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Original Research Article

Cardiac Parasympathetic Function in Type 2 Diabetes Mellitus: A Follow-Up Study of One Year

Subbalakshmi NK[1], Prabha Adhikari PMR[2]

[1]Associate Professor, Department of Physiology, Kasturba Medical College, Manipal University, Mangalore, India
[2]Professor, Department of Medicine, Kasturba Medical College, Manipal University, Mangalore, India

Corresponding Author: Subbalakshmi NK

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ABSTRACT

Introduction: Diabetic autonomic neuropathy is reported to be an independent predictor of mortality. But little is known about its natural course especially in patients with type 2 diabetes mellitus.
Objective: To quantify change in cardiac parasympathetic function in one year period in patients with type 2 diabetes.
Materials and methods: Heart rate and heart response to deep breathing (HR_{DB}) was recorded in 104 patients with type2 diabetes at the time of entry into the study and at the end of one year follow-up period. 141 age and sex matched controls were used to define normal range of HR_{DB} at baseline in different class intervals of age. Based on the HR_{DB} study group was divided into group A (n = 82, HR_{DB} within normal range); group B (n = 22, impaired HR_{DB}). Statistical analysis was done by unpaired and paired t test. p value less than 0.05 was considered significant.
Result: Heart rate increased and HR_{DB} declined significantly in study subjects (n = 104; $p < 0.001$; $p = 0.01$ respectively). In group A HR_{DB} declined significantly ($p < 0.001$). In group B there was no significant decline in HR_{DB}. 5 deaths were observed during the study period. In 4 of the subjects HR_{DB} was impaired at baseline and in the 5^{th} it declined to become impaired.
Conclusion: Cardiac parasympathetic function deteriorates over a period of time in patients with type 2 diabetes mellitus. Therefore periodic assessment of autonomic function is essential.

Key words: parasympathetic dysfunction, heart rate variation, mortality

INTRODUCTION

Autonomic neuropathy has significant negative impact on survival and quality of life in people with diabetes. [1,2] It is generally believed that parasympathetic neuropathy manifests much before the involvement of the sympathetic fibers. [3] In the intact heart parasympathetic fibers are inhibitory and sympathetic are excitatory. Inhibitory actions of cardiac parasympathetic nerves are reported to provide electrical stability to the heart and

thus preventing ventricular tachycardia in humans. [4] However little is known about natural course of autonomic neuropathy especially in patients with type 2 diabetes mellitus. Thus a follow-up study of one year duration was undertaken in patients with type 2 diabetes mellitus in relation to cardiac parasympathetic function.

MATERIALS AND METHODS

It was a hospital based follow up study of one year in subjects with type 2 diabetes. The study was under taken after the approval by the Institutional Ethical Committee looking into human studies.

Study group included 104 patients with clinically diagnosed type 2 diabetes mellitus. Based on the heart rate response to deep breathing test (HR_{DB}) the study subjects were further divided into group A (n = 82, HR_{DB} within normal range) and group B (n = 22 with impaired HR_{DB}).Control group comprised of 141 non-diabetic healthy subjects matched for age and sex of study subjects. They were used to define normal range of HR_{DB} at baseline in different class intervals of age.

Procedures:

Cardiac parasympathetic function was quantified by HR_{DB} and resting heart rate. In study subjects HR_{DB} was quantified once at the time of entry into the study and again at the end of one year study period. Similarly, fasting blood sugar was measured at baseline and at the end of study period. In addition, in study subjects any change in the clinical profile was documented during follow-up period. In control group, HR_{DB} was measured only at baseline.

Procedure followed in recording heart rate response to deep breathing (HR_{DB})

HR_{DB} was recorded with the subject in supine position, connected to the limb leads of a standard electrocardiogram. Before beginning the test, subjects were taught to breathe at six breaths a minute: five seconds for each inhalation and five seconds for each exhalation. The examiner raised his hand to signal the start of each inhalation and lowered it to signal the start of each exhalation; this was supported by verbal signals. Lead II electrocardiogram was then recorded continuously at a speed of 25 mm/s for 60 seconds while the subject breathed as instructed. The R-R intervals were measured accurately. The change in heart rate was calculated as the difference between the shortest and the longest R-R interval. HR_{DB} was expressed as beats per minute. [5] Abnormal scores had been defined as those more than 2 standard deviation (SD) below the mean value in normal subjects. Scores between 1.5 and 2 SD below the mean value have been called borderline.Mean and standard deviation of HR_{DB} was estimated for different class intervals of age: (They were 31-40 years, 41-50 years, 51-60 years and 61 years and above). [6,7]

Statistical analysis:

Data analysis was done by unpaired and paired 't' test. Statistical significance was taken to be a p value of less than 0.05.

RESULTS

The data on controls and study subjects at baseline and at follow-up is presented with suitable side headings below.

Comparison of baseline characteristics of study subjects and controls

Data on comparison of measured baseline characteristics of study subjects with controls is presented in table 1. Data is presented as mean ± SD. There was no significant difference in age between study subjects and controls (table 1). Heart rate of study subjects was higher compared to control ($p= 0.011$, table 1). HR_{DB} was lower in study subjects compared to controls ($p<0001$, table 1).

