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Original Article

Research of R-R Interval Recording Sensitivity in Diabetic Autonomic Neuropathy Diagnosis

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Abstract

Objective: This study aimed to evaluate the R-R interval recording sensitivity in the early diagnosis of diabetic autonomic neuropathy (DAN).

Methods: Sixty patients who applied to neurology outpatient clinics and were thought to have diabetic polyneuropathy were accepted to the study. The control group was formed by 31 healthy volunteers. The standard nerve conduction study and R-R interval measurements during resting and deep breathing were evaluated in the patient and control groups.

Results: When R-R interval measurements of the patient and control groups during resting and deep breathing were compared, no statistically significant difference between the groups was determined.

Conclusion: In the diagnosis of DAN, data about the recording of R-R interval measurements that show heart rate variability in resting and deep breathing as significant was not obtained. In larger patient groups, there is a need for broader studies in which Valsalva maneuver and tilt table test methods are also performed.

Keywords: Diabetes mellitus, autonomic neuropathy, R-R interval

Introduction

Diabetic autonomic neuropathy (DAN) is a common, serious complication of diabetes mellitus (DM). It is known that DAN is responsible for a significant proportion of mortality and subclinical morbidity induced by DM (1). Cardiovascular autonomic neuropathy (CAN) is a clinically significant form of DAN. This situation includes damage in autonomic nerve fibers, which ends with abnormal heart rate control and abnormality in vascular dynamics and innervates cardiac veins and blood vessels (2). Electrophysiological analyses have an important place in DAN diagnosis. Because they are short, cheap, and noninvasive, they can be used in practice. In this study, with the aim of evaluating autonomic function in diabetic patients who have neuropathic complaints and whose standard nerve conduction studies were evaluated as normal, it was aimed to record heart rate variability and R-R interval measurements.

Methods

Sixty patients in total who applied to neurology outpatient clinics were accepted to the study. They were clinically diagnosed with diabetic polyneuropathy. Twenty of them were men and forty of them were women. The control group was formed from 31 healthy volunteers who have no neuropathic complaints, DM, or any other endocrine pathology and toxic substance exposure. The inclusion criteria were as follows: age group of 30–70 years, clinical diagnosis of DM, diabetic neuropathy symptom scale is 1 or above, and the presence of electrophysiological symptoms in support of polyneuropathy in nerve conduction studies. The exclusion criteria were as follows: presence of any other disease that may cause neuropathy except diabetes and/or using drugs and substances that may cause neuropathy, pregnancy, presence of any other diseases that may affect the autonomic nervous system (ANS) functions except DM, use of drugs that may affect autonomic tests at the time of application, and presence of any heart and/or lung diseases in the medical history. Clinical evaluation tests, examination symptoms, age, gender, duration of disease, and drug usages of all patients were recorded. Neurological examination was confirmed as normal in the entire control group.

Electrophysiological examination of the patient and control groups was made using two-channeled Dantec Keypoint Portable model EMG device (Alpine Biomed ApS, Skovlunde, Denmark). In the standard nerve conduction study, the sensory and motor responses of three different peripheral nerves were recorded at a proper room temperature.

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R-R interval records were taken by placing disc electrodes to the dorsum of both hands while the patient is in a lying position. During resting and deep breathing (6 frequency/min), R-R recordings were taken. The shortest and the longest R-R evaluations were made. The proportion of the longest R-R interval to the shortest R-R interval was stated as E:I proportion, and this proportion was calculated separately during resting and during deep breathing using the following formula: R-R max. interval / R-R min. interval (measured automatically by the device). The value received during resting was indicated as R%. The value received during deep breathing was indicated as D%. The difference of two values was indicated as D%–R%, and their proportion to each other was indicated as D%/R%.

The research protocol was approved by the local ethical committee at İstanbul Training and Research Hospital. All patients gave their written informed consent.

Statistical analysis

The Statistical Package for the Social Sciences for Windows programversion 15 (SPSS, Inc.; Chicago, IL, USA) was used for statistical analysis. Student's t-test was used for comparisons between two groups when there is a normal distribution of numeric variables. The differences of categorical variables among the groups were tested using chi-square analysis. When the conditions were not provided, it was interpreted using Monte Carlo simulation. The relationships of numeric variables were tested with Spearman's correlation analysis. The value of p<0.05 was considered statistically significant.

