Original article:

Heart rate variability in type 1 diabetes mellitus patients

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ABSTRACT:

INTRODUCTION: Diabetes mellitus (DM) is a leading cause of morbidity in India. Its long term complications include Cardiac Autonomic Neuropathy (CAN). Heart rate Variability is a simple non invasive tool to assess CAN in these individuals. Assessment of Cardiac Autonomic Neuropathy in Type 1 Diabetes mellitus patients using Heart Rate Variability as an investigative tool was our aim.

MATERIALS & METHODS:HRV was recorded for30 type 1 DM individuals for 20 minutes at supine rest and compared with 30 Age & gender matched normal healthy individuals.

RESULTS: All time domain indices were significantly reduced ($p < 0.05$*) in cases. In frequency domain measures LF/HF ratio was significantly increased & HF was significantly reduced in cases.

CONCLUSION: This study has effectively shown that autonomic dysfunction can be detected very early, even in the asymptomatic period, using HRVanalysis.

KEY WORDS: Type 1 Diabetes, Heart rate Variability, Cardiac Autonomic Neuropathy

INTRODUCTION

Diabetes mellitus (DM) is considered an important health, economic and social problem owing to the long-term complications such as premature death[1,2].Furthermore, the DM complications like neuropathies and renal failure increase the morbidity and cardiovascular mortality[3]. For this reason, the global health care expenditure on complications rises each year [4].CAN in diabetes has been called a 'silent killer'[5] .Type 1 diabetes is a chronic autoimmune disease in which destruction or damage to the beta-cells in the islets of Langerhans results in insulin deficiency and hyperglycemia[6].The National Diabetes Data Group and World Health Organization have issued diagnostic criteria for Diabetes mellitus which includes symptoms of diabetes plus random blood glucose concentration ≥11.1mmol/L (200 mg/dl) or Fasting plasma glucose ≥7.0mmol/L (126mg/dl) or Two-hour plasma glucose ≥ 11.1 mmol/L (200mg/dl) during an oral glucose tolerance test[7] Individuals with long standing type 1 DM may develop signs of autonomic dysfunction. DM-related autonomic neuropathy can involve multiple systems including the cardiovascular, gastrointestinal, genitourinary and metabolic systems. Autonomic neuropathies affecting the cardiovascular system cause a resting tachycardia and orthostatic hypotension. Heart rate variability is a non-invasive estimate of the function of sympathetic and parasympathetic nervous system. It is a window for analyzing ANS. HRV indices are the earlier markers of CAN[8]

AIM & OBJECTIVE:

To study the Cardiovascular Autonomic function in Type 1 Diabetics by doing Heart Rate Variability(HRV) analysis .

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MATERIALS AND METHODS

The study was conducted in the Neurophysiology Lab of the Department of Physiology, Stanley Medical College, Chennai.

CASES:

INCLUSION CRITERIA

Type 1 Diabetes mellitus patients (based on WHO criteria) attending Diabetology out-patient department

Age: 10 to 30 years, both gender

Type 1 diabetic patients on Insulin treatment and with fairly good glycemic control

Type 1 DM patients with duration of disease > 2 years

EXCLUSION CRITERIA

Smokers , Alcoholics, Hypertension, Coronary artery disease, Renal disorders, Psoriasis ,Thyroid disorders and patients with history of autonomic dysfunction

CONTROLS

30 age and gender matched healthy subjects attending the Master health check up programme, Stanley Medical College.

Study Design : Case Control Study

The study protocol was approved by the Ethical committee of Stanley Medical College. The detailed procedure and purpose of the study was explained in the regional language, and then an informed and written consent was obtained from the subjects if they were 16 years of age or over and from their parents if they were younger than 16 years.

EQUIPMENT FOR HRV :

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 transducer.

METHODOLOGY OF HRV

The recordings were done between 10 a.m. and 12.00 noon.

The subjects were clearly instructed not to take coffee, tea or cool drinks 1½ hours before test.

