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CARDIOVASCULAR AUTONOMIC NEUROPATHY IN PATIENTS WITH DIABETES MELLITUS

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ABSTRACT

The cardioautonomic reflexes of 82 diabetic subjects and 40 age and sex matched healthy controls were studied using blood pressure and heart rate variation in response to standing, deep breathing, isometric exercise, cold pressor test and determination of QTc interval. Among the 82 patients, 68 patients were found to have cardiac autonomic neuropathy (CAN). Results showed that diabetics had significantly impaired cardioautonomic reflexes compared to non-diabetics, which increases with the duration of diabetes. Out of 68 patients with CAN, QTc prolongation was observed in 64 patients. In conclusion the autonomic nervous system integrity is appeared to be greatly affected by diabetes mellitus and the degree of impairment was dependent on duration of the disease.

KEY WORDS

Diabetes, Cardiac Autonomic Neuropathy, CPT, DAN, Handgrip, QTc

INTRODUCTION

Diabetic Autonomic Neuropathy (DAN) is among the least recognized and less understood complication of diabetes despite its significant impact on survival and quality of life in people with diabetes[1,2]. One of the most over looked of all serious complications of diabetes is Cardiovascular Autonomic Neuropathy (CAN) which encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels resulting in abnormalities in heart rate control as well as defect in central and peripheral vascular dynamics[3,4,5]. The assessment of autonomic neural involvement is usually done by evaluating cardiac autonomic reflex functions[6]. As the clinical importance of Diabetic Autonomic Neuropathy (DAN) has become recognized the need has grown for simple objective tests to confirm its presence or absence[6-8]. Numerous non-invasive tests which we consider reliable, reproducible and simple have been used for diagnosis of Cardiac Autonomic Neuropathy (CAN)[8,9].Thus the present study aims to evaluate and correlate the cardiovascular autonomic neuropathy using simple Ewing's tests[10] with QTc interval in diabetic patients.

MATERIAL AND METHODS

STUDY SUBJECTS

The patients were divided into three groups according to the duration of diabetes [Group I: < 5 years, Group II: 5-10 years, Group III: > 10 years]. 82 diabetic patients attending the Department of General Medicine of Owaisi Hospital and Research Center, Hyderabad formed the subjects of this study. Out of these 82 subjects, 10 were insulin dependent and the rest were non-insulin dependent diabetic patients. The demographic data of subjects are included in Table 1.

After obtaining the clinical history and followed the physical examination, Ewing's tests were done. There was no history of cardiovascular or neurological diseases. A twelve lead ECG was done and patients with ECG evidence of ischemic heart disease (IHD) were excluded from the study.

Forty age matched healthy controls were assessed for the presence of cardiac autonomic neural dysfunction. The study received prior approval by the Institutional Ethics Committee. All participating subjects gave informed consent to their participation in the study after the rationale and the nature of the procedures has been fully explained.

STUDY PROTOCOL

All the 82 patients were subjected to the tests in the morning hours between 10 am to 12 noon. The temperature of the investigation room was between 22^{o}C and 24^{o}C. No smoking was allowed on the morning of the study and subjects were instructed not to take medication like Aspirin, Vitamins or anti-histamines for at least 48 hours before the tests. To be prepared for the test, each subject rested for 10-15 minutes in a quite room to ensure full relaxation. Baseline ECG, heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP) of all the participants were recorded.

The autonomic dysfunction was tested by a battery of well established cardio circulatory tests including the resting heart rate, deep breathing test, handgrip test, the orthostatic test, the cold pressor test and QTc interval and correlated with the duration of diabetics.

TESTS FOR CARDIAC PARASYMPATHETIC ACTIVITY

(i) Resting heart rate

Resting heart rate was observed over a period of one minute in all the patients after a rest period of 5 minutes. Datex ECG Monitor with lead II configuration was used. Patients with resting heart rate of more than 90 beats /minute were considered to have resting tachycardia[11].

(ii) Heart rate variation during deep breathing

After taking resting heart rate, patients were instructed to take deep breaths at the rate of 6 breaths per minute with five seconds of inspiration and five seconds of expiration for one minute. During this process continuous ECG monitoring was done[12]. The E/I ratio was calculated using equation no. (1).

(iii) QTc interval

QTc interval was calculated by Burdick E 600 interpretive electrocardiograph. The QTc was determined with Bazett's formula, equation no. (2) and a value exceeding 440msec was considered prolonged[13,14].

$$\text{E/I ratio} = \frac{\text{Longest R-R interval during expiration}}{\text{Shortest R-R interval during inspiration}} \quad (1)$$

$$QTc = \frac{QT}{\sqrt{R-R \text{ interval}}} \quad (2)$$

(iv) Immediate heart rate response to standing

Patient is asked to stand up unaided and the starting point of standing is marked on the electrocardiogram. The shortest R-R interval at or around 15th beat and longest R-R interval at around 30th beat after starting to stand are measured with the ruler. The characteristic heart rate response is expressed by 30/15 ratio[10,14].

