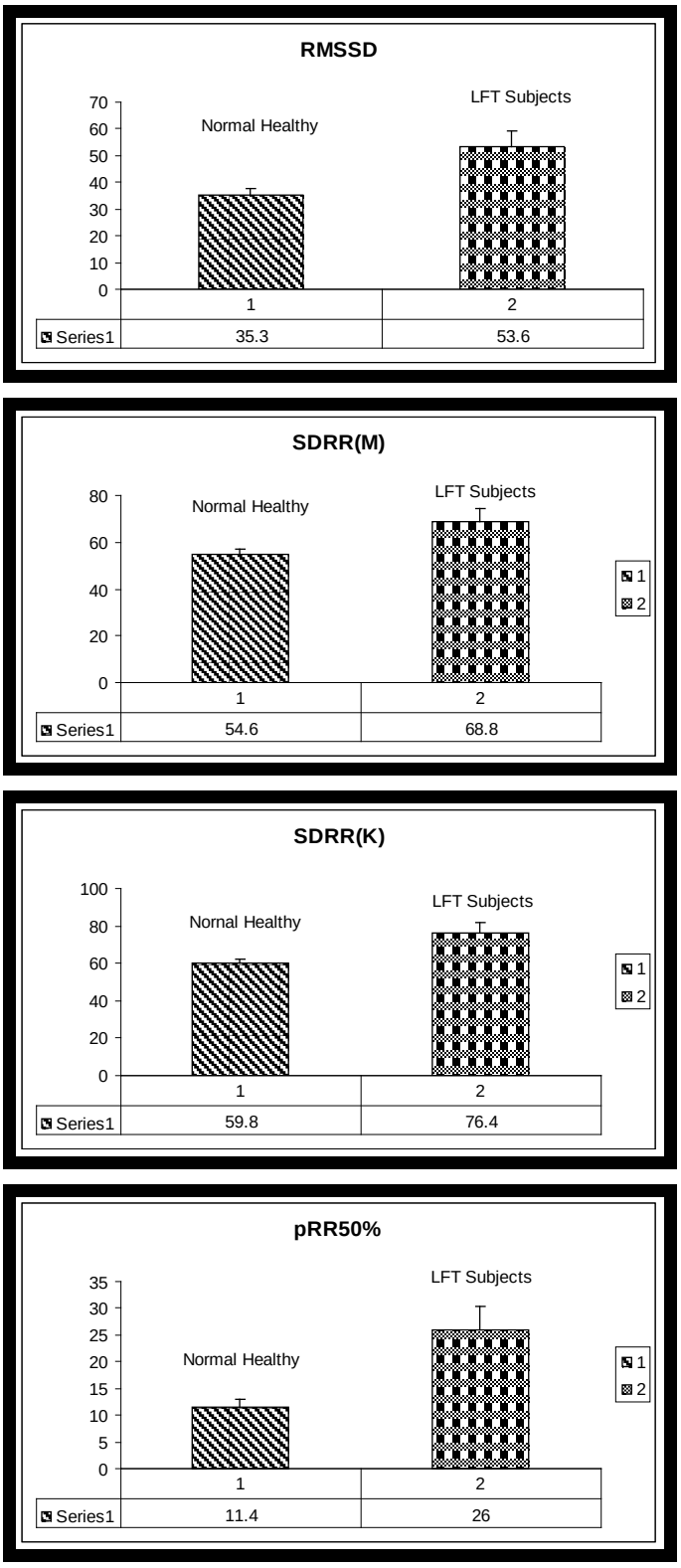

Fig 1: Graphical representation of hrv parametrs between normal healthy subjects and liver functions elevated subjects

All the values are represented as Mean ± SEM

CONCLUSION

The conclusion drawn from this study shows that HRV of liver functions elevated subjects are found to be higher than the normal population reference range. This is the first study of its kind to evaluate time domain of HRV in asymptomatic liver functions elevated healthy subjects. The result of this study shows that pRR50% (26 ±4.4), SDRR-Magid (68.8 ±. 5.4) ms, SDRR-Kleiger (76.4 ± 5.4) ms and RMSSD (53.6 ± 5.8) ms. The mean of heart rate in liver fuctions elevated subjects was found to be ± 65 b/min. which was lower than the mean of heart rate of normal healthy subjects ± 85 b/min. This indicates that liver functions elevated subjects in this study had bradycardia. Bradycardia is known to lead to higher HRV. Further studies with larger no. of subjects are required to confirm the findings of this study.

Impact of finding on practice

Increasing severity of liver failure is associated with a reduction in total heart rate variability and regularity. Measurement of HRV offers a simple, noninvasive means of assessing the cardiovascular and autonomic effects of liver disease.

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CONFLICTS OF INTEREST

None to declare

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