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Original article:

Frequency-domain analysis of R-R Variability in non-alcoholic portal hypertensive patients in urban population

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Abstract:

Portal hypertension is the most common and lethal complication of chronic liver disease.Liver cirrhosis being the common as a free portal vein pressure in excess of the normal by 5 to 10 mm Hg which represents an increasingmorbidity and mortality among alcoholics but our main focus of our research is on in non alcoholic portal hypertensive patients.Autonomic dysfunction occurs in those patients and is sometimes responsible for major complications, likevariceal bleeding, hepatic encephalopathy or arrhythmias. Heart rate variability (HRV) is a known marker of the autonomic imbalance.The aim of our research study was toassess the role of HRV parameters in evaluation of heart rate variability in non alcoholic portal hypertension patients. Heart rate variability (HRV) is a marker of autonomic activity and can be analyzed using time-domain and frequency-domain methods. This study was undertaken to compare the HRV in patients with non-alcoholic portal hypertension patientsand normal subjects.Heart rate variability in 30 controls (Group I) and 30 patients with portal hypertensive patients with non alcoholic etiology (Group II) aged 25-45 yrs was studied by using electrocardiographic data obtained during HRV analysis as ECG signals Conversion of the resting ECG signal was done using AD converter with sampling frequency of 1024/sec. Power spectral analysis of the converted ECG signal was done using Fast Fourier transformation.Low frequency (LF) power, High frequency (HF) power and Low frequency/ High frequency ratio (LF/HF) were analyzed using frequency-domain analysis. There was a significant difference ($p < 0.001$) in LF power and LF/HF ratio of patients with non-alcoholic portal hypertension when compared to the controls, with the values of the non-alcoholic portal hypertension patients being higher, indicating a strong sympathetic activity and a significant difference ($p < 0.001$) in HF power, with the values of the non alcoholics portal hypertension patients being lower, suggesting parasympathetic blunting. Analysis of HRV can be used as a non invasive method to evaluate the severity, early detection and type of autonomic impairment in non alcoholics portal hypertension patients.

Key words: Heart rate variability, non alcoholic portal hypertension, autonomic dysfunction

Introduction

Portal hypertension is the elevated pressures in the portal venous system. Portal hypertension may becaused by intrinsic liver disease, obstruction, or structural changes that result in increased portal venous flow or increased hepatic resistance(Kowalski HJet al., 1953). Normally, vascular channels are smooth, but liver cirrhosis can cause them to become irregular and tortuous with accompanying increased resistance to flow. This resistance causes increased pressure, resulting in varices or dilations of the veins and tributaries. Pressure within the portal system is dependent upon both input from blood flow in the portal vein, and hepatic resistance to outflow. Normally, portal vein pressure ranges between 1–4 mm Hg higher than the hepatic vein free pressure, and not more than 6 mm Hg higher than right atrial pressure (Sleisenger and Fordtranset al., 7th edition). Pressures that exceed these limits define portal hypertension. Complication begins when portal pressure reaches values equal to or higher than 12 mmHg. The heart rate variability (HRV) parameters are well known as predictors of mortality and cardiovascular events in both normal persons (Dekker JM et al., 2000;102: 1239-44)and patients with cardiac failure (Galinier M et al.,Eur Heart J 2000; 21(6): 475-82&La Rovere MT et al., Circulation 2003; 107: 565-70) or myocardial infarction (La Rovere MT et al. & Lancet 1998; 351: 478-84,Zuanetti G et al Circulation 1996;94: 432-36). Liver cirrhosis represents an increasing medical burden. Recent studies suggest that, up to 1% of the world population possibly have histological cirrhosis(Schuppan D et al., Lancet 2008;371(9615): 838-51). HRV(Heart Rate Variability) is also known as a marker of the imbalance between the two elements of the autonomic system: the sympathetic and vagal component (Hayano J et al., Am J Cardiol 1991; 67: 199-04). The pathophysiology of autonomic dysfunction in liver cirrhosis has several mechanisms due to increased concentration of vasodilators, like nitric oxide(Abraldes JG et al., Am J PhysiolGastrointest Liver Physiol 2006; 290(5):G980-87) leading to the activation of reninangiotensin-aldosterone system, increased plasma angiotensin II levels, interacting with the parasympathic control of HRV, and overproduction of inflammatory cytokines, as well as oxidative stress(Mani AR et al., Am J PhysiolGastrointest Liver Physiol 2009; 296(2): G330-38. &Møller S, Henriksen JH Gut 2008; 57: 268-78). Many previous studies correlates autonomic dysfunction with alcoholic etiology but afterwards, there were studies confirming that viral etiology is also associated with impaired autonomic nervous system function (Osztovits J et al., Liver Int 2009; 29(10): 1473-78.)Resting five minutes Holter monitor allows recording the heart's activity providing valuable information on cardiac autonomic regulation by assessing HRVthrough time and frequency domain parameters. Several studies confirm that HRV parameters, as generated by the Holter electrocardiogram recordings,are inversely correlated with the severity of cirrhosis (Hendrikse MT et al.,ClinAuton Res 1993; 3: 227-31).and can be used as predictors of mortality in these patients (Ates F, Topal E, Kosar F, Karincaoglu M, Yldirim B, et al. Dig Dis Sci 2006; 51:1614-18). In view of the above findings ofdifferent researchers, the present study was therefore undertaken to compare the heart rate variability (HRV) in patients diagnosed non alcoholic portal hypertension and normal subjects using electrocardiographic data obtained from time and frequency-domain analysis.

