Cardiac Autonomic Neuropathy In Relation To Cardiovascular Reflex Tests and QTc Prolongation In Diabetes Mellitus

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Abstract: Background and objectives: Cardiac autonomic neuropathy (CAN) contribute to the poor prognosis of Coronary heart disease (CHD) and Congestive heart failure (CHF) in diabetes. This study was done to evaluate the prevalence of cardiac autonomic neuropathy in diabetic patients by cardiovascular reflex tests and to investigate relation between QTc prolongation and cardiac autonomic neuropathy (CAN).Methods: The study was conducted at the Department of Internal Medicine, Medical College, Baroda by selecting 70 documented diabetic patients as per criteria recommended by the American diabetes association (ADA). Patients were subjected to different cardiovascular reflex tests and ECG was done to calculate corrected QT interval. Statistical analysis was done with help of epi info software. Results: In this study, definitive CAN was found in 34 (49%) cases with early CAN in 27(39%) and severe CAN in 7(10%) of diabetic patients. Most affected parameter was heart rate variability on deep breathing in34 (100%).In the ECG, out of 33 patients with definite CAN, corrected QT interval (QTc) was prolonged in 24 (73%) patients. Conclusion: Evaluation of cardiovascular reflexes constitute an important feasible and bedside clinical technique to detect CAN at earliest. QTc interval prolongation in ECG can be used for early diagnosis of CAN in busy outdoor setting. [Archana G NJIRM 2017; 8(4):68-72]

Key Words: cardiac autonomic neuropathy, cardiovascular reflex test, diabetes

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Introduction: The cardiovascular complications of DM canbe classified into three groups: Atherosclerotic Coronary Artery Disease, Diabetic Cardiomyopathy and Cardiac Autonomic Neuropathy (CAN)[1].Diabetic patients with abnormal cardiovascular reflex tests (CVR) may have increased mortality, and those combined with postural hypotension have higher mortality than those without[2].A summary of 15 reports on CAN has suggested that the prevalence is in between 2.6% and 90% in diabetic population[3].Presenceofsymptomsalong with abnormal cardiovascular function tests suggest poor prognosis and increased incidence of silent myocardial infarction, cardiac arrest, sudden death, and inadequate response to stressful events, e.g., anaesthesia and surgery[1].In 1980, for the first time, an association of prolonged QTc interval with cardiac autonomic neuropathy was noted. Further studies demonstrated an association of prolonged QTc interval with cardiac dysautonomia in diabetes mellitus[4].

Methods: The study was an observational cross sectional study that included both outdoor and indoor diabetic patients and patients of the Diabetic Clinic at Medical College, Baroda and SSG Hospital by selecting 70 documented diabetic patients as per criteria recommended by the ADA. Study was approved by scientific and review committee and ethics committee of Medical College, Baroda. Patients were selected Irrespective of the duration of disease and therapeutic status. The inclusion criteria was all diabetic patients (type I& II) diagnosed on basis of American Diabetes Association (ADA) criteria with patients of either sex and > 18yrs of age.

ADA 2014 Criteria for the Diagnosis of Diabetes Mellitus[5]

- Symptoms of diabetes or hyperglycemic crisis plus random blood glucose concentration11.1 mmol/L (≥200 mg/dL) or
- Fasting plasma glucose 7.0 mmol/L (≥ 126 mg/dL)(Fasting is defined as no caloric intake for at least 8 h) or
- Two-hour plasma glucose 11.1 mmol/L (≥200 mg/dL) during an oral glucose tolerance testor
- Haemoglobin A1C > 6.5 percent

While all patients on drugs, which prolongs QT interval and patients with documented heart diseases, renal failure and electrolyte imbalance were excluded from study. Written Informed consent was taken from the patients and a standardized questionnaire was used, and details pertaining to medical and family history were collected. Body mass index (BMI) and blood pressure (BP) were also recorded. Mercury

sphygmomanometer and electrocardiography machine were used for evaluation of cardiovascular reflexes.

