

Frequency Domain Analysis of Heart Rate Variability in Type II Diabetes Mellitus Patients in a Tertiary Care Hospital

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Abstract :

Background : Heart rate variability is used in early detection of cardiac autonomic neuropathy in type 2 Diabetes Mellitus.

Aim: To study the Cardiovascular autonomic function in type 2 Diabetes Mellitus patients by doing frequency domain analysis of Heart rate Variability.

Materials and methods: This is a cross sectional study done in type 2 Diabetes Mellitus patients attending Diabetic OPD of Stanley Medical College and Hospital, Chennai. The study was done in 30 healthy controls and 30 type 2 Diabetes Mellitus patients. Heart rate variability was measured in different postures and the results were compared between the two groups.

Result: There was a significant decrease in the high frequency(HF) component in cases when compared to controls. ($p < 0.001$) in the lying posture. The value of low frequency(LF) component and LF/HF ratios are showing high values in the diabetic group compared to the control group in the lying posture.

Conclusion: This study suggests that reduction in vagal modulation of RR intervals occurs in the study group. An increase in LF power indicates sympathetic overactivity. This is due to unopposed action of sympathetic activity caused by vagal neuropathy

Keywords: Type 2 Diabetes Mellitus, Cardiac autonomic neuropathy, LF, HF, LF/HF ratio

I. Introduction

Diabetes mellitus type 2 is a metabolic disorder that is characterized by chronic hyperglycemia due to defect in insulin secretion or insulin action or both[1]. It is a chronic, progressive metabolic disorder of polygenic inheritance which is gradually increasing in prevalence because of sedentary lifestyles and adaptation of western food habits. This disorder affects the major organs of the body particularly the Autonomic Nervous System[2]. Diabetes Mellitus is the most common cause for secondary acquired autonomic neuropathy. Hyperglycemia causes increased levels of intracellular glucose in nerves, leading to saturation of the normal glycolytic pathway. Extra glucose is shunted into the Polyol pathway and converted to sorbitol and fructose by the enzymes aldose reductase and sorbitol dehydrogenase. Accumulation of sorbitol and fructose lead to reduced nerve myoinositol, decreased membrane Na^+/K^+ -ATPase activity, impaired axonal transport, and structural breakdown of nerves, causing abnormal action potential propagation. The nonenzymatic reaction of excess glucose with proteins, nucleotides and lipids results in advanced glycation end products that may have a role in disrupting neuronal integrity and repair mechanisms through interference with nerve cell metabolism and axonal transport. The increased production of free radicals in diabetes may be detrimental. These include direct damage to blood vessels leading to nerve ischemia and facilitation of AGE reactions. Also there will be altered gene expression with altered cellular phenotypes, changes in cell physiology relating to endoskeletal structure or cellular transport, reduction in neurotrophins, and nerve ischemia[3].

HRV refers to the beat to beat alteration in heart rate i.e. the oscillation in the interval between consecutive heart beats as well as the oscillation between consecutive instantaneous heart rate. To describe oscillation in consecutive cardiac cycles other terms have been used in the literature, for example, cycle length variability, heart period variability, RR variability, and RR tachogram. Variation in the beat-to-beat interval is a physiological phenomenon. The SA node receives several different inputs and the instantaneous heart rate or RR interval is the sum of these inputs. The main inputs are the sympathetic nervous system and the parasympathetic nervous system. Other factors that affect the input are the baroreceptor reflex, thermoregulator mechanisms, hormones, sleep-wake cycle, meals and stress. HRV appears to be a marker of two processes (1) frequent activation (short term dips in HRV in response to acute stress); and (b) inadequate response (long-term vagal withdrawal, resulting in the over-activity of the counter-regulatory system – i.e. the sympathetic control of cardiac rhythm). Frequency-domain methods are preferred for short-term recordings and normally five-minute recordings are used. The following frequency bands have been defined in humans. i) High Frequency

