Cough test in diabetic cardiac autonomic neuropathy

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Noninvasive cardiovascular reflex tests have been used to assess autonomic function. Forthy five diabetic subjects were tested and separated into four groups based on the presence and degree of cardiac autonomic neuropathy with cardiovascular reflexes. And then we measured the heart rate response following three force-full coughs performed over a 3 s. period. The corrected **0-7** *interval was determined at rest with Bazett's formula. The mean QT_c interval was longer in diabetics than in the control subjects. Decreased cough test ratio was found in 44.4% of diabetic patients with cardiac autonomic neuropathy. Cough test ratio showed a negative correlation with the age and QT_c interval. We found the cough test to be simple to perform and useful for the evaluation of cardiovascular autonomic reflexes. [Turk J Med Res 1994; 12(5): 217-221]*

Key Words: Diabetes mellitus, Autonomic neuropathy, Autonomic function tests, QT interval, Cough

Various disturbance of autonomic function may develop in patients with long-standing diabetes mellitus. Cardiac autonomic neuropathy (CAN) in diabetics may include abnormalities of cardiovascular reflexes (1-3). These abnormalities can be demonstrated by a variety of tests even in absence of symptoms. Five simple noninvasive tests have been used in the assessment of CAN. They are the heart rate responses to deep breathing, standing up and Valsalva manoeuvre and the blood pressure responses to standing up and sustained hand-grip (4,5). Another noninvasive diagnostic test is corrected QT (QT_c) interval. Imbalance of sympathetic innervation of the heart may result in prolongotion of the interval (6,7).

Recently, the heart rate response to cough has been described and cough test (CT) succeeds in assessing the parasympathetic cardiac autonomic neuropathy in diabetes mellitus (8).

The present study was undertaken to investigate the value of CT as a potential marker for the presence of CAN of patients with diabetes mellitus and relationship between CT and other tests.

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PATIENTS AND METHODS

Forthy five patients with either insulin dependent (n:24) or noninsulin dependent (n:21) diabetes mellitus were studied. The control group consisted of twenty-five healty volunteers. Study subjects were free of any cardiovascular, kidney disease or the idiopathic long QT interval syndrome and were not receiving any cardioactive medication such as p-blokers, antihypertensive, vasodilators or antiarrhythmic agents. Informed consent was obtained from all subjects. Five simple autonomic function tests were performed lunch and approximately 3 hours after injection of insulin or taking of oral hypoglycemic agents in all diabetic subjects, while continuous electrocardiogram was recorded.

Valsalva manoeuvre: The patients blow into aneroid pressure gauge at a pressure of 40 mmHg for 15 seconds. The ratio of longest RR interval to the shortest RR interval was measured. The mean of the three Valsalva ratio was taken as a final value.

Beat to beat heart rate variability: This was determined with the patient breathing deeply at 6 breaths/min. The maximum and minimum heart rate during each 10 second breathing cycle was measured. The mean of the differences during six breathing cycles was taken as a final value.

Heart rate response to standing: The ratio of the RR interval at the 30th beat after standing to the RR interval at the 15 beat was calculated.

Blood pressure respond to standing: Blood pressure were measured with the patient in the supine position and at the end of 1 min. standing. The postural fall in blood pressure is taken as the difference between the systolic blood pressure lying and systolic blood pressure standing.

Blood pressure response to sustained hand-grip: Hand-grip was maintained at 30% of maximum voluntary contraction up to a maximum of five minutes and the blood pressure was measured each minute. The difference between the diastolic blood pressure just before release of hand-grip and before starting is taken as the measure of response.

The response to each test was graded as normal, borderline and abnormal. The individual score was the sum of the points for all the indices (0 given to a normal response, 1 to a borderline response and 2 to an abnormal response). Each diabetic patient was then classified by the total score as group 0, 1, 2 and 3 or 4.

QT_c interval study: After 15 min. resting, the QT intervals of five sinus beats were measured on electrocardiogram tracings taken at a paper speed of 50 mm/s. We calculated the corrected QT interval according to Bazett's formula.

$$Q\text{-}T_c: \frac{QT}{(R\text{-}R)^{1/2}}$$

The QTc interval for each patient was taken as the mean value of the measurements made.

The cough test (CT) performed in supine position, consisted of giving three maximal coughs spaced evenly over 3 s. when signaled each beginning with a brief inspiration. CT ratio was the ratio between the baseline RR interval and the shortest RR in the first 12 s. after coughing on electrocardiogram tracing taken at a paper speed of 50 mm/s.

Statistical Methods:

Results are expressed a meantSD. Differences between groups and variables were tested with Student's unpaired t test and x^2-test. Correlations among variables were tested by linear regressions.