Height and weight were taken. Blood Pressure was recorded using sphygmomanometer. 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 test. 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 20 minutes to get accustomed to the new ambient environment. ECG Lead II was recorded in supine rest with normal respiratory rate of 12 to 16 per minute. Task force[9] guidelines were followed.

RESULTS

Statistical Package for Social Sciences (SPSS) software 11.5 version was used for statistical analysis. The Student independent unpaired ‘t‘ test was used to compare cases and controls

TABLE 1

ANTHROPOMETRIC MEASUREMENTS OF SUBJECTS

(Age, Height, Weight & BMI expressed as Mean ± SD)

	CASES	**CONTROLS**	**'t'value**	**p value**
n	30	30	-	-
Males:Females	18:12	18:12	-	-
Age in years	23.06 ± 6.06	22.86 ± 5.92	0.12	0.89
Height in cm.	155.96 ± 9.25	156.80 ± 9.57	-0.34	0.73
Weight in kg.	53.83 ± 7.86	54.23 ± 7.88	-0.19	0.84
B.M.I. kg/m2	22.07 ± 2.31	21.98 ± 2.17	0.15	0.87

BMI – Body Mass Index

The parameters were analyzed using Student independent unpaired 't'test.

p< 0.05* is taken as significant

TABLE 2

HEART RATE & BLOOD PRESSURE MEASUREMENTS

	GROUP (n=30)	**MEAN**	**STANDARD DEVIATION**	**Student independent 't' test**
Resting Heart rate in bpm	Cases	87.3	8.4	t = 4.05 **p < 0.01****
	Controls	76.4	12.01	
Systolic B.P. (mm.Hg.)	Cases	120.60	5.61	t=1.597 p=0.116
	Controls	118.00	6.92	
Diastolic B.P. (mm.Hg).	Cases	79.40	4.64	t=0.858 p=0.395
	Controls	78.33	4.98	

The parameters were analyzed using Student independent unpaired 't'test.

p< 0.05* is taken as significant ;p < 0.01** is taken as highly significant.

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TABLE 3

COMPARISON OF BLOOD SUGAR LEVEL

	GROUP (n=30)	**MEAN**	**STANDARD DEVIATION**	**Student Independent 't' test**
Fasting mg%	Cases	124.06	18.20	t= 12.22
	Controls	82.33	4.29	p< 0.01**
Post prandial mg%	Cases	158.34	31.22	t=8.77
	Controls	107.93	3.94	p<0.01**

The parameters were analyzed using Student independent unpaired t'test.

p< 0.05* was taken as significant ;p < 0.01** was taken as highly significant.

