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CARDIAC AUTONOMIC FUNCTIONS ARE COMPROMISED IN DIABETES MELLITUS – A STUDY ON SOUTH INDIAN ELDERLY PATIENTS

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ABSTRACT: Diabetes is known to affect almost all functions of the body. Long standing diabetics show several detrimental symptoms including in the heart. Diabetic neuropathy affects the cardiac autonomic function and may be reflected in the HRV (Heart rate variability). In the present study, we investigated the HRV in elderly diabetic patients in two groups, viz. moderate (FBS <126 mg/dl) and those with more FBS (FBS>126) and compared the results of Lipid profile, glycosylated Hb and HRV(both normal breathing, nb & Deep breathing, db) with the parameters in age matched controls. We found that the glycosylated Hb was significantly more in diabetics and it is proportional to the FBS ($p<0.001$). The HRV was found to be lower in diabetic patients. However in the moderate diabetic patients the HRV did not show significant decline, but in severe diabetics, it was significantly lower. From our studies we could reconfirm the decline in the cardiac autonomic control over a period in diabetic patients over and above the age related decrease in HRV. Therefore this result will also reinforce that HRV could be useful for analysis of the diabetic neuropathic effect on the heart.

Key words: Heart rate variability, diabetes mellitus and Elderly Patients

INTRODUCTION

Diabetes is a debilitating disease which affects several million people worldwide. It is a metabolic and endocrine disease with a socio-cultural origin also and therefore it can be called a life style disease. India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed “diabetes capital of the world”. According to the Diabetes Atlas 2006 published by the International Diabetes Federation, the number of people with diabetes in India (currently around 40.9) is expected to rise to 69.9 million by 2025 unless urgent preventive steps are taken (Mohan,S. et al. 2007). Many people with type 2 diabetes mellitus (DM) suffer from cardiac autonomic neuropathy (CAN) which leads to impaired regulation of blood pressure, heart rate and heart rate variability (HRV) (Vinik AI,et al. 2003). Cardiac autonomic neuropathy can be assessed by heart rate variability analysis(Rollins MD,et al. 1992). Changes in HRV is regarded as one of the early signs of cardiac autonomic neuropathy (Rollins MD,et al. 1992; Spallone V, Menzinger G 1997, Pavy-Le Traon A, et al. 2010). An assessment by of heart rate variability which is a noninvasive, reliable and easy method can be of value (Bellavere F: 1995).

Cardiovascular autonomic diabetic neuropathy (CADN) is also associated with reduced heart rate variability. Such patients have poor cardiovascular prognosis, with 5-year mortality greater than 50%. Some of these may be attributed to micro- or macrovascular diseases. Clinically detectable autonomic failure is usually evident many years or decades after the onset of diabetes. It is likely that these patients develop subtle deficits in HRV much earlier, and these may include diminution in time-domain analysis. Detection of such changes may be used as markers of pathology, particularly to study the benefits of therapeutic interventions. Diabetes with symptoms of autonomic neuropathy is associated with a marked reduction or even absence of heart rate variation when compared with normal subjects (Awdah Al-Hazimi, et al. 2002). Results of the tests of parasympathetic functions are commonly abnormal in diabetics than tests of sympathetic functions. The parasympathetic damage occurs more commonly in diabetics and its onset is earlier in the history of this disorder. However autonomic function tests have been shown to worsen with time and more so in some diabetics who have both parasympathetic and sympathetic damage (DJ Ewing, Clarke PF. (1982). Abnormal heart rate variability in diabetics increased risk for ventricular arrhythmias, as well as total cardiovascular morbidity and mortality (Shephard RJ, Balady GJ. (1999). Recent advances in technology have enabled accurate recordings and the automated analysis of 24-hour ECG to detect beat-to-beat variability, providing not only more detailed, but much more precise information than the earlier tests[5]. Apart from this, HRV during Valsalva maneuver, deep breathing standing up also can be used to assess cardiovascular reflexes and reflect parasympathetic component of autonomic functions (Malpas SC, Maling TJ: 1990; Tarsy D, Freeman R: 1994). Frequency domain measures can be used to quantify sympathetic component of autonomic function (Bellavere F, *et al*: 1992).

MATERIAL AND METHODS

This study was conducted in a diabetic camp held by ASHRAYA GROUP, KASTURBA MEDICAL COLLEGE, which is a free geriatric clinic. Fifty (50) type 2 diabetes mellitus patients who attended the camp and 20 age matched healthy subjects (age group 50-70years) were included in this study. Ethical clearance obtained from "INSTITUTIONAL ETHICS COMMITEE", KMC MANGALORE, MANIPAL UNIVERSITY. Informed consent was taken from each patient.