(v) Heart rate response to sustained handgrip

The patients were asked to perform sustained handgrip for one minute. At the end of one minute the heart rate was recorded during sustained handgrip test[14].

TESTS FOR SYMPATHETIC ACTIVITY

(i) Blood pressure response to standing

Basal blood pressure was taken with the patient lying down quietly. The patient was asked to standup and a second reading was taken. A difference of systolic blood pressure (SBP) more than 30mmHg between the standing and lying blood pressure was considered positive for autonomic neuropathy[10].

(ii) Blood pressure response to sustained handgrip

The patient was asked to perform sustained handgrip for one minute. At the end of one minute blood pressure was recorded. An increase in diastolic blood pressure (DBP) of less than 15mmHg was considered positive[10].

(iii) Blood pressure response to cold pressor test

Blood pressure was measured after ½ and 1 minute interval of immersion of the hand in water at 4^{o}C. In addition blood pressure measurement continued after the removal of the hand from the cold water in order to detect delayed pressor effect[15,16].

STATISTICAL ANALYSIS

Data was analyzed using Mann Whitney U test and Chi square test. Values of variables measured during each test were compared with baseline values in each group by student's t test. *p* value less than 0.05 was regarded as significant.

RESULTS

Eighty two diabetic subjects were compared to forty age and sex matched healthy control subjects. The diabetic group was further sub divided into three sub groups based on the duration of diabetes.

Table 1 shows demographic data of the study groups. Results revealed no statistically significant difference in the age, BMI and gender distribution. Out of the 82 patients, 10 patients (12%) were found to be type 1 diabetic, while the remaining were type 2 diabetics (88%). There was a significant difference in the fasting glucose when observed between the control and the study group.

Table 2 shows the duration of diabetes and the percent of autonomic neuropathy in diabetics. In the first group 89%, 86% in the second group and 75% in the third group of the patients were found to have cardiac autonomic neuropathy. Statistically significant difference was observed between the E/I, 30/15 and QTc interval of patients and controls as depicted in table 3. No significant difference was observed in the E/I ratio between the sub-groups. 30/15 ratio in group I was normal, however in group II and III significant difference was observed (p<0.001). A significant increase in QTc interval was observed as the duration of diabetes increases.

Figure 1 shows the difference in the DBP in the control and patients during sustained handgrip. No change in SBP was found during handgrip, however significant variation was observed in DBP. The change in heart rate between the control and subjects (Inset figure 1) significantly differed in sustained handgriptest.

Table 1. Demographic data of studied groups

Parameters	Controls	Diabetics		
		Group I	Group II	Group III
Age (Years)	48±14	42±8	46±12	52±12
Sex (% Males)	28 (70%)	10 (55%)	25 (69%)	21 (75%)
Body Mass Index (kg/m^2)	23±4	25±3	26±3	23±5
Type I Diabetes (%)	-	1 (5%)	4 (11%)	5 (18%)
Current smokers (%)	10 (25%)	6 (33%)	12 (33%)	8 (21%)
Alcohol Consumption (%)	21 (53%)	12 (67%)	23 (64%)	16 (57%)
Fasting glucose level (mg/dL)	98±13	142±30 (p<0.001)	168±36 (p<0.001)	159±40 (p<0.001)

Table 2. Relationship of duration of diabetes with cardiac autonomic neuropathy

Duration of Diabetes	Number of Patients (n=82)	Cardiac Autonomic Neuropathy
Group I (upto 5 Years)	18 (22%)	16 (89%) (p<0.001)
Group II (5- 10 Years)	36 (44%)	31 (86%) (p<0.001)
Group III (>10 Years)	28 (34%)	21 (75%) (p<0.001)

Table 3. Results of the cardio-autonomic reflex test in control and diabetic groups.

Variables	Control	Diabetic		
		Group I	Group II	Group III
Comparison of E/I ratio	1.28±0.12	1.05±0.08 (p=0.04)	1.03±0.06 (p=0.01)	1.02±0.02 (p=0.02)
Comparison of 30/15 ratio	1.11±0.18	0.990±0.03 (p=0.008)	0.986±0.06 (p<0.001)	0.978±0.08 (p=0.003)
QTc interval (msec)	353.71±11.12	372.31±42.22 (p<0.001)	442.41±34.26 (p<0.001)	453.22±31.41 (p<0.001)

