

## HEART RATE VARIABILITY AND CARDIOVASCULAR SYMPTOMS IN PATIENTS WITH DIABETES MELLITUS

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### Abstract

**Background.** The autonomic nervous system is often imbalanced in patients with type 2 diabetes mellitus (DM) and this may be clinically inapparent. Cardiovascular autonomic neuropathy (CAN) is a common form of autonomic dysfunction in DM patients and associates abnormalities in heart rate control, as decreased heart rate variability (HRV) and in central and peripheral vascular dynamics.

**Subjects and methods.** The study group consisted of 64 patients, diagnosed with type 2 diabetes mellitus. The control group consisted of 55 healthy subjects. Chronic heart failure and uremia was excluded. We created two study groups, with and without cardiovascular symptoms. Exercise tolerance was measured using rating of perceived exertion scale in correlation with a standard effort. HRV was measured using a 24-hour ECG monitoring system. Time domain parameters used are: SDNN, SDANN and pNN50 %; frequency domain parameters are: low frequency (LF), high frequency (HF) and LF/HF ratio.

**Results.** There are significant differences between disease duration (and not age), in patients with cardiovascular symptoms. Orthostatic hypotension was found in 13 patients and heart rate increased over 100 at rest was found in 28 patients. HRV parameters are lower in DM group but differences are significant only for SDNN and LF, HF, and normalized units HF. From the total group, more than half had HRV parameters below the normal range (51%), and 72% of them had also cardiovascular symptom. Of the asymptomatic patients, 14 (51.85%) had abnormal HRV parameters.

**Conclusion.** Subclinical autonomic neuropathy should be detected using autonomic function tests. Waiting for symptoms to appear is not recommended, as clinical signs and symptoms not always progress, so are not reliable tools in early diagnosis and risk stratification.

**Keywords:** autonomic neuropathy, cardiovascular symptoms, diabetes mellitus, heart rate.

## VARIABILITATEA FRECVENȚEI CARDIACE ȘI SIMPTOMELE CARDIOVASCULARE LA PACIENȚII CU DIABET ZAHARAT

### Rezumat

**Premize.** Sistemul nervos autonom este adesea dezechilibrat la pacienții cu diabet zaharat tip 2 (DZ), dar fără simptome sau semne vizibile. Neuropatia autonomă cardiovasculară este o formă frecventă a neuropatiei autonome în DZ și include anomalii ale controlului frecvenței cardiace (cum ar fi reducerea variabilității frecvenței cardiace - VFC) și în dinamica sistemului vascular central și periferic.

**Metode.** Grupul de studiu a fost format din 64 de pacienți cu DZ tip 2. Grupul de control a fost format din 55 de subiecți sănătoși. Au fost excluși pacienții cu insuficiență cardiacă și/sau renală cronică. Grupul de studiu a fost împărțit în două subgrupuri, cu și fără simptome cardiovasculare. Toleranța la efort a fost măsurată cu ajutorul unei scale de cuantificare a percepției intensității efortului depus. VFC a

*fost măsurată cu ajutorul înregistrărilor ECG pe 24 de ore și s-au analizat parametrii de timp (SDNN, SDANN, pNN50 %) și de frecvență (LF, HF și raportul LF/HF).*

**Rezultate.** *Sunt diferențe semnificative între durata bolii (dar nu și vârstă), în favoarea celor cu simptome cardiovasculare. Hipotensiunea ortostatică a fost înregistrată la 13 pacienți, iar FC crescută peste 100 în repaus, la 28 de pacienți. Parametrii VFC sunt mai mici la cei cu DM, diferențe semnificative înregistrându-se doar pentru SDNN, LF, HF și HFnu. Din grupul total, mai mult de jumătate dintre pacienți au parametrii VFC sub limita normală (51%), iar 72% dintre aceștia au și simptome cardiovasculare. Dintre pacienții asimptomatici, 14 (51.85%) au avut parametrii VFC modificați.*