Grouping: Diabetic patients are grouped into those having FBS less than 125 mg/dl and those who had more than 125 mg/dl. All patients both male and females were included.

GROUP 1- Control, 50 – 70 years, FBS <106mg/dl (n=20)
GROUP 2- Diabetic, 50-70 years, FBS<126mg/dl (n=23)
GROUP 3- Diabetic, 50-70 years, FBS>126mg/dl (n=27)

The examination of the subject was carried out in fasting condition with empty stomach in the morning.

A detailed clinical history with relevant past history, family history, drug history and personal history was taken. General physical examination, vital signs and complete medical examination was done.

INCLUSION CRITERIA: Patients were classified as having diabetes on the basis of history, regardless of duration of disease.

EXCLUSION CRITERIA: Patients with history of myocardial infarction, congestive cardiac failure were excluded. Patients with respiratory ailments and those patients who cannot undergo deep breathing tests were also not included.

METHODS: Heart rate variability in Deep Breathing (HRV-db)

HRV – db is approximately double than during quiet breathing. So due to larger variation in intervals, HRV – db is probably more precise measure of cardiac autonomic function. Recently HRV-db has been shown to be an independent prognostic marker after myocardial infarction (Task Force, 1996).

SDANN: The standard deviation of the average NN intervals calculated over short periods, usually 5 minutes which is an estimate of the changes in heart rate due to cycles longer than or equal to 5 minutes (Wheeler T,Watkin's PJ. (1973).

MEASUREMENT OF HRV.

1) ECG appliance with jelly and electrode.

2) Digital data acquisition system.

3) HRV soft 1.1 VERSION , AIIMS,NEW DELHI.

A high quality ECG was recorded under standardized condition to minimize artifacts, using a standard 12 lead ECG machine. The ECG signal is first recorded, analog & then digitally converted. Analysis of this in time domain was done using 1.1 VERSION, AIIMS, NEW DELHI.

Recording was done in the morning between 8.30 to 9.30 am in a cool room temperature between 20 to 28 degree Celsius. They were requested to come in a relaxed condition & quiet mood. They were requested to breathe spontaneously at their own comfortable. After a resting period, the subject's ECG was recorded in the supine position during normal breathing for 2 minutes. Then the next ECG was taken during deep breathing for 1 minute. The subject was asked to inspire for the first 5 seconds from the count of 1 to 5 and then expire the next 5 seconds from the count of 5 to 1. This recording was taken for 6 such cycles i.e 1 minute.

Apart from the HRV, other parameters namely the fasting blood glucose (FBS), HB_1Ac, lipid profile (Total cholesterol, triglycerides and LDL), BMI, W/H ratio were also recorded meticulously from the laboratory report.

The procedure was explained to them and a signed consent was obtained from each subject. Prior approval was obtained from the institutional ethics committee for the study.

STATISTICS: Statistical analyses was done using MANN WHITNEY U TEST. p value was taken as significant at 5 percent confidence limit($p<0.05$).

RESULTS

Table 1: Comparison of parameters between control & diabetic patients.

	CONTROL		DIABETIC			
	Median	IR	Median	IR	Z	P
Hb1Ac(mg/dl)	5.7	0.5	7.4	1.4	-6.186	0.001vhs
Cholesterol(mg/dl)	190.0	10.0	216.0	46.25	-3.602	0.001vhs
Triglyceride(mg/dl)	158.0	4.0	146.0	67	-1.807	0.071
LDL(mg/dl)	118.0	5.0	138.0	27.25	-3.705	0.001vhs
BMI	23.10	1.0	24.65	4.85	-2.385	0.017sig
W:H	0.9	0.04	0.92	0.11	-0.881	0.378
SDANN(nb)	15.9	6.0	13.79	10.26	-2.257	0.024sig
SDANN(db)	25.8	4.8	18.63	17.02	-2.519	0.012sig

sig – significant ($p<0.05$)
vhs – very high significance ($p<0.001$)

Table 2: Comparison of parameters between group 1 (Control) and group 2 (Diabetic, 50-60 years, FBS<126mg/dl).