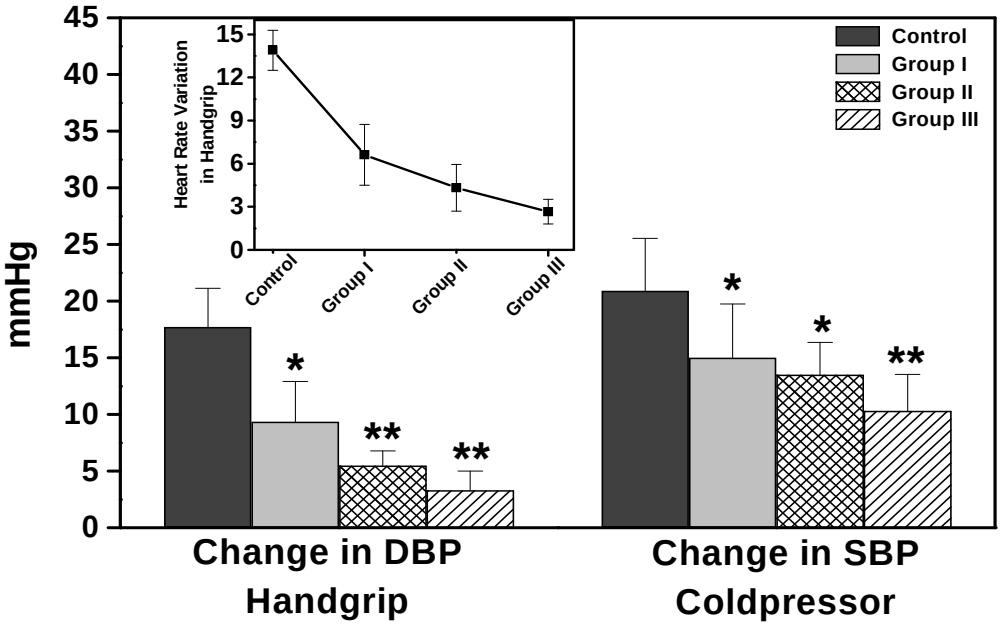

Figure 1. Change in DBP in handgrip and SBP in cold pressor in controls and diabetics with duration. Inset shows heart rate variation in handgrip test in controls and diabetics with duration.

Statistically significant difference was observed in change in SBP and DBP between controls and diabetics during cold pressor test. We also found a statistically significant decreasing trend in change in SBP and DBP with duration of diabetes. Diabetics with CAN had statistically significant QTc prolongation as compared to control group and diabetics without CAN.

DISCUSSION

The activity of the autonomic nervous system is of crucial importance in the moment to moment regulation of heart rate and blood vessel resistance, thereby controlling arterial pressure, cardiac output and tissue perfusion. Autonomic neuropathy can occur in both Type 1 and Type 2 diabetes, which can modify the cardiovascular responses[17,18].

CAN is one of the most challenging problem amongst all the complications of diabetes[19]. Development and degree of CAN is not an all or none phenomenon but a progression of disease which may precede development of symptoms of diabetes[5]. The early detection of CAN is imperative for successful intervention. Ewing et al has advocated five autonomic function tests out of which at least two must be abnormal for a definite diagnosis of CAN[10].

Our result showed that the mean value of E/I ratio of the diabetic group with or without CAN were significantly lower than in control subjects. E/I ratio is a ratio between Expiration induced deceleration in heart rate to inspiration induced acceleration in heart rate[18]. Heart rate increases during inspiration because of the decrease in the vagal activity to the heart. The decrease in the E/I ratio in the diabetic group may be due to the decrease vagal tone to the heart (bradycardia phase) during the expiration[18]. Our result also suggest that E/I ratio decreases with duration of diabetes, which depicts the severity of CAN with duration.

Diabetic patients had abnormal heart rate response to standing (relative bradycardia at the 30th beat to relative tachycardia at the 15th beat after

standing up). Diabetics with CAN had mean 30/15 ratio significantly lower than the control and also it decreased with duration of diabetes. This reflex phenomenon to standing is due to unloading of the baroreceptors[20]. Loss of this reflex may be due to loss of the sympathetic and parasympathetic response to standing. We also observed that as the duration of diabetes increased, sympathetic and parasympathetic response to standing decreases.

In control subjects during sustained hand grip, a sharp rise in blood pressure of more than 15mmHg occurred due to heart rate dependent increase in cardiac output with unchanged peripheral vascular resistance, however in diabetics with autonomic damage the rise in blood pressure is abnormally small[21]. In response to contraction of muscles that activate small fibres in the afferent arm of the reflex arc the heart rate rise due to decreased parasympathetic activity, however in diabetic patients the rise is very small[21].

The Hines cold pressor test (CPT) is considered to be potentially useful indicator of autonomic neuropathy in diabetes[22]. The mechanism of the attenuated change of SBP in CPT in diabetic patients compared to the control could be due to impairment either of afferent limb or/and of the efferent sympathetic pathway mediating the vascular response of CPT[23]. Our data suggest that attenuated change SBP in diabetic patients is due to impaired sympathetic response rather than due to impairment of the afferent limb of the CPT reflex.

There is an association of prolonged QTc interval with cardiac dysautonomia in diabetes mellitus[24]. The exact mechanism of QTc prolongation is not clearly defined. It is generally agreed that parasympathetic system have little influence on QTc modulation. QTc prolongation in diabetic patients stands favorable as sympathetic dysfunction parameter when compared to other autonomic function tests[5,24]. Further QTc prolongation has linear correlation with the degree of CAN.

It is inferred from the present study that E/I ratio, 30/15 ratio, handgrip test, cold pressor test and QTc prolongation in diabetics with otherwise normal heart can be used as a diagnostic tests for assessment of cardiac autonomic neuropathy and even be considered as cardiac autonomic function test with prognostic significance.

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