RESULTS

The clinical characteristics of study subjects were shown in Table 1. There were no difference in sex, age and BMI between control subjects and diabetic patients.

Table 1. Clinical characteristics of study subjects

	Control (n-25)	IDDM (n=24)	NIDDM (n«21)	Total diabetics (n=45)
Age (years)	30.64i8.89*	23.95i4.69[1]	45.14l7.12[1]	33.84i12.20*
Sex (F/m)	12/13*	9/15	13/8	22/23*
BMI (kg/m²)	25.13±4.79*	21.63i2.74[1]	27.49i4.37[1]	24.37l4.62*
Diabetes Duration (yr.)		7.93+5.94	7.2814.60	7.6315.31
Fruktozamin (mMol)		3.25±1.03	2.9710.62	3.1410.89
Microalbuminuria (mg/24 h.)		18.1 ±22.3	58.94i93.29	35.0i64.21
Q-T_c ms.	399.04±13.2*	411.19±28.12*	416.75121.73	413.79125.21*
CT ratio	1.3210.09[1]	1.19±0.11*	1.1310.10*	1.1610.11[1]

MeaniSD
* : N.S.
[1] p<0.0001
* : p<0.01

Table 2. Clinical characteristics of Diabetic Patients with CAN and without CAN

Diabetes CAN scores	0 (n-11)	(n-21)	2 (n-8)	3-4 (n=5)
Age (yr)	28.717.0	39.5112	33.7114	38.2114
Sex (F/m)	3/8	11/10	6/2	2/3
BMI (kg/m²)	21.9i3.2	25.414.8	24.114.6	25.515.2
Diabetes duration (yr.)	4.614.7	7.915.9	8.5±3.9	11.612.3
Fructozamine (mMol)	3.1 ±1.1	3.010.7	3.7i 1.0	2.6±0.1
Microalbuminuria (mg/24 h)	61.911 20.0	28.9150	18.8H2	33.3H0
QT_c ms.	412.6119.5*	405122.1	427.8133.0	429.0i23.0*
CT ratio	1.210.1*	1.1710.1	1.1410.1	1.0410.03*

MeaniSD
* : p<0.01

There were no difference in sex, duration of diabetes, fructosamine and microalbuminuria between patients with IDDM and patients with NIDDM. Of the 45 patients with diabetes 34 had at least one abnormal CAN tests and 11 had no evidence of autonomic dysfunction (Table 2).

The QTc interval ranged from 365.5 to 418.8 ms (mean±SD 399.04±13.24) for control subjects and from 349.2 to 462.2 ms (mean±SD 413.79±25.21) for patients with diabetics ($p<0.01$). The mean QT_c interval was longer in diabetics than in control subjects. There was no statistically significant difference between QT_c interval of IDDM and NIDDM (411 19±28.12 vs. 416.75±21.73). QT_c interval>425.5 ms. was considered prolonged. Eleven diabetic group 0 and 1 there was a greater frequency of prolonged QTc interval in group 2 ($p<0.05$).

The CT ratio ranged from 1.00 to 1.46 (mean±SD 1.16+0.11) patients with diabetes and from 1.17 to 1.48 (mean±SD 1.32±0.09) for control subjects. There was no statistically significant difference between CT ratio of IDDM and NIDDM (1.19±0.11 vs. 1.13±0.10).

Diabetic patients in group 3 had significantly decreased CT ratio compared with healthy control subjects and diabetic patients with group O ($p<0.05$). CT ratio<1.14 was considered decreased and twenty diabetic patients (44.4%) had a decreased CT ratio. CT ratio showed a negative correlation with the age and QT_c interval ($p<0.05$). Heart rate responses to deep breating, standing up and the blood pressure response to sustained hand-grip were positively correlated with CT ratio (Figure 1,2,3,4,5).

DISCUSSION

Chronotropic response to intrathoracic pressure changes generated by cough, provides a reliable, noninvasive and quick index of cardioacceleratory capacity (9).