The tests for autonomic cardiovascular function, performed as beside procedures suggested by Ewing[6] are described below:

A. Tests reflecting cardiac parasympathetic action:

I. Resting heart rate

II. Heart rate response to Valsalva: Patient was asked to blow into a mouthpiece connected to a sphygmomanometer and holding it at a pressure of 40 mmHg for 15 seconds while a continuous ECG was recorded. The ratio of maximum heart rate during blowing to the minimum heart rate during the compensatory bradycardia after stopping is calculated. The maneuver was performed 3 times with an interval of one minute in- between. The result was expressed as the Valsalva ratio. The mean of three Valsalva ratios was taken as the final value (normal Valsalva ratio 1.21; borderline between 1.11 and 1.20; abnormal < 1.10).

III. Heart rate variation (HRV) during deep breathing: The patient sat quietly and breathed deeply at six breaths a minute (5 seconds in, and 5 seconds out) for one minute. An ECG was recorded throughout the period of deep breathing with a mark used to indicate the onset of each inspiration and expiration. The maximum and minimum R-R intervals during breathing cycle were measured and converted to beats/minute. The result was then expressed as the mean of the difference between maximum and minimum heart rates for the 6 measured cycles in beats/minute; (normal response >15 beats/minute, borderline 11 - 14 beats/ minute; abnormal response < 10 beats/ minute).

B. Tests reflecting cardiac sympathetic action:

I.BP response to standing: The test was performed by measuring the patient's BP while he was lying down quietly and again when he stood up. The postural fall after 2 minutes in BP was taken as the difference between systolic BP lying and the systolic BP standing (normal response< 10 mmHg; borderline 11 - 29 mmHg; abnormal response> 30 mmHg).

II. BP response to sustained handgrip: After instructions in using handgrip of an inflated BP cuff, the subject gripped maximally with his dominant arm for a few seconds; this was repeated thrice. Highest of the three readings is called maximum voluntary contraction (MVC). Now the subject was instructed to maintain handgrip. Blood pressure was measured at one-minute intervals during the handgrip. The result was expressed as the difference between the highest diastolic blood pressure during handgrip exercise and mean of 3 diastolic blood pressure readings taken before hand grip began (normal response > 16 mmHg; borderline 11- 15 mmHg; abnormal< 10 mmHg).

After doing these tests patients were divided into No CAN, Early CAN and Severe CAN as per Ewing's method[6]. Table:1 shows scoring system of Ewing's method.

Estimation of glycated haemoglobin (HbA1C) by HPLC and fasting blood sugar, post prandial blood sugar and other biochemical tests like serum creatinine, blood urea, electrolytes and complete blood count with urine routine micro were done.

QT interval was counted in ECG and calculation of corrected QT interval (QTc) with modified Bazzet's formula was done. QTc = QT / √RR interval Data was entered in the excel sheet and analyzed by using epi info software. Chi square test was done. Sensitivity, Specificity, Positive predictive value, Negative predictive valueand Accuracy of corrected QT interval (QTc) was calculated.