**Concluzii.** *Neuropatia autonomă subclinică ar trebui căutată cu ajutorul testelor funcționale autonome. Nu este recomandat să se aștepte apariția simptomelor, deoarece acestea nu progresează întotdeauna în paralel cu agravarea neuropatiei autonome, iar lipsa lor nu exclude boala, nefiind o unealtă diagnostică validă pentru diagnosticul precoce și stratificarea riscului cardiovascular.*

**Cuvinte cheie:** neuropatie autonomă, simptome cardio-vasculare, diabet zaharat, frecvență cardiacă.

## Introduction

The autonomic nervous system is often imbalanced in patients with type 2 diabetes mellitus (DM) and this may be clinically inapparent. Cardiovascular autonomic neuropathy (CAN) is a common form of autonomic dysfunction in DM patients and associates abnormalities in heart rate control, as decreased heart rate variability (HRV) and in central and peripheral vascular dynamics [1].

The pathogenesis of CAN includes: disorders of polyol metabolism, disorders of fatty acid metabolism, accumulation of glycated proteins, endoneural hypoxia, oxidative stress, destruction of nerve growth factors and axonal transport and immunological processes [2]. CAN occurs in about 17% of patients with type 1 diabetes and about 22% of those with type 2 [3].

Several epidemiological studies among individuals with diabetes showed that the 5-year mortality rate is almost five times higher for individuals with CAN than for individuals without cardiovascular autonomic involvement [4,5,6,7,8,9].

The stronger association observed in studies defining cardiovascular autonomic neuropathy by the presence of two or more abnormalities may be due to more severe autonomic dysfunction in these patients or a higher frequency of other co-morbid complications that contributed to their higher mortality risk [10].

Symptoms and signs associated with CAN are: **resting tachycardia** is an early sign, associated with the loss of heart rate variations during sleep [11]; **exercise intolerance**, as a result of impaired parasympathetic/sympathetic responses. Also, exercise tolerance may be limited by systolic and diastolic dysfunction, potentially a result of CAN [1]; **orthostatic hypotension** (OH),

characterized by a defect in the reflex that ensure the proper increase of blood pressure on standing. OH results in weakness, dizziness, faintness, visual impairment, and syncope. The definition of OH is a fall in blood pressure on standing more than 20-30 mmHg for systolic, and/or more than 10 mmHg for diastolic [12]; **abnormal circadian pattern of blood pressure**, when BP rises during night and decreases in the morning [11]; **intraoperative cardiovascular lability**, with a 2 to 3 fold increase in cardiovascular intraoperative mortality and morbidity for diabetic patients [9]; **painless myocardial ischemia** is the inability to detect ischemic pain in patients with DM.

The relation between heart rate variability and cardiovascular symptoms is widely discussed; it seems that the absence of symptoms doesn't account for a normal HRV. At the time of diagnosis, a reduced HRV is evident in type 2 DM which reflects the asymptomatic process over the years, before diagnosis [2,13,14].

Autonomic nervous function can be assessed according to the consensus statement of the American Diabetes Association and the American Academy of Neurology, using four tests, the description of which is beyond the interest of this study; the presence of CAN is established if at least two of four tests are positive. 24-hour ECG recording is another method used more and more in the last decade, as an alternative of above mentioned tests, and seems more reliable and more sensitive [11].

The objective of this study was to evaluate the impact of diabetes mellitus on heart rate variability parameters measured on 24-hour ECG recording in a group of type 2 diabetes mellitus with or without symptoms of CAN and also between heart rate variability and other associated complications.

## Subjects and methods

### Study population

The study group consisted of 64 patients, males

and females, diagnosed with type 2 diabetes mellitus and followed up at an outpatient clinic. Data on complications of diabetes were recorded. The control group consisted of 55 healthy subjects who were matched for age and sex. Patients with chronic heart failure and uremia were excluded from this study.

We created two study groups of patients, with and without cardiovascular symptoms: tachycardia at rest, exercise intolerance, orthostatic hypotension (dizziness, syncope). For the last one, the symptoms were taken into account only if there was an objective correlation demonstrated between symptoms and low blood pressure at standing. Exercise tolerance was measured using rating of perceived exertion scale in correlation with a standard effort [15]. Inform consent was obtained from all patients and the study was conducted according to the Declaration of Helsinki.