Results

Twenty of the patients who participated in the study were male (33.3%), and 40 of the patients were female (66.6%). The average age was 55.17±8.11 years. Fourteen patients in the control group were male (49.25%) and 17 were female (54.84%). The average age of the control group was 49.00±12.09 years. According to the healthy controls, the average age of the patient group was significantly high (p=0.014). There was no difference between groups in terms of gender (p=0.269). The average diabetes duration of the patients was 8.78±7.54 years. In total, 21.6% of the patients were using insulin, and 78.3% of them were using oral anti-diabetics (OADs). When R-R interval measurements of the patient and control groups (R%, D%, D%/R%, D%–R%) were evaluated, a statistically significant difference between groups was not determined (p= 0.120, p=0.715, p=0.235, p=0.244) (Table 1).

R-R interval measurement averages in the patient group were evaluated according to gender groups. R-R interval values in deep breathing (D%) was significantly high (p=0.030) in women compared with men. In other measurements, a statistically significant difference was not determined in gender groups (p=0.082, p=0.150, p=0.333) (Table 2).

R-R interval measurement averages were evaluated according to treatment groups. In normal breathing (R%), the values of R-R interval was significantly high in OAD users compared with insulin users (p=0.019). In the other measurements, a statistically significant difference was not determined in treatment groups (p=0.445, p=0.818, p=0.159) (Table 3).

R-R interval measurements during normal breathing (R%) and deep breathing (D%) in the patient group were moderately statistically related in a negative manner (p<0.001, p=0.003). A statistically significant relationship between D%–R%, D%/R% levels, and age was not determined (p=0.537, p=0.637).

A statistically significant relationship between parameters evaluated and diabetes duration was not determined (p=0.095, p=0.449, p=0.581, p=0.383) (Table 4).

Table 1. Means of R-R interval measurements of the patient and control groups

		Patient	Control	p
R-R interval measurement	Normal breathing (R%)	11.25±5.22 (10.57)	12.95±5.09 (12.33)	0.120
	Deep breathing (D%)	17.15±8.38 (16.00)	17.15±7.41 (18.25)	0.715
	D%–R%	5.93±6.88 (4.73)	4.20±5.81 (4.07)	0.235
	D%/R%	1.64±0.79 (1.44)	1.37±0.52 (1.40)	0.244

Table 2. Evaluation of R-R interval measurements in the patient group according to gender

		Male	Female	p
R-R interval measurement	Normal breathing (R%)	9.09±5.99 (7.90)	11.84±4.89 (11.15)	0.082
	Deep breathing (D%)	15.42±8.20 (15.67)	17.63±8.45 (15.90)	0.030
	D%-R%	6.32±4.58 (7.13)	5.82±7.43 (4.20)	0.150
	D%/R%	1.79±0.58 (1.81)	1.60±0.84 (1.40)	0.333

Table 3. Evaluation of R-R interval measurements according to treatment groups

		Insulin	OAH	p
R-R interval measurement	Normal breathing (R%)	9.09±5.99 (7.90)	11.84±4.89 (11.15)	0.019
	Deep breathing (D%)	15.42±8.20 (15.67)	17.63±8.45 (15.90)	0.445
	D%-R%	6.32±4.58 (7.13)	5.82±7.43 (4.20)	0.818
	D%/R%	1.79±0.58 (1.81)	1.60±0.84 (1.40)	0.159

OAH: oral anti-diabetic

Discussion

Cardiovascular changes due to the effected ANS in diabetes mellitus may occur at any time of the disease. CAN is estimated to be present in at least 25% of type 1 diabetes and 30% of type 2 diabetes. CAN, which occurs in accordance with DM, increases the risk of ventricular arrhythmias and cardiac mortality (3). Therefore, early diagnosis and treatment has an important place in the management of the disease. Heart rate variability parameters are valuable symptoms that can be detected before the clinical changes occur at an early stage of disease (3-5). Decreased heart rate variability is considered to be a sign of an early and asymptomatic symptom of DM polyneuropathy (6).

Table 4. Evaluation of R-R interval measurements according to age and DM duration

	Age (n=91)		DM duration (n=60)	
	RHO	p	RHO	P
Normal breathing (R%)	-0.374	<0.001	-0.218	0.095
Deep breathing (D%)	-0.305	0.003	-0.100	0.449
D%-R%	-0.066	0.537	0.073	0.581
D%/R%	0.050	0.637	0.115	0.383

DM: diabetes mellitus

R-R interval measurements are examined in rest, Valsalva, hyperventilation, and postural changes tests. If the R-R interval variability is deviated by more than 50% compared to normal values, we can consider the involvement of the cardiac parasympathetic ANS (7). In the study by Khoharo and Abdul Waheed (8) conducted in 186 patients with type 2 diabetes, it was found that the risk of CAN is higher in patients with diabetes for more than 5 years. Heart rate variability was also observed to be related with the duration of diabetes and the control level of diabetes. At the end of the study, it was specified that the conduction of the test is useful to be performed in patients with diabetes for ≥5 years (8). In our study, there was no statistically significant relationship between the duration of diabetes and R-R interval measurements. This instance may be related with the lack of patients and a short disease duration.