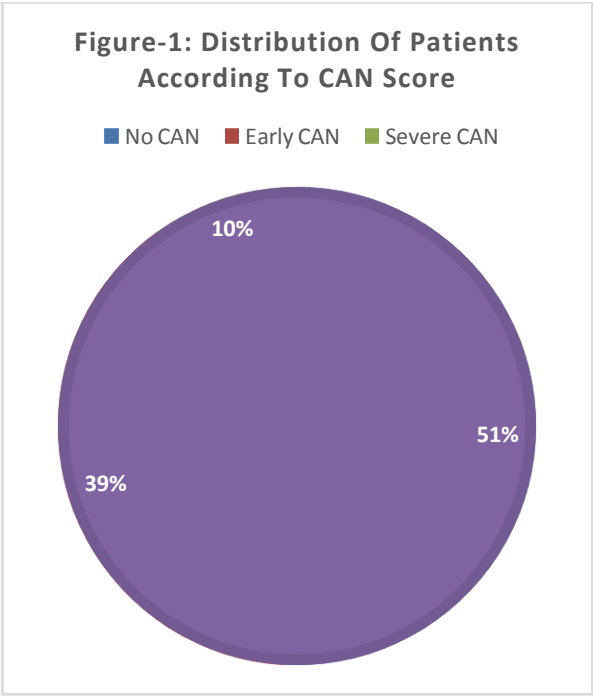

Table: 1 Bedside tests for cardiac autonomic neuropathy diagnosis Ewing Method[6]

Test	Points		
	0	0.5	1
Resting heart rate	<100	100-110	>110
Postural hypotension	<20	20-30	>30
Valsalva ratio	>1.2	1.2-1.10	<1.10
Heart rate variability on deep breath	>15	15-10	<10
Increase diastolic BP during handgrip	>15	15-10	<10

No CAN – 0, Early CAN - 0-1.5, Severe CAN - >1.5

Table 2: Prevalence of Different Parameters of CAN among Study Group

Parameters of CAN	Definite CAN	%
Resting heart rate	20	59%
Postural hypotension	10	29%
Valsalva ratio	4	12%
HRV* on deep breathing	34	100%
Increase diastolic BP on hand grip	19	56%

*Heart rate variation

Table 3: Correlation between Severity of CAN and Qtc*Prolongation in Study Group

QTc in m-sec	Severe CAN	%	Early CAN	%	No CAN	%	p value
>440	06	86	18	67	09	25	0.0001
<440	01	14	09	33	27	**75**	0.0001

*corrected QT interval (QTc)

Table 4: Sensitivity and Specificity of Qtc Prolongation in Diagnosis of CAN

Screening test Results QTc(Msec)	Interpretation		Total
	Definitive CAN + ve	No CAN	
>440	24 (a)	09 (b)	33
< 440	10 (c)	27 (d)	37
Total	34	36	70

Sensitivity = a / a+c= 24/34 x 100 = 71 %
Specificity = d/b+d = 27 / 36 x 100 = 75 %

Results: A total 70 cases of diabetic patients were included in the study group after using proper exclusion criteria. There were equal numbers of male 35(50%) and females 35 (50%).In our study group out of 70 patients 11 (15%) had type 1 diabetes and59 (85%) had type 2 diabetes. Among 70 patients of study group 36 (51%) had no CAN and 27 (39%) had early CAN and 7 (10%) had severe CAN as per Ewing's method. [Figure: 1] Prevalence of definite CAN was 34 (49%) in our study group.

Regarding the various autonomic functions, heart rate response to deep breathing was the most sensitive test to determine autonomic neuropathy. It is abnormal in 34 (100%) patients. This was followed by resting heart rate, which was abnormal in 20 (59%) patients. Abnormal handgrip test was seen in 19 (56%) patients. Postural hypotension was abnormal in 10 (29%) patients. The least sensitive test to detect autonomic neuropathy was Valsalva ratio. This was abnormal in 04 (12%) cases [Table 2].

Correlation of QTc prolongation in ECG with cardiac autonomic neuropathy in diabetic patients was studied. QTc interval prolongation was seen in 06 (86%) patients of severe CAN, which was much significant compared to 09 (25%) patients of no CAN. Prolongation of QTc interval is well correlated with Cardiac Autonomic Neuropathy {P value = 0.0001(highly significant)} with application of chi square test [Table 3].

Amongst 34 patients with definite CAN, corrected QT interval (QTc) was prolonged in 24 patients. As per Table 4 Sensitivity means the ability of QTc prolongation to identify true positives is calculated as 71% and the Specificity means ability of QTc prolongation to identify the true negatives is calculated as 75%. The accuracy of corrected QT interval (QTc) was 72.85%. The positive predictive value of corrected QT interval (QTc) was 72.72. The negative predictive value of corrected QT interval (QTc) was 72.97%.