#### Heart rate variability

HRV was measured using a 24-hour ECG monitoring system (Holter Digital recorder AsPEKT 812) in all subjects during normal daily activity. Time domain parameters used are: SDNN expressed in milliseconds (ms) accounts for standard deviation of all NN intervals. SDANN expressed in ms accounts for standard deviation of the averages of NN intervals in all 5 min segments of the entire recording. pNN50 % is the number of pairs of adjacent NN intervals divided by the total number of all NN intervals. Frequency domain parameters used are: low frequency and high frequency components of spectral analysis expressed in squared milliseconds (ms<sup>2</sup>) or normalized units.

#### Statistical analysis

The data are presented as mean  $\pm$  SD unless otherwise specified. Comparison between groups of subjects for various parameters was performed by ANOVA using SPSS 8 for Windows. Student's paired t test and Pearson's linear correlation coefficients were also used to evaluate the data (for statistical significance and for pairs of continuous variables). A p value less than 0.05 was considered statistically significant.

#### Results

Characteristics of the DM patients are shown in table 1 and demographic data in table 2.

There are significant differences between disease duration (and not age), in favor of patients with cardiovascular symptoms; symptomatic patients are more prone to take insulin, while more asymptomatic patients are on oral therapy. There are also significant differences regarding disease control, which is worse in symptomatic patients.

Orthostatic hypotension was found in 13 patients (20.3%), and heart rate increased over 100 at rest was found in 28 patients (43.75%). Both OH and resting tachycardia strongly correlated with disease duration ( $r = 0.73$  and  $r = 0.80$  respectively).

#### Heart rate variability parameters

Heart rate variability parameters are lower in DM group as compared with control group, but differences are significant only for SDNN (from time domain parameters) and LF, HF and normalized units HF (for frequency domain

**Table 1.** Demographic characteristics of the study group.

Parameter	Diabetes mellitus	Control
<b>Number</b>	64	55
<b>Gender</b>	<b>B:</b> 34 (53.1%) <b>F:</b> 30 (46.8%)	<b>B:</b> 29 (52.7%) <b>F:</b> 26 (47.2%)
<b>Age</b>	61.34 ( $\pm 8.71$ )	59.55 ( $\pm 6.78$ )
<b>Disease duration (years)</b>	10.22 ( $\pm 9.67$ )	NA
<b>Insulin treatment</b>	12 (18.75%)	NA
<b>Per os treatment (sulfonyluree)</b>	14 (21.8%)	NA
<b>Per os treatment (biguanids)</b>	26 (40.6%)	NA
<b>Cholesterol (mg%)</b>	236.88 ( $\pm 66.93$ )	165.21 ( $\pm 38.91$ )
<b>Triglycerides (mg%)</b>	183.45 ( $\pm 93.07$ )	110.33 ( $\pm 49.21$ )
<b>Fasting plasma glucose (mg%)</b>	159.42 ( $\pm 53.63$ )	81.02 ( $\pm 11.33$ )
<b>HbA1c (%)</b>	7.20 ( $\pm 1.59$ )	4.1 ( $\pm 2.1$ )