	Control		Group 2			
	Median	IR	Median	IR	Z	p
Hb1Ac(mg/dl)	5.7	0.5	7.2	0.80	-3.86	0.001vhs
Cholesterol(mg/dl)	190.0	10.0	217.0	30.0	-3.77	0.001vhs
Triglyceride(mg/dl)	158.0	4.0	145.0	40.0	-0.625	0.532NS
LDL(mg/dl)	118.0	5.0	138.0	35.00	-3.884	0.001vhs
BMI	23.10	1.0	22.89	5.80	-0.431	0.667 NS
W:H	0.9	0.04	0.90	0.09	-0.043	0.965 NS
SDANN(nb)	15.9	6.0	14.02	15.3	-0.539	0.590 NS
SDANN(db)	25.8	4.8	24.24	18.22	-0.861	0.389 NS

Table 3: Comparison of parameters between group 1(Control) & group 3 (Diabetic, 50-60 years, FBS>126mg/dl).

	Control		GROUP 3			
	Median	IR	Median	IR	Z	p
Hb1Ac(mg/dl)	5.7	0.5	8.1	1.7	-4.219	0.001vhs
Cholesterol(mg/dl)	190.0	10.0	219.0	48.50	-4.213	0.001vhs
Triglyceride(mg/dl)	158.0	4.0	150.0	57.0	-0.369	0.712 NS
LDL(mg/dl)	118.0	5.0	141.0	18.5	-3.454	0.001vhs
BMI	23.10	1.0	24.91	2.29	-2.889	0.004sig
W:H	0.90	0.04	0.90	0.16	-0.372	0.710 NS
SDANN(nb)	15.90	6.0	11.90	11.50	-0.320	0.01Sig
SDANN(db)	25.80	4.80	22.83	17.12	-0.025	0.05Sig

The results of our study showed a significant increase in the HbA1c in the diabetic patients compared to the controls (Table 1, 2, 3). The level of HbA1c was proportional to the diabetic control and duration of diabetes; that is in a long standing diabetic patient, the level of Glycosylated Hb was more ($p<0.001$). We also observed an increased total Cholesterol and LDL levels in diabetic subjects ($p<0.001$), while their TG level was not different from controls. The BMI in moderate diabetics was not significantly more compared to controls but that in diabetics with more FBS than 126 mg/dl showed significantly higher BMI ($p<0.01$).

Heart rate variability in normal breathing and deep breathing (SDANN (nb) & SDANN (db)) were estimated. We found that there was a decline in the diabetic subjects (Table 1; $p<0.05$). However on comparison of moderate diabetics HRV with controls, there was no statistically significant decline, whereas the decline in HRV was significant in severe diabetics (SDANN(nb) $p<0.001$; SDANN(db) $p<0.05$).

DISCUSSION

In the present study HRV was measured in 50 diabetic subjects and 20 normal subjects in the age group of 50 to 70 years. The result showed that diabetic patients had a statistically lower HRV compared to the healthy controls. The result correlates with previous studies of Wheeler and Watkins in 1973 who observed that diabetics have a marked reduction of HRV when compared with normal subjects (Schroeder EB, et al. 2005). This observation has been confirmed subsequently by many others (Vinik AI, et al. 2003). Diabetes is an organic disorder in which several of changes takes place in the body. The pathophysiology involves almost all the tissues. The autonomic nerves being affected by diabetes mellitus shows the signs of neuropathy. This could be the cause for the altered autonomic control on the heart in chronic diabetics. In the present study we included male diabetes patients who had moderate and high FBS (Group 2 & Group 3). The diabetic patients with higher FBS (>126 mg/dl) had significantly lower HRV than the moderately diabetic patients (Table 2, Table 3) and the HRV in controls. This finding is in agreement with the views expressed by other authors. The lower HRV in severe diabetes could point out at the higher neuropathic damage in such patients. Low HRV is reportedly associated with cardiovascular morbidity and mortality. Therefore diabetics are more susceptible to heart attacks and death due to cardiovascular disorders. Schroeder and coworkers investigated the consequence of diabetes and pre diabetic metabolic impairments on the 9 year change in heart rate variability and observed that diabetic subjects had a rapid decrease in HRV than non-diabetic subjects and they also found cross sectional associations between decreased HRV and diabetics (Schroeder EB, et al. (2005). Studies conducted in our laboratory earlier also showed similar results as far as HRV changes were concerned (Bhagyalakshmi S, 2007). They discovered that there was marked improvement in the cardiac autonomic control following integrated exercise in the diabetic patients.

In the present study we observed that those patients with well controlled diabetes (Group 1) showed a higher HRV than those with poor control (Group 2). Masaoka S et al., (1985) suggested that there exists a close relation of HRV in diabetics with their age and duration of disease. They observed that HRV decreases as age advances in diabetic subjects. Therefore control of glycemic status is the key for better cardiovascular performance in elderly.