band (HF) between 0.15 and 0.4 Hz. HF is driven by respiration and appears to derive mainly from vagal activity ii)Low Frequency band (LF) between 0.04 and 0.15 Hz. LF derives from both parasympathetic and sympathetic activity and has been hypothesized to reflect the delay in the baroreceptor loop iii)Very Low Frequency band (VLF) band between 0.0033 and 0.04 Hz.The origin of VLF is not well known, but it had been attributed to thermal regulation of the body's internal systems iv)Ultra Low Frequency (ULF) band between 0 and 0.0033 Hz. The major background of ULF is day–night variation and therefore is only expressed in 24-hour recordings. The ratio of low-to-high frequency spectra power(LF/HF) is has been proposed as an index of sympathetic to parasympathetic balance of heart rate fluctuation. The measurement of VLF, LF, and HF power components is usually made in absolute values of power (milliseconds squared). LF and HF may also be measured in normalized units, which represent the relative value of each power component in proportion to the total power minus the VLF component. The representation of LF and HF in normalized units emphasizes the controlled and balanced behaviour of the two branches of the autonomic nervous system. Moreover, the normalization tends to minimize the effect of the changes in total power on the values of LF and HF components. Nevertheless, normalized units should always be quoted with absolute values of the LF and HF power in order to describe completely the distribution of power in spectral components[4].

This study is undertaken to show that frequency domain analysis of HRV can be used as a tool to predict adverse cardiovascular events due to cardiac autonomic neuropathy and assess the balance between the sympathetic and parasympathetic influences on the heart in type II Diabetes Mellitus patients.

II. Materials And Methods

The study was undertaken after obtaining clearance from the Institutional Ethical Committee. 30 type 2 Diabetes Mellitus patients attending Diabetic OPD of Stanley Medical College and Hospital, Chennai were recruited for the study.The subjects were briefed about the procedure and a written consent was obtained from them. Patients in the age group 30 to 40 years whose fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) or with a Glucose tolerance test, two hours after the oral dose a plasma glucose ≥ 11.1 mmol/l (200 mg/dl) based on the WHO criteria were included in the study[1]. Patients with history of autonomic dysfunction, respiratory disorders, liver disorders, smokers, alcoholics, hypertension and coronary artery disease are excluded from the study. The control group was obtained from 30 normal volunteers attending Master Health Check-up OPD of Govt. Stanley Medical College Hospital.

The tests were performed in the Neurophysiology lab of the Department of Physiology, Stanley Medical College, Chennai between 10 AM and 1 PM. The lab environment was quiet , the temperature was maintained between 25 to 28°C and the lighting subdued. Subjects were asked to empty their bladder before the tests. The test did not involve any intravascular instrumentation or administration of any drugs at any stage. The subjects were made to sit in the lab for 10 minutes to get accustomed to the new environment. The subjects were clearly instructed not to take coffee, tea or cooldrinks 1½ hours before test. Thorough clinical examination was performed to rule out any acute or chronic illness and also for autonomic dysfunction. The subjects height in meters and weight in kilogram was measured.

2.1.Equipment

ECG was acquired using RMS Polyrite D hardware 2.2 (India), and instantaneous heart rate at RR intervals were plotted using RMS 2.5.2 software on a Microsoft window based PC. The RMS Polyrite 2.5.2 helps to save multiple records and provided with additional filter settings, calculation tools, automated analysis and auto report generation. Respiratory movements were recorded using respiratory belt which analyses inspiration and expiration.

2.2.ECG recording

A.Electrodes were fixed in the following position after cleaning with spirit to record the ECG

Electrode	Position
Exploring Electrode	Left shoulder
Exploring Electrode	Right shoulder
Reference Electrode	Right leg

B. Respiratory belt was tied around the chest at the level of the nipple to record respiratory movement

C.The electrodes and the respiratory belt were connected to RMS Polyrite D equipment

i) HR and HRV response to Lying - ECG was recorded for 10 minutes to determine the HRV at supine rest with the eyes closed with normal quiet respiratory movement

ii) HR and HRV response to standing - After recording in the supine position the subject is asked to stand without support on a wooden plank within 3 seconds and his BP and HR were recorded at the end of 5 sec, 2 min and 5 min after assumption of standing position.

2.3.Blood glucose estimation: Serum concentration of glucose was estimated by Glucose oxidase method in the central laboratory of Stanley Medical College and Hospital.

III. Results

The study shows that the resting heart rate, systolic BP and diastolic BP were significantly higher in the diabetic group compared to the controls. Frequency domain analysis shows that the LF and LF/HF ratios were significantly higher in the diabetic group compared to the controls in the lying down position. HF values were significantly lower in the diabetic group compared to the control group in the lying down position. The frequency domain values were not statistically significant in the standing position.