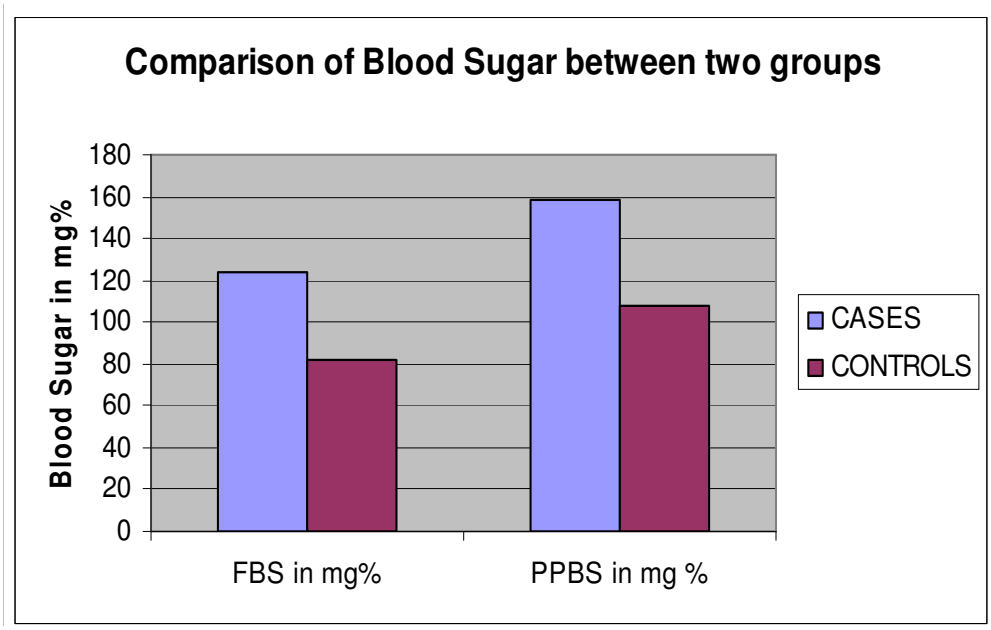

TABLE 4

CHANGES IN FREQUENCY DOMAIN MEASURES DURING SUPINE REST

Frequency Domain Measures	**Cases (n=30)**		**Controls (n=30)**		Student independent 't' test
	Mean	**SD**	**Mean**	**SD**	
Mean RR in sec.	0.69	0.07	0.80	0.12	t=-4.019 p< 0.01**
LF ms²	23.21	13.99	15.18	12.45	t= 2.34 p< 0.05*
HF ms²	7.7	6.0	17.22	14.84	t= -3.25 p< 0.01**
LF/HF	3.46	1.88	1.16	0.75	t=6.20 p< 0.01**
TOTAL POWER ms²	30.91	18.69	32.40	23.70	t=-0.27 p=0.788
LF n.u.	74.29	8.80	49.11	14.97	t= 7.94 p< 0.01**
HF n.u.	25.50	8.79	50.87	14.91	t= - 8.02 p< 0.01**

p< 0.05* was taken as significant ;p < 0.01** was taken as highly significant

TABLE 5

CHANGES IN TIME DOMAIN MEASURES DURING SUPINE REST

Time Domain Measures	Cases (n=30)		Controls (n=30)		Student independent 't' test
	Mean	SD	Mean	SD	
SDNN in ms	28.54	13.45	56.61	23.42	t= - 5.69 p<0.01**
RMSSD in ms	24.48	12.73	68.57	28.04	t=- 7.84 p<0.01**
NN50 Count	9.73	14.48	116.83	74.26	t= - 7.75 p<0.01**
pNN50%	2.42	3.84	33.55	23.56	t= - 7.14 p<0.01**

The parameters were analyzed using Student independent unpaired't'test.