Cough test is in reflex nature and under cholinergic control. The normal response of cough test is characterized by an immediate RR shortening that is

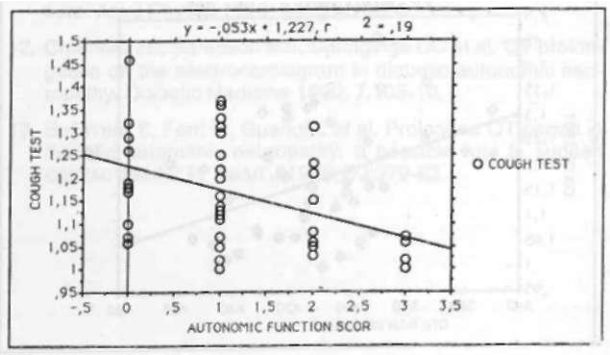
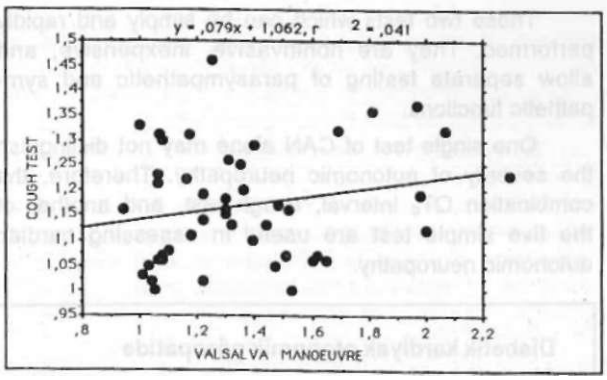
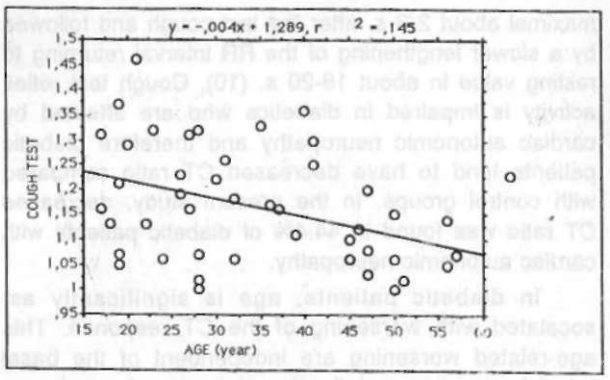


Figure 1. Correlation between cough test and autonomic function score





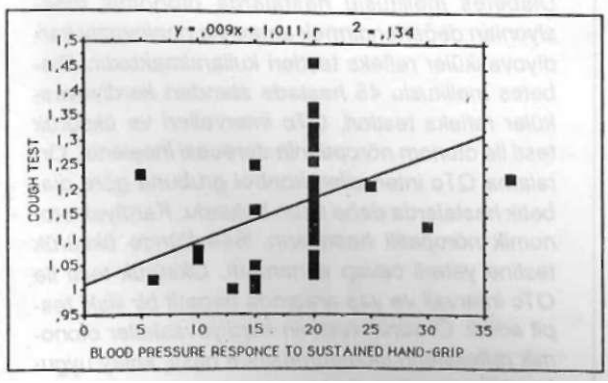


Figure 2. Correlation between cough test and indices of cardiovascular reflex tests

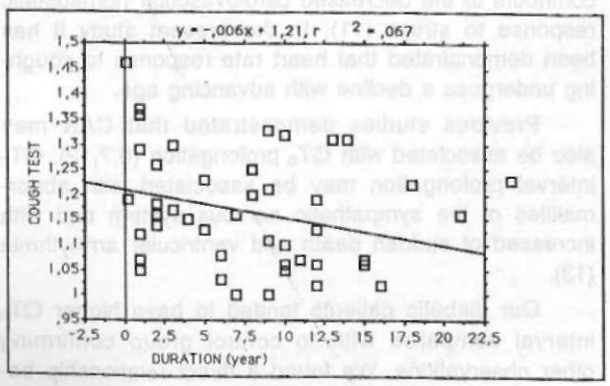
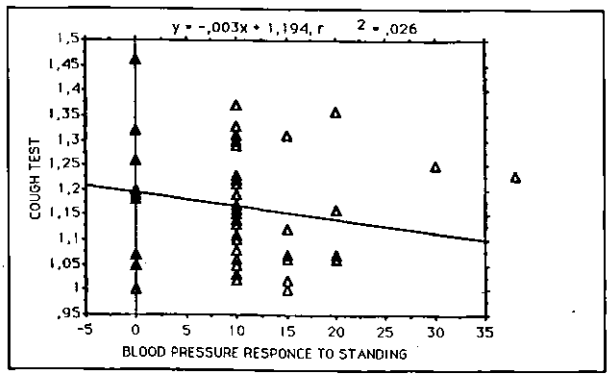


Figure 3. Correlation between cough test and indices of cardiovascular reflex tests