IV. Figures and Tables

Table 1 Comparison of Resting heart rate and blood pressure

	Case n=30		Control n=30		Student independent t test
	Mean	SD	Mean	SD	
RHR	88	5.38	75.6	5.09	t=9.15, p<0.001 significant
SBP	134.8	5.1	118.06	8.6	t=9.12, p<0.001 significant
DBP	89	4.22	78.73	6.71	t=7.08, p<0.001 significant

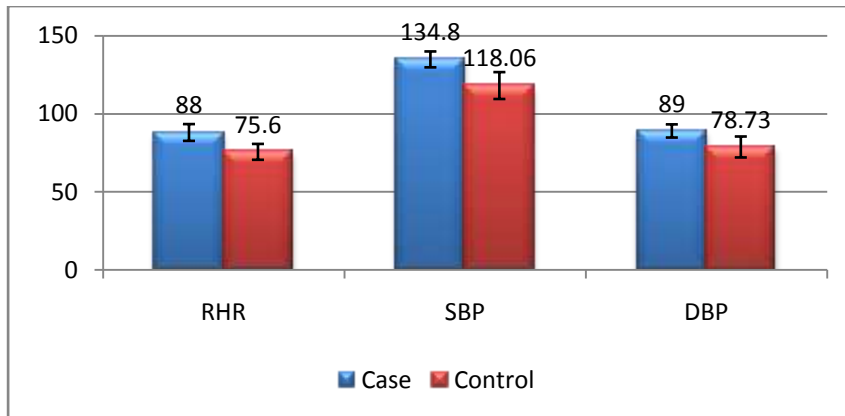


Figure.1

Table 2 Changes in Frequency Domain measures during lying

Frequency Domain Measures in ms ²	Case		Control		Student independent t test
	Mean	SD	Mean	SD	
LF	75.74	6.25	71.22	6.54	t=2.73 p=0.008, significant
HF	23.26	5.58	30.57	5.61	t=5.05 p<0.001, significant
LF/HF	3.66	0.89	2.44	0.69	t=5.87 p<0.001, significant

There was a significant decrease in the HF component in cases when compared to controls in lying posture (p<0.001). The values of LF and LF/HF ratio are showing significantly high values in lying.

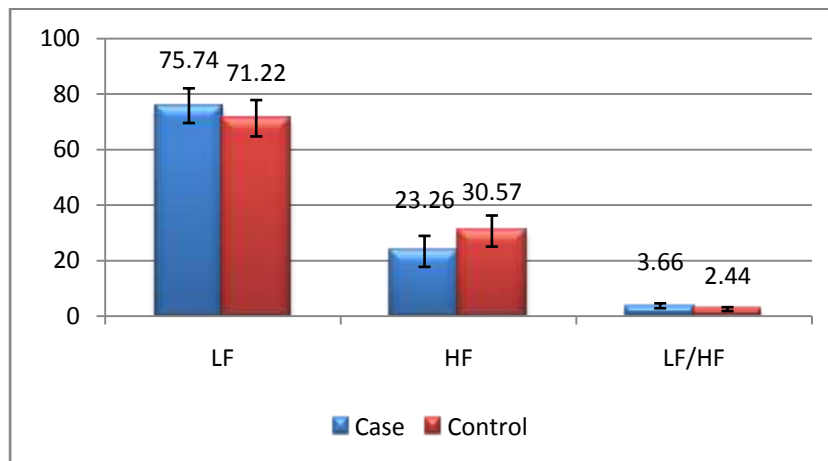


Figure.2

Table 3 Changes in Frequency Domain measures during standing

Frequency Domain Measures in ms ²	Case n=30		Control n=30		Student independent t test
	Mean	SD	Mean	SD	
LF	82.56	8.79	81.26	4.75	t=0.711 p<0.48, not significant
HF	18.72	7.56	20.65	3.07	t=1.29 p<0.19,not significant
LF/HF	5.06	2.28	4.01	0.66	t=2.40 p<0.019, significant

There were no significant changes in Frequency Domain measures during standing between the diabetic group and the control group.