The analysis of Lipid profile of the study groups revealed that the diabetic patients had an elevated total cholesterol and LDL levels, which was on agreement with the previous observations. These factors could aggravate the cardiovascular disorders in the diabetics.

The patients with high FBS (Group 3) showed significantly lower BMI suggesting the metabolic alterations (Tables 1, 2 &3). When cardiovascular autonomic neuropathy is identified aggressive treatment to control cardiovascular risk factors is needed as they are associated with cardiovascular neuropathy which can be reversed by insulin therapy (Kudat HV. et al. 2006). Our observations were in line with the existing literature and further suggests that active intervention and rigid diabetic control will improve the cardiac autonomic function in such patients.

REFERENCES

1. V. Mohan , S. Sandeep, R. Deepa, B. Shah & C.Varghese.(2007) Epidemiology of type 2
2. diabetes: Indian scenario. Indian J Med Res, 125: 217-230.
3. Vinik AI, Maser RE, Mitchell BD, Freeman R (2003) Diabetic autonomic neuropathy. Diabetes Care, May;26(5):1553-79.
4. Rollins MD, Jenkins JG, Carson DJ, McGlure BG, Mitchell RH, Imam SZ: (1992) Power spectral analysis of the electrocardiogram in diabetic children. Diabetologia, 35**:**452-455.
5. Spallone V, Menzinger G: (1997) Diagnosis of cardiovascular autonomic neuropathy in diabetes. Diabetes, 46**:**S67.
6. Pavy-Le Traon A, Fontaine S, Tap G, Guidolin B, Senard JM, Hanaire H. (2010) Cardiovascular autonomic neuropathy and other complications in type 1 diabetes. Clin Auton Res. 20(3):153-60. Epub 2010 Mar 31.
7. Bellavere F: (1995) Heart rate variability in patients with diabetes and other noncardiological disease. In: Heart Rate Variability (Malik M, Camm AJ, eds).Armonk, NY: Futura Publishing, 507– 516.
8. Awdah Al-Hazimi, Nabil Al-Ama, Ahmad Syiamic,;Reem Qosti, Khidir Abdel-Galil. (2002) Time-domain analysis of heart rate variability in diabetic patients with and without autonomic neuropathy. Annals of Saudi Medicine, 22:5-6.
9. DJ Ewing, Clarke PF. (1982) Diagnosis and Management of Diabetic Autonomic Neuropathy. British Medical Journal, 285:916-918.
10. Shephard RJ, Balady GJ. (1999) Exercise as cardiovascular therapy. Circulation. 99:963-972.
11. Malpas SC, Maling TJ: (1990) Heart-rate variability and cardiac autonomic function in diabetes. Diabetes, 39**:** 1177 – 1181.
12. Tarsy D, Freeman R: The nervous system and diabetes. In: Joslin's Diabetes Mellitus (Kahn CR,Weir GC, eds). Philadelphia: Lea & Febiger, 1994;792.
13. Bellavere F, Balzani I, De Masi G, Carraro M,Carenza P, Cobelli C, *et al*: (1992)Power spectralanalysis of heart-rate variations improvesassessment of diabetic cardiac autonomic neuropathy. Diabetes 41**:** 633 – 640.
14. Task Force of the European Society of Cardiology and the North American Society of pacing and Electrophysiology Heart Rate Variability. Standards of measurement, Physiological interpretation and Clinical use. Circulation.1996;93:1043-1065.
15. Wheeler T,Watkin's PJ. (1973) Cardiac denervation in diabetes. Brit Med J, 4: 584-586.
16. Schroeder E B ,Chambless L E, Liao D,Prineas RJ,Evans W,Rosamond W,Heiss G. (2005) Diabetes, glucose, insulin and heart rate variability: the atherosclerosis risk in community study. Diabetes Care 28(3):668-74.
17. Bhagyalakshmi S, Nagaraj H, Anupama BK, Ramesh, M Bhat, Prabha A, Murthy Niranjan, Avabrata Shridhar. (2007) Effect of supervised integrated exercise on heart rate variability in type II diabetes mellitus. Kardiologia Polska, 65:363-368.
18. Masaoka S, Lev-Ran A, Hill LR, Vakil G, Hon EH. (1985) Heart rate variability in diabetes: relationship to age and duration of the disease. Diabetes Care, 8:64-8.
19. Kudat H, V Akkaya,Sozen AB et al. (2006) Heart Rate Variability in Diabetes Patients. The Journal of Interational Medical Research, 34:291-296.