Table I. Baseline characteristics of subjects in control and study group

Variables	Data		t value	P value
	Control group (n=141)	Study group (n=104)		
Age (years)	55.45± 10.53	56.32±10.59	0.63	NS
Resting heart rate (beats /min)	79.79±10.26	83.69 ±12.91	2.546	= 0.011
HR_{DB} (beats/min)	28.75±7.39	19.82 ± 7.54	9.268	< 0.0001

HR_{DB} = heart rate variation during deep breathing. Values are mean ± SD

Parasympathetic function during follow-up period in study subjects:

The data on fasting blood sugar, heart rate and HR_{DB} at baseline and at the end of follow-up period in study subjects as a single group is presented in table 2. In them, the mean heart rate was significantly higher at follow-up compared to baseline ($p < 0.0001$, table 2); HR_{DB} was significantly lower at follow-up compared to baseline ($p = 0.011$, table 2)

Table 2. Fasting blood sugar and cardiac parasympathetic function of study subjects (n =104) at baseline and at the end of one year follow-up period

Variables	At baseline	At follow-up	Mean difference	P value
Fasting blood sugar (mg %)	171.02 ± 66.03	160.72 ± 45.98	8.91 ± 65.06	0.19
Heart rate (beats/min)	83.69 ± 12.91	89.07 ±14.58	-5.37 ± 12.32	< 0.0001
HR_{DB} (beats/min)	19.82 ± 7.54	17.82 ± 9.31	2.003 ± 7.86	= 0.01

Comparison of change in HR_{DB} and heart rate in one year period in subgroups

There were 22 study subjects with impaired HR_{DB} (abnormal and borderline HR_{DB} compared to normal range, group B). 82 were having HR_{DB} within normal range (group A). The data on HR_{DB} of these two subgroups at baseline and at follow-up is presented in table 3. In group A HR_{DB} was significantly lower at follow-up compared to baseline ($p = 0.001$, Table 2). In group B there was no significant difference in HR_{DB} at follow-up compared to baseline (table 3).

Table 3. Comparison of heart rate response to deep breathing in subgroups of study subjects (values are mean ± SD)

Subgroups	At baseline	At follow-up	Mean difference	P value
Group A* (n = 82)	21.97 ± 6.77	18.90 ± 9.18	3.07±7.28	<<0.001
Group B** (n = 22)	11.35 ± 3.19	12.20 ± 6.61	- 0.846 ± 6.50	NS

* Heart response to deep breathing in normal range
** Heart rate response to deep breathing impaired
NS = Non-significant

Association between symptoms of autonomic neuropathy and follow-up HR_{DB}:

During study period, persistent constipation was observed in 4 study subjects. In them HR_{DB} was either low at baseline (n=3) or declined during the follow- up period to become abnormal (n=1).

Association between morbidity and mortality with follow-up HR_{DB}:

During the follow-up period 5 diabetic subjects died and in one morbidity was observed. In 4 of the diabetics who died HR_{DB} was impaired at baseline. In the 5th HR_{DB} declined to become abnormal during study period. All the 5 died within a week of follow-up recording. 3 subjects died of acute myocardial infarction and one died of pneumonia. In one diabetic in whom HR_{DB} became impaired during the study period suffered cerebrovascular accident.

DISCUSSION

Aging has profound impact on autonomic nervous system. [8] HR_{DB} an

index of cardiac parasympathetic function declines steadily with advancing age. [9-13] Therefore we generated age related normal range in different class intervals of age from healthy subjects for defining impaired HR_{DB} in our study subjects. Accordingly, in 22 study subjects, HR_{DB} was impaired and in 82 patients HR_{DB} was within normal range.

The follow-up HR_{DB} and heart rate was compared in relation to baseline in 104 patients as a group initially; and then HR_{DB} was compared in HR_{DB} within normal range group and impaired HR_{DB} group separately. In the present study, during study period HR_{DB} declined and heart rate increased significantly in study subjects (table 2). The significant decline in HR_{DB} accompanied by significant rise in heart rate found in the present study suggests progressive deterioration of cardiac autonomic function over time. A significant decline in HR_{DB} in one-year period observed in this study (Table 2) is in accordance with the findings of Mackey JD et al [6] Jermendy G et al. [14] However these studies were carried out in type1 diabetic patients unlike in type 2 diabetics in the present study.

In the present study HR_{DB} declined significantly in diabetics who had HR_{DB} within normal range at baseline. Similar kind of observation was also made by previous investigators. [6,15,16] However their observation was made in type 1 diabetics unlike type 2 in the present study. In majority of the diabetics who had either abnormal or borderline HR_{DB} at baseline, the HR_{DB} value neither further decreased nor improved (table 3). This result suggests that once the HR_{DB} becomes impaired usually they remain so. This finding is in agreement with the previous workers who also had made similar observation. [6,11,12]

In the present study 5 deaths were observed. All the five diabetics who died or faced morbidity during the follow-up period either had abnormal HR_{DB} at baseline or declined to become abnormal within one year time. There are several studies documenting autonomic neuropathy as an independent predictor of mortality in diabetics. [17-20] However the number of deaths with impaired HR_{DB} during the follow-up period in our study was small. This could be owing to the too short period to evaluate the predictive value of reduced heart rate variability in poor prognosis of diabetics with autonomic neuropathy unlike other studies on mortality that had followed up the patients for 5-10 years of duration. [15,18,20] However in spite of short duration of follow-up period, the present study too pointed out at poor prognosis in patients with diabetic cardiac autonomic neuropathy.

CONCLUSION

Thus based on our study finding it could be concluded that cardiac parasympathetic function declines with time. Therefore the periodic evaluation of autonomic function in patients with type 2 diabetes mellitus is essential. Additionally, the natural tendency of deterioration of parasympathetic activity over a period of time in subjects with type 2 diabetes should be considered while evaluating the efficacy of any intervention procedures.

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