Discussion: One of the most overlooked of serious complications of diabetes is cardiovascular autonomic neuropathy. (CAN)[7-9] CAN encompasses damage to the autonomic nerve fibres that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics[10].CAN is a significant cause of morbidity and mortality associated with a high risk of cardiac arrhythmias and sudden death[4].

Cardiovascular reflex tests are bedside, simple and non-invasive for diagnosis of CAN. They are validated, reliable and reproducible[11]. Their use to exclude the condition is at least as important as its confirmation;

the tests are extremely sensitive and at least one fifth of diabetic patients have one or more abnormalities.

Prevalence of CAN was 49% in our diabetic study population. Lakhotia M et al found prevalence of CAN to be 64% in diabetic patients[12].In another descriptive study from Pakistan; researchers found the incidence of definitive CAN in patients with type 2 diabetes mellitus to be 30%[13].

In our study, heart rate variability during deep breathing was abnormal in 34 out of 34 patients with definite CAN giving a sensitivity of 100%. Abnormal HRV during deep breathing is indicative of early autonomic neuropathy. Other most affected parameter was resting tachycardia with sensitivity of 59% and increase diastolic BP on hand grip (56%).

Vinik et al[14] studied and published a data of sensitivity of autonomic function tests done on a population of 3516 patient with type 1 and type 2 diabetes. The calculated sensitivity of HRV during deep breath was 98%.Meta-analysis of published data demonstrate that reduced cardiovascular autonomic function as measured by HRV is strongly associated with an increased risk of silent myocardial ischemia and mortality.

Other tests for detection of CAN are spectral analysis of heart rate variation[15], measurement of bar reflex sensitivity and measurement of QTc interval.

The length of QTc interval is influenced by autonomic nervous tone. Electrical instability reflected by abnormally long QTc interval increase the risk of arrhythmias and sudden cardiac death. Studies have shown that QTc prolongation is associated with major degree of autonomic neuropathy[16].In cohort based prospective study QTc prolongation was predictive of increase mortality in type I diabetic patients[17].

In the ECG, out of 34 patients with definite CAN, corrected QT interval (QTc) was prolonged in 24 patients, which gives a sensitivity of 71% and specificity of 75% respectively. In this study the correlation between CAN and QTc prolongation was significant (p=0.0001).

Pappachan J M et al[1] studied the utility of prolongation of QTc in the ECG to diagnose CAN in patients with diabetes. They calculated the sensitivity and specificity of QTc prolongation for the diagnosis of CAN were 77% and 62.5% in type1 diabetes and 76.5% and 75% in type 2 respectively. They concluded that QTc interval in ECG can be used to diagnose CAN with reasonable sensitivity and specificity. However, usefulness of QTc interval to detect CAN is under debate. A meta-analysis concluded that QTc prolongation is a specific albeit insensitive indicator of autonomic failure[18].

Limitation of this study was that newer techniques for measuring autonomic functions like the computer aided power spectral analysis of heart-rate variability could not be used because of limitations in resources and cost.

Conclusion: Evaluation of cardiovascular reflexes in diabetic subjects with paucity of related symptoms constitutes an important feasible and reproducible bedside clinical technique to detect CAN. It should be included as a routine in work-up of patients of diabetes. Prevalence of definite CAN in diabetics of this study was 49%.

Heart rate response to deep breathing is the most sensitive parasympathetic cardiac autonomic function test, which detects CAN.

Prolongation of QTc interval correlates well with degree of cardiac autonomic neuropathy in diabetics. Sensitivity and specificity of QTc prolongation to detect CAN was 71% and 75% respectively in this study. QTc prolongation can be considered as pointer towards diabetic cardiac autonomic neuropathy in the busy outpatient setting where it is not possible to perform the conventional battery of tests.

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