Age- and diabetes-related CAN have been found to be associated in many studies (9, 10). In our study, patients with normal respiration (R%) and deep breathing (D%) R-R interval measurements with age showed a significantly moderately negative correlation. The age increase seems to be increasing the CAN formation with chronic hyperglycemia. In addition, both sympathetic and loss of function in parasympathetic ganglia develops as age advances, and nerve conduction seems to be reduced for various reasons (oxidative damage, decline in neuroprotective agents, synaptic degradation of organelles, extracellular matrix, etc.) on ANS's different pathways (11, 12). The observational study Stein et al. (13) conducted on healthy people for 5 years also shows that heart rate variability decreases with the age advancement. In summary, the increase of exposure to chronic hyperglycemia with age and several physiological changes that occur in ANS may explain the relationship between age and CAN.

The R-R interval measurement in our study found out that when evaluated according to gender, (D%) R-R interval values were found to be significantly higher in women. In other measurements, no significant difference between gender groups was determined. Spallone et al. (14), due to the DM, did not find a significant relationship between genders with CAN. In another study, female gender was found to be associated with the decrease of heart rate variability in insulin-dependent patients (15). In our study, R-R interval variability in deep inspiration was found lower with the male group. Given the conflicting results from studies of gender, the effects on autonomic neuropathy seem unclear.

When R-R interval measurement averages in the patient group were evaluated according to treatment groups, R-R interval values of OAD users was significantly high compared with insulin users during normal breathing (R%). In the other values, a statistically significant difference in the treatment groups was not determined. Relations of anti-diabetic treatment and autonomic neuropathy could not be shown in most of the studies (9, 14). However, in some studies, it is indicated that insulin treatment can provide CAN regression (16, 17). In our study, the observation of the difference in resting not being followed in deep breathing may be because the glycemic control level in the treatment groups is unknown. There is a need for studies with a larger number of patients, in which the relationship between treatment and autonomic neuropathy is examined. Numerous studies show that diabetes causes ANS damage and reduction in heart rate variability (18-21). In a study with 42 patients and 42 control groups, although a difference between R-R interval variability of two groups was not observed during resting, a significant drop in the diabetic group was observed when it was evaluated with deep breathing and tilt table tests (22). In our study, a significant difference between R-R interval measurements of the patient and control groups was not determined, although the average age of the patient group was older.

The limitations of our study were as follows: there are sympathetic skin responses that were used in the evaluation of ANS, not adding additional methods such as Valsalva maneuver and tilt table test in R-R interval records, and the small number of patients and age difference between the patient and control groups.

Conclusion

Decreased heart rate variability is considered to be a sign of an early and asymptomatic symptom of diabetic polyneuropathy. Based on these symptoms, in patients whose nerve conduction studies were determined as normal in the electrophysiological examinations of diabetic polyneuropathy, data about the recording of R-R interval measurements that shows heart rate variability during resting and deep breathing as significant was not obtained. In larger patient groups, there is a need for broader studies in which Valsalva maneuver and tilt table test are performed.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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References

1. Tarsy D, Freeman R. Nervous system and diabetes. In: Kahn CR, Joslin EP, editors. Joslin's Diabetes Mellitus. 13th ed. Philadelphia: Lippincott Williams & Wilkins; 1994. p. 792-817.
2. Pfeifer MA, Schumer MP. Clinical trials of diabetic neuropathy: past, present, and future. Diabetes 1995; 44: 1355-61. [CrossRef]