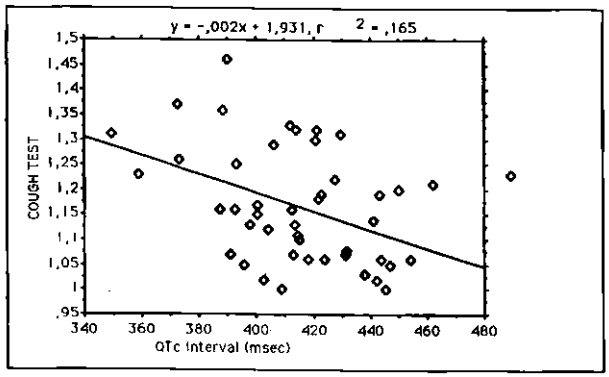
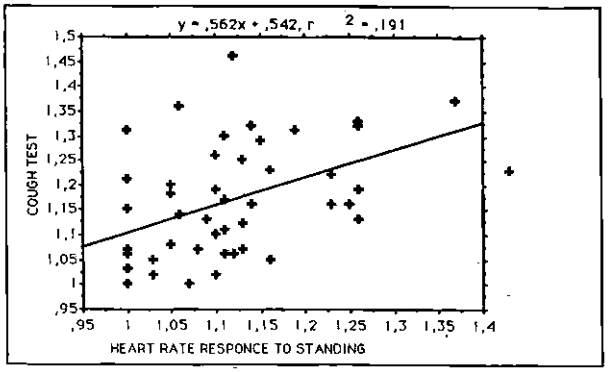


Figure 4. Correlation between cough test and indices of cardiovascular reflex tests



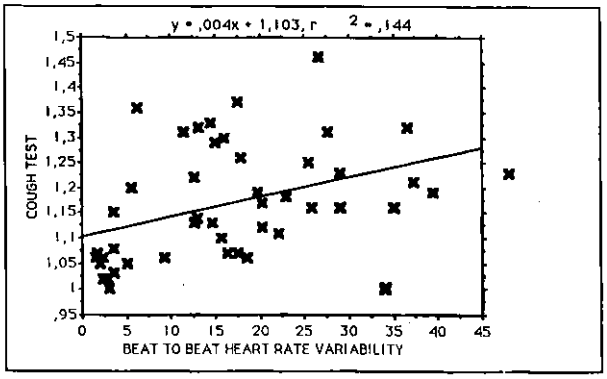


Figure 5. Correlation between cough test and indices of cardiovascular reflex tests

maximal about 2-3 s. after the last cough and followed by a slower lengthening of the RR interval returning to resting value in about 18-20 s. (10). Cough test reflex activity is impaired in diabetics who are affected by cardiac autonomic neuropathy and therefore diabetic patients tend to have decreased CT ratio compared with control groups. In the present study, decreased CT ratio was found In 44.4% of diabetic patients with cardiac autonomic neuropathy.

In diabetic patients, age is significantly assocaiated with worsening of the CT response. This age-related worsening are independent of the basal arterial pressure and the basal heart rate and may contribute to the decreased cardiovascular homeostatic response to stress (11). In the present study it has been demonstrated that heart rate response to coughing undergoes a decline with advancing age.

Previous studies demonstrated that CAN may also be associated with QT_c prolongation (6,7,12). QT_c interval prolongation may be associated with abnormalities of the sympathetic nervous system and with increased of sudden death and ventriculer arrthythmia (13).

Our diabetic patients tended to have higher QT_c interval compared with to control group confirming other observations. We found a direct relationship between the QT_c interval prolongation and worsening of the CT responce in patients with diabetes mellitus.

These two tests which can be simply and rapidly performed. They are noninvasive, inexpensive, and allow separate testing of parasympathetic and sympathetic functions.

One single test of CAN alone may not distinguish the severity of autonomic neuropathy. Therefore, the combination QT_c interval, cough test, and another of the five simple test are useful in assessing cardiac autonomic neuropathy.

Diabetik kardiyak otonomik nöropatide öksürük testi

Diabetes mellituslu hastalarda otonomik fonksiyonları değerlendirmek amacıyla noninvaziv kardiyovasküler refleks testleri kullanılmaktadır. Diabetes mellituslu 45 hastada standart kardiyovasküler refleks testleri, QTc intervalleri ve öksürük testi ile otonom nöropatinin derecesi incelendi. Ortalama QTc intervalleri kontrol grubuna göre diabetik hastalarda daha uzun bulundu. Kardiyak otonomik nöropatili hastaların %44.4'ünde öksürük testine yeterli cevap alınamadı. Öksürük testi ile QTc intervali ve yaş arasında negatif bir ilişki tespit edildi. Öksürük testinin kardiyovasküler otonomik reflekslerin incelenmesinde basit, kolay uygulanabilir ve güvenilir bir metod olduğu gösterildi. [TurkJMedRes1994, 12(5): 217-221]

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