p< 0.05* was taken as significant ;p < 0.01** was taken as highly significant

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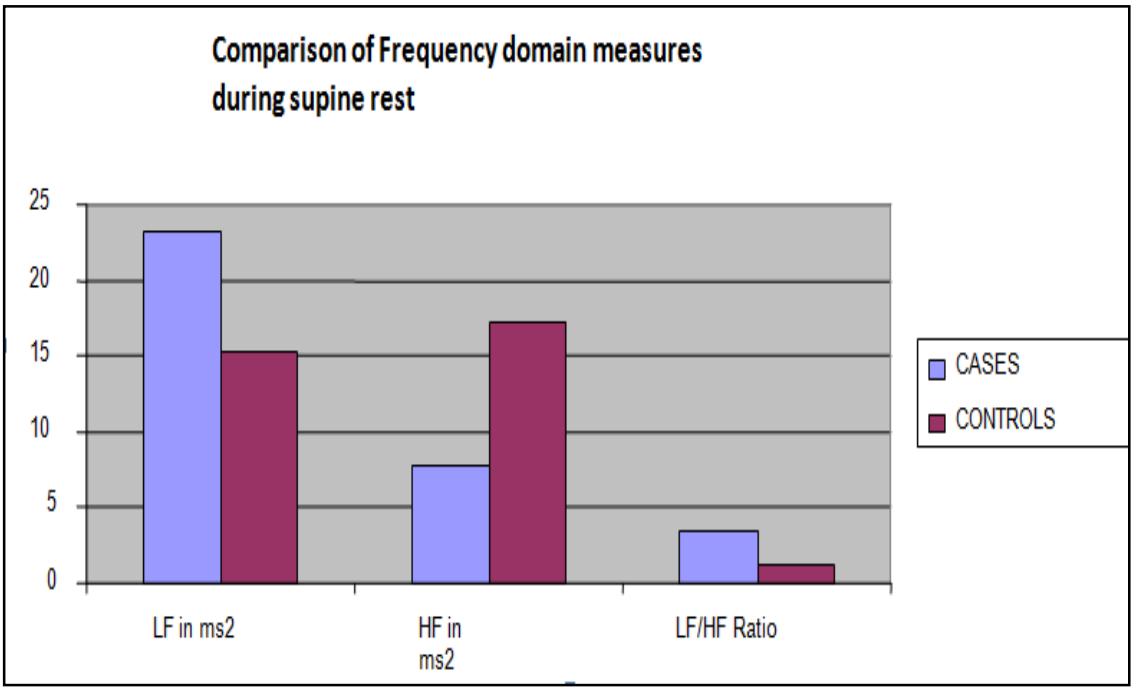
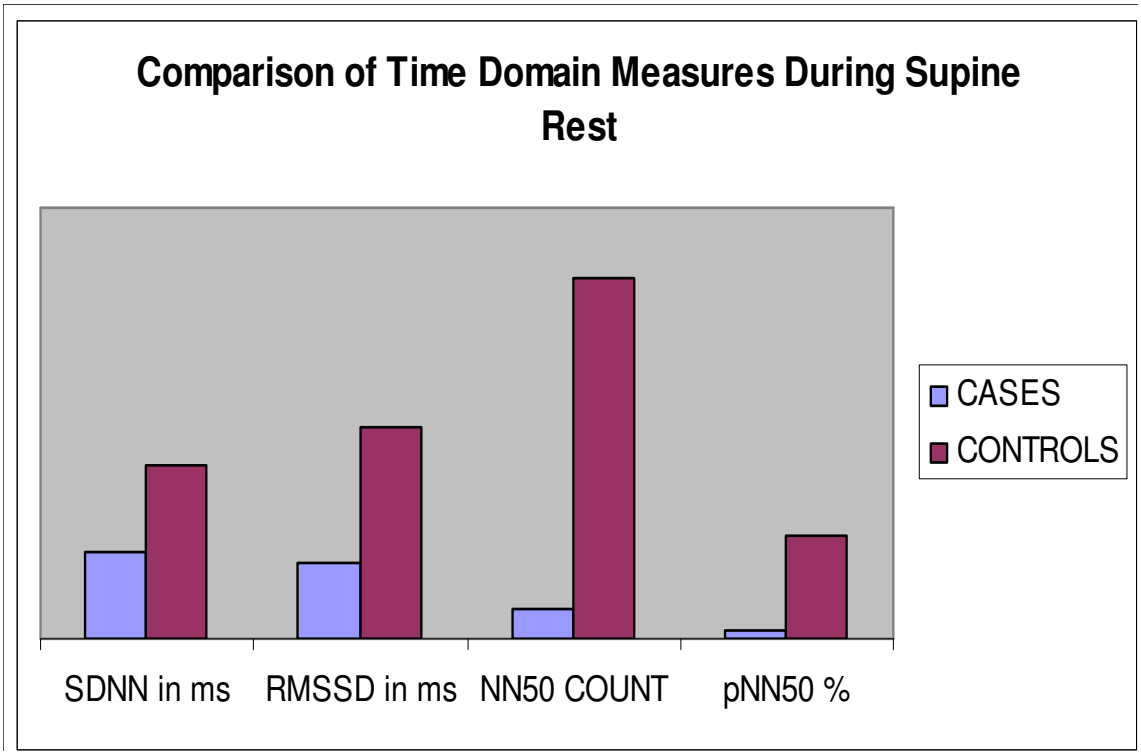

Comparison of Frequency domain measures during supine rest
25
20
15
10
5
0
LF in ms2
HF in ms2
LF/HF Ratio
CASES
CONTROLS


Comparison of Time Domain Measures During Supine Rest
SDNN in ms
RMSSD in ms
NN50 COUNT
pNN50 %
CASES
CONTROLS

DISCUSSION:

In type 1 diabetes mellitus, Cardiovascular autonomic neuropathy (CAN) is ultimately the result of complex interactions among degree of glycemic control, disease duration and systolic and diastolic blood pressure (Witte DR et al 2005)[10]. Experimental data implicate a number of pathogenic pathways that may impact autonomic neuronal function in diabetes including formation of advanced glycation end products, increased oxidative/nitrosative stress with increased free radical production, activation of the polyol and protein kinase C pathways, activation of poly ADP ribosylation and activation of genes involved in neuronal damage (Vinik AI et al 2003) [11].Chronic hyperglycemia promotes progressive autonomic neural dysfunction. The vagus nerve, the longest autonomic nerve, mediates 75% of all parasympathetic activity (Ziegler D et al 1992) [12]. Neuropathy is seen first in the longest fibers- the earliest manifestation of autonomic neuropathy in diabetes tends to be associated with parasympathetic denervation [13] .Rodica Pop-Busui et al (2010) [14] confirm that early in the progression of CAN complicating type 1 diabetes, there is a compensatory increase in the cardiac sympathetic tone.

Clinical symptoms of autonomic dysfunction may not appear until long after diabetes onset. However, subclinical CAN, manifested as changes in HRV, may be detected within 1 year of diagnosis in type 2 diabetes and within 2 years of diagnosis in type 1 diabetes (Pfeifer et al 1984) [15].

The Resting heart rate was significantly increased in the Type 1 diabetic patients compared to controls ($p<0.01$**).This resting tachycardia is due to vagal impairment associated with a relative increase in the sympathetic activity . This is similar to the findings observed in the review by Vinik AI et al (2003) [11]

FREQUENCY DOMAIN MEASURES:

It is an index of parasympathetic modulation of instantaneous heart rate and is also dependent upon the sensitivity of effectors to acetylcholine. The efferent vagal activity is a major contributor of the HF component as seen in clinical and experimental observations of autonomic maneuvers such as electrical vagal stimulation, muscarinic receptor blockade and vagotomy (Akselrod et al 1981) [16].In accordance basal High frequency power is significantly reduced in the diabetics compared to controls ($p<0.01$**). HF nu which represents parasympathetic activity was significantly lower in the diabetic group. The LF component is considered by some as a marker of sympathetic modulation, especially when expressing it as normalized units and by others as a parameter that includes both sympathetic and parasympathetic influences. LF power was significantly increased in diabetics compared to controls ($p<0.05$*). LF nu was highly significantly increased in diabetics. LF/HF ratio is considered to mirror sympatho-vagal balance (Malik M et al 1993) [17]. LF/HF was significantly increased in the diabetic group. Type 1 diabetics exhibit altered sympatho-vagal balance with decreased parasympathetic activity at the cardiac level. Similar changes in HRV parameters were observed by Massimo Chessa et al 2002[13]

TIME DOMAIN INDICES:

The variations in heart rate may be evaluated by a number of methods. Perhaps the simplest to perform are the time domain measures. The simplest variable to calculate is the standard deviation of the NN intervals (SDNN) that is, the square root of variance. Since variance is mathematically equal to total power of spectral analysis, SDNN reflects all the cyclic components responsible for variability in the period of recording. The SDNN was significantly decreased in type 1 diabetics.The findings are in accordance

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with the results of Dariusz Korczak et al 1997 [8] In our observations, RMSSD and pNN50 was significantly reduced . NN50 count was also reduced significantly in the cases ($p < 0.01$**).All these observations are a pointer towards a reduced parasympathetic activity in diabetics. The most frequent finding in subclinical CAN is reduced heart rate variability (Ziegler D et al 1994) [18].

LIMITATIONS:

1. HbA1C was not estimated for Type 1 DM patients
2. C-peptide was not assessed for Type 1 DM patients

CONCLUSION:

HRV analysis can detect early subclinical alterations of the autonomic nervous system in asymptomatic patients with Type 1 diabetes mellitus which is mainly a parasympathetic impairment. Early detection of Cardiac autonomic dysfunction will help to motivate patients to improve their diabetes control and thereby delay the development of complications.

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