Materials and methods

This study was conducted in the Institute of Physiology & Experimental Medicine, Madras Medical College, Chennai, Tamil Nadu, India. 30 normal controls (Group I) and 30 patients with portal hypertensive patients with non alcoholic etiology (Group II) aged 25-45 yrs with less than two years diseasedurationparticipated in the study.

Controls were age and BMI matched.The diagnosis of portal hypertensive patients with non-alcoholicetiology was based on history, clinical examination.Individuals with other liver diseases, co-existing Diabetes Mellitus, systemic hypertension, ischemic heart disease, congestive heart failure, renal disease and neuromuscular disorders; chronic lung disease, electrolyte imbalance,neoplastic disease, active drinkers,patients with limitation in exercise tolerance and patients with history of intake of drugs affecting the autonomic nervous system like antiarrhythmic drugs or beta blockers were excluded.The control group consists of 30 subjects similar in sex and age with the study group, free from the above mentioned exclusion criteria were enrolled for the study in the same medical institute. All patients signed a written informed consent and the Ethics Committee of Institute of Gastroenterology and Hepatology of Madras Medical College approved the study protocol, in accordance with the ethical standards laid down in the Declaration.All the patients and controls were instructed to lie down in supine posture and relax for 5 minutes. Resting Heart rate and blood pressure were recorded. By applying 3 electrodes(black, red and green),black colour electrode was placed in the right infraclavicular on the bone, red colour electrode to the left infraclavicular on the bone and the third green colour electrode to the right loin and resting HRV was recorded in the supine posture using ECG recorder. The leads were connected to the ECG recorder which in turn was connected by signal processing unit to the computer. The recording was made for 5 minutes (320 seconds). After screening the data for artifacts and after properly editing it the data was opened through HRV analysis software version 1.1 to obtain converted ECG signal. The analog to digital conversion of the resting ECG signal was done using AD converter with sampling frequency of 1024/sec.

Heart Rate Variability (HRV) was evaluated from the electrocardiographic data. Each QRS complex was identified, and the RR interval was calculated. Only normal to normal beats were considered for analysis. Power spectral analysis of the converted ECG signal was done using fast Fourier transformation.(Marek Malik, John Camm.A.The American Journal of Cardiology: Vol. 72: Oct 1: 1993). Low frequency (LF) power, High frequency (HF)power and Low frequency/ High frequency ratio (LF/HF) were analyzed using frequency-domain analysis. These variables were chosen as the high frequency band (0.15-0.40 Hz) is influenced by parasympathetic input and the low frequency band (0.04-0.15 Hz) is influenced by sympathetic input (both expressed in normalized units) while the low frequency/high frequency ratio can be used as an estimate of sympathovagal balance. Data thus collected was subjected to statistical analysis using SPSS 17. Values were expressed as Mean ± SD. Unpaired Student t test was used to compare the parameters between the two groups and a 'p' value of < 0.05 was considered as being significant.

Results

This study was done to compare the Heart Rate Variability in 30 patients with portal hypertension with non alcoholic etiology and 30 normal controls using electrocardiographic data obtained from ECG recorder and frequency-domainanalysis. There was a significant difference in the LF power (p value < 0.001) of the non alcoholicportal hypertension patients in Group II whencompared to the controls in Group I, with the values of Group II being higher. There was also asignificant difference in theHF power ($p<0.001$) of non alcoholic portal hypertension patients in Group II when compared to the controls in Group I with the values of Group IIbeing lower. It was also found that

the LF/HF ratio of the non alcoholicportal hypertension patients in Group II was significantly higher ($p<0.001$) than that of the controls (Table 1).

Table 1: Comparision of the Heart Rate Variability (HRV) variables between controls (Group I) and non alcoholicportal hypertension patients(GroupII).