3. Jelinek H, Flynn A, Warner P. Automated assessment of cardiovascular disease associated with diabetes in rural and remote health care practice. The National SARRAH Conference; 2004 August 26-28; Northern Territory, Australia; 2004. p. 1-7.
4. Geevarghese PJ, Abraham AK, Annie P. The mechanism of diabetes mellitus. In: Geevarghese PJ, editor. A Hand Book for Diabetics. 8th ed. Cochin: India; 1999. p. 8-9.
5. Uehara A, Kurata C, Sugi T, Mikami T, Shouda S. Diabetic cardiac autonomic dysfunction: parasympathetic versus sympathetic. Ann Nucl Med 1999; 13: 95-100. [CrossRef]
6. Dyck JB, Dyck PJ. Diabetic polyneuropathy. In: Dyck PJ, Thomas PK editors. Diabetic Neuropathy. Philadelphia: W.B. Saunders; 1999. p. 255-78.
7. Ertekin C. Diyabetik Nöropatiler. In: Ertekin C, editor. Santral ve Periferik EMG Anatomi-Fizyoloji-Klinik. 1st ed. İzmir: Nobel Tıp Kitabevleri; 2006. p. 211, 228, 897-908.
8. Khoharo HK, Abdul Waheed H. QTc-interval, heart rate variability and postural hypotension as an indicator of cardiac autonomic neuropathy in type 2 diabetic patients. Journal of Pakistan Medical Association 2012; 62: 328-31.
9. Jaffe RS, Aoki TT, Rohatsch PL, Disbrow EA, Fung DL. Predicting cardiac autonomic neuropathy in type I (insulin-dependent) diabetes mellitus. Clin Auton Res 1995; 5: 155-8. [CrossRef]
10. Veglio M, Carpano-Maglioli P, Tonda L, Quadri R, Giannella R, Rosa C, et al. Autonomic neuropathy in non-insulin-dependent diabetic patients: correlation with age, sex, duration and metabolic control of diabetes. Diabete & Metabolisme 1990; 16: 200-6.
11. Docherty JR. Age-related changes in adrenergic neuroeffector transmission. Autonomic Neuroscience 2002; 96: 8-12. [CrossRef]
12. White M, Roden R, Minobe W, Khan MF, Larrabee P, Wollmering M, et al. Agerelated changes in beta-adrenergic neuroeffector systems in the human heart. Circulation 1994; 90: 1225-38. [CrossRef]
13. Stein PK, Barzilay JI, Chaves PH, Domitrovich PP, Gottdiener JS. Heart rate variability and its changes over 5 years in older adults. Age Ageing 2009; 38: 212-8. [CrossRef]
14. Spallone V, Maiello MR, Cicconetti E, Menzinger G. Autonomic neuropathy and cardiovascular risk factors in insulin-dependent and non insulin-dependent diabetes. Diabetes Res Clin Pract 1997; 34: 169-79. [CrossRef]
15. Maser RE, Pfeifer MA, Dorman JS, Kuller LH, Becker DJ, Orchard TJ. Diabetic autonomic neuropathy and cardiovascular risk. Pittsburgh Epidemiology of Diabetes Complications Study III. Arch Intern Med 1990; 150: 1218-22. [CrossRef]
16. Cerutti F, Rabbia F, Rabbone I, Bobbio A, Ignaccolo MG, Greco G, et al. Impairment of cardiovascular autonomic pattern in obese adolescents with Type 2 diabetes mellitus. J Endocrinol Invest 2010; 33: 539-43. [CrossRef]
17. Schnell O, Kilinc S, Rambeck A, Standl E. Insulin therapy improves cardiac autonomic function in type 2 diabetic patients (in German). Herz 2004; 29: 519-23.
18. Bellavere F. Heart rate variability in patients with diabetes and other noncardiological disease. In: Malik M, Camm AJ, editors. Heart Rate Variability. Armonk, NY: Futura Publishing, 1995. p. 507-16.
19. Maser RE, Lenhard MJ. Cardiovascular autonomic neuropathy due to diabetes mellitus: clinical manifestations, consequences, and treatment. J Clin Endocrinol Metab 2005; 90: 5896-903. [CrossRef]
20. Meyer C, Milat F, McGrath BP, Cameron J, Kotsopoulos D, Teede HJ. Vascular dysfunction and autonomic neuropathy in type 2 diabetes. Diabet Med 2004; 21: 746-51. [CrossRef]
21. Schroeder EB, Chambless LE, Liao D, Prineas RJ, Evans GW, Rosamond WD, et al. Diabetes, glucose, insulin, and heart rate variability. Diabetes Care 2005; 28: 668-74. [CrossRef]
22. Asahina M, Yamanaka Y, Akaogi Y, Kuwabara S, Koyama Y, Hattori T. Measurements of sweat response and skin vasomotor reflex for assessment of autonomic dysfunction in patients with diabetes. Journal of Diabetes and Its Complications 2008; 22: 278-83. [CrossRef]