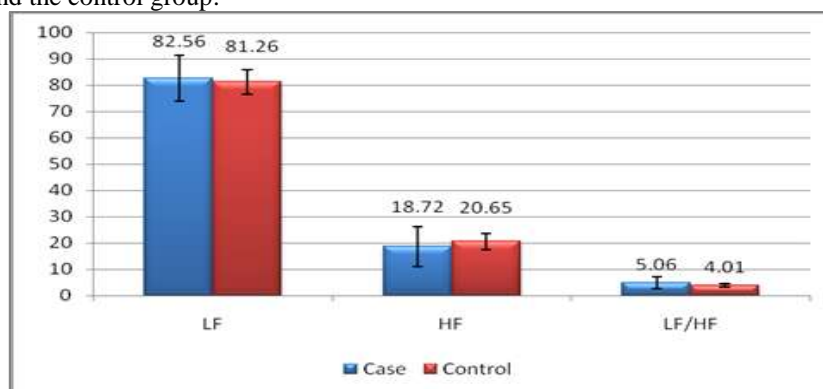


Figure.3

V. Discussion

The present study shows a significant increase in the resting heart rate in the Diabetic group compared to control. According to D.J.Ewing et al the increased resting heart rates in diabetics may be due to cardiac parasympathetic damage alone and in others to combined parasympathetic and cardiac sympathetic damage. The sequential heart rate changes support the view that the vagus nerve is affected before the cardiac sympathetic nerves[5]. An elevated resting heart rate is an independent risk factor for sudden death in middle aged men[6]. The systolic and diastolic blood pressures in diabetic group is more than the control group. Hypertension is common in newly diagnosed type 2 diabetes and is associated with obesity[7].

In our study, the LF values and LF/HF ratios were significantly higher and the HF values were significantly lower in the diabetic group compared to the control group in the lying posture. Veglio et al (1996) showed that patients with symptoms of autonomic neuropathy had values for heart rate response to deep breathing and to standing significantly lower than those without autonomic neuropathy[8] Paganì et al (2000) found that normalized units provide an estimate of the balance between sympathetic and vagal modulatory activity.

In our study, LF component and LF/HF ratios were higher in the study group but were not statistically significant. Similarly HF component was lower in the study group in standing position compared to controls but were not statistically significant. In states of sympathetic predominance, such as during orthostatic positions, LF increases and HF decreases[9]. Hejjet et al (2001) proved that the beat-to-beat fluctuation of the heart rate originates from the momentary summing of sympathetic and parasympathetic influences on the sinus node[10].

Vinik et al(2003) showed that reduced cardiovascular autonomic function as measured by heart rate variability (HRV) is strongly associated with an increased risk of silent myocardial ischemia. Regular HRV testing provides early detection and thereby promotes timely diagnostic and therapeutic interventions[3]. Colberg SR(2003) found that individuals with diabetic autonomic neuropathy (DAN) exhibit an increased resting heart rate but depressed maximal heart rate[11]. Sztajzel et al(2004) proved the use of HRV as a marker reflecting the activity of the sympathetic and vagal components of the ANS on the sinus node, and as a clinical tool for screening and identifying patients particularly at risk for cardiac mortality[12]. Manzella D et al(2005) showed that reduced cardiovascular autonomic function, as measured by heart rate variability, is strongly associated with an increased risk of silent myocardial ischaemia and mortality[13]. Gottsater A et al (2006) found that decreased heart rate variability may predict the progression of carotid atherosclerosis in type 2 diabetes. A low LF HRV may predict the progression of atherosclerosis in these patients[14]. Perciaccante A et al (2006) showed that in type 2 diabetes mellitus both insulin resistance and hyperglycemia are considered responsible for autonomic dysfunction[15]. Urbancic-Rovan et al(2007) found that patients with diabetes have increased sympathetic and decreased parasympathetic cardiac activity regardless of the presence of autonomic

neuropathy[16]. Akselrod et al found that power spectrum analysis of heart rate fluctuations provides a quantitative noninvasive means of assessing the functioning of the short-term cardiovascular control systems[17]. Impaired blood flow to peripheral nerve trunks makes a major contribution to the neuropathic complications of diabetes mellitus(Cameron NE et al ,2001)

VI. Conclusion

Heart Rate Variability in type II Diabetes Mellitus individuals have shown that the High Frequency component were significantly lower in the lying position in the diabetic group indicating vagal neuropathy. Low frequency and LF/HF ratio were significantly higher in the lying position in the diabetic group indicating unopposed sympathetic activity. In the standing position, though the HF component was lower in the diabetic group, the values were not statistically significant. Likewise the LF component and the LF/HF ratios were higher in the diabetic group, but were not statistically significant.

The present study shows that cardiac autonomic neuropathy occurs in Diabetes Mellitus and the involvement of vagus occurs earlier than the involvement of sympathetic nerves. Frequency domain analysis of Heart Rate Variability is used to assess the cardiac autonomic neuropathy before the onset of clinical features and therefore play a crucial role in the prevention of cardiovascular morbidity and mortality.

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