S.No.	HRV variable	Group I (Controls)	Group II (Non alcoholicportal hypertension)	p value
1.	LF power	43.64 ± 8.13	61.71±9.73	< 0.001*
2.	HF power	53.21 ± 8.22	19.45±2.47	< 0.001*
3.	LF/HF	0.87 ± 0.31	3.18±0.68	< 0.001*

Results expressed as mean and standard deviation of the Low frequency (LF) power and High frequency (HF) power expressed in normalized units (n.u) and the LF/HF ratio, obtained by frequency-domain analysis of the heart ratevariability (HRV) in the two groups, $p< 0.05$ being considered significant.

Discussion

Our study revealed that there was a significant difference ($p <0.001$) in LF power and LF/HF ratio of patients withnon alcoholicportal hypertension patients when compared to the controls, with the values of the non alcoholicportal hypertension patientsbeinghigher, indicating a strong sympathetic activity. Paola Sandroniet al., found that these values were higher in patients with severe non alcoholicportal hypertension patients when compared to moderate non alcoholicportal hypertension patientsand they concluded that the frequency-domain indices of heart rate variability revealed the difference between the groups better (Oribe.E. and Appenzeller ,1990).Hendrikse MTet al., found that circadian rhythms of the LF, HF, and LF/HF ratio differed significantly in patients with severe non alcoholicportal hypertension patients when compared with those with mild non alcoholicportal hypertension patientsand controls .Portal Hypertensive patients showed increased variations from the mean than control. Similarly LF, HF and LF/HF showed significantly high LF and low HF in patients. This has caused the shift of LF /HF balance towards LF indicating increased sympathetic activity as stated by Hitoshi Miyajima et al. It can also bedue to decreased Para sympathetic action. The very highly significantdecrease in HF when compared with the control shows Para sympatheticattenuation and the significant elevation of LF shows increasedsympathetic activity. In addition, we found that there was a significant difference ($p <0.001$) in HF power, with the values of the non alcoholicportal hypertension being lower than that of the controls suggesting parasympathetic blunting. The LF/HF ratio represents sympathovagal balance. Although we had not classified our non alcoholicportal hypertension patients on the basis of their severity, we too did find that the LF/HF ratio was higher in the non alcoholicportal hypertension patients when compared to the controls. Our findings regarding the heart rate variability in patients with non alcoholicportal hypertension need to be considered in the light offindings of other researchers(Singh G et al Biomed Res 2011; 22:

85-9).,who studied heart rate variability (HRV) and even found evidence ofdecrease in cardiac vagal modulation in asymptomatic non alcoholicportal hypertension subjects using time-domain and frequency-domain HRVindices. They proposed conducting further studies to explore the possibility of using heart rate variability for the noninvasivescreeningof portal hypertensive patients before they develop full blown disease. Theyeven felt that there may be a link between the degree of alteration in cardiovascular variability and the severity ofportal hypertensive . They also found that the alteration in heart rate variability is seen even in the absence of other diseases likehypertension and heart failure. We had specifically excluded patients suffering from these diseases in our study. Accuratescreening and prompt treatment are therefore required and from our findings it appears that frequency-domain analysis ofHeart Rate Variability has potential for use in screening. Ates Fet al., however suggest the use of time-domain heart ratevariability analysis as an accurate, sensitive and inexpensive tool for screening patients with suspected portal hypertension .Limitations of our study include the sample size; possibility of blunting of HRV due to co-existent undiagnoseddiseases like Diabetes Mellitus in spite of strict exclusion criteria being used. However our intention wasonly to get preliminary data about the HRV using frequency-domain analysis in our patients with non alcoholicportal hypertension using the availableresources; further studies can be planned to compare all the HRV variables using both time-domain methods and frequency domainmethods in a larger sample using other devices, and possibly even in asymptomatic patients suspected tohave portal hypertension . Thus Resting HRV is a very valuable tool by itself for risk stratification incardio vascular diseases. It assesses the autonomic tone at rest. TheLow Frequency component (LF), High Frequency (HF) and Low Frequency / High Frequency (LF/HF) signifies sympathetic, Parasympathetic and Sympatho- vagal balance respectively in Autonomicfunction.

Conclusion:

Our study done to compare the heart rate variability using frequency- domain analysis in patients with non alcoholicportal hypertension revealed that there was evidence of increased sympathetic activity and a parasympathetic attenuation in patients with non alcoholicportal hypertension as evidenced by the higher LF and LF/HF ratios and the lower HF in the non alcoholicportal hypertension patients. Further studies in larger samples can be planned to evaluate these frequency-domain indices and also the time-domain indices for the non-invasive screening of asymptomatic patients suspected to have non alcoholicportal hypertension, even before they develop non alcoholicportal hypertension or cardiovascular disease.

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