**Table 2.** Demographic characteristics according to the presence and absence of symptoms.

Parameter	Symptoms + Value (mean $\pm$ SD) or N, %	Symptoms - Value (mean $\pm$ SD) or N, %
<b>Number</b>	37	27
<b>Gender</b>	<b>B:</b> 19 (51.35%) <b>F:</b> 18 (48.60%)	<b>B:</b> 15 (55.55%) <b>F:</b> 12 (44.44%)
<b>Age</b>	60.23 ( $\pm 8.02$ )	58.11 ( $\pm 7.88$ )
<b>Disease duration (years)</b>	10.14 ( $\pm 9.67$ )	6.88 ( $\pm 10.55$ )*
<b>Insulin treatment</b>	9 (24.32%)	3 (11.11%)*
<b>Per os treatment (sulfonylureic compounds)</b>	4 (10.8%)	10 (37.03%)*
<b>Per os treatment (biguanids)</b>	10 (27.02%)	16 (59.25%)
<b>Cholesterol</b>	266.58 ( $\pm 76.63$ )	249.18 ( $\pm 67.36$ )
<b>Triglycerides</b>	191.45 ( $\pm 100.05$ )	184.68 ( $\pm 99.11$ )
<b>Fasting plasma glucose</b>	189.72 ( $\pm 23.13$ )	129.72 ( $\pm 43.76$ ) *
<b>HbA1c</b>	8.40 ( $\pm 1.15$ )	7.10 ( $\pm 1.66$ ) *

parameters). From the total group, more than half had HRV parameters below the normal range (51%), of which 72% had also cardiovascular symptoms. Of the asymptomatic patients, 14 (51.85%) had abnormal HRV parameters. HRV parameters are displayed in table 3.

**Table 3.** Heart rate variability parameters according to the presence and absence of symptoms.

Parameter	Symptoms + (mean $\pm$ SD)	Symptoms - (mean $\pm$ SD)
<i>SDNN</i>	116.17 ( $\pm$ 41.24)	107.37 ( $\pm$ 37.42) *
<i>SDANN</i>	89.64 ( $\pm$ 34.18)	83.94 ( $\pm$ 59.28)
<i>p50NN %</i>	24.72 ( $\pm$ 12.98)	22.53 ( $\pm$ 16.85)
<i>LF</i>	637.19 ( $\pm$ 285.35)	564.11 ( $\pm$ 280.75)*
<i>HF</i>	537.78 ( $\pm$ 357.28)	445.68 ( $\pm$ 339.13)*
<i>LFnu</i>	39.47 ( $\pm$ 12.09)	31.17 ( $\pm$ 19.05)
<i>HFnu</i>	22.43 ( $\pm$ 8.11)	16.44 ( $\pm$ 6.13)*
<i>LF/HF</i>	1.75 ( $\pm$ 0.54)	1.70 ( $\pm$ 0.51)

### Discussions

CAN is best evaluated using heart rate variability (HRV) on 24-hours recordings. A reduction in time-domain parameters of heart rate variability seems not only to carry negative prognostic value but also to precede the clinical expression of autonomic neuropathy [16,17,18,19]. In diabetic patients without evidence of autonomic neuropathy, reduction of the absolute power of low-frequency (LF) and high-frequency (HF) during controlled conditions was also reported [18]. LF and very-low frequency (VLF) components account for sympathetic dysfunction and HF component accounts for parasympathetic dysfunction.

However, when the LF/HF ratio is considered or when LF and HF are analyzed in normalized units, no significant difference in comparison to normal individuals is present [20].

In advanced cardiac autonomic neuropathy all the components of HRV are reduced (both for sympathetic and parasympathetic activity), along with LF/HF ratio [11].

In our study, we found a positive correlation between disease duration and HRV parameters, and the presence of cardiovascular symptoms. The strongest correlation was between HF and disease duration ( $r = 0.75$ ). The correlation between disease duration and autonomic damage is still under debate. As we already said, at the time of diagnosis, a reduced HRV is frequently discovered in type 2 DM patients, which reflects the manifestation of the asymptomatic process during many years. The connection between autonomic neuropathy and disease duration of diabetes and patient's age are still unclear. On the other hand, symptoms and signs of autonomic dysautonomy may be stable over time, both in type 1 and type 2 DM patients [2]. This suggests the need of reliable, objective diagnostic tools, other than clinical ones, to allow early risk stratification.

Exercise tolerance is limited as a result of impaired sympathetic/parasympathetic response. For diabetic patients suspected of CAN, cardiac stress testing should be performed before beginning an exercise rehabilitation

program [1]. The use of heart rate to evaluate exercise tolerance may be inappropriate in these patients, as maximal heart rate is depressed in patients with CAN. In our group we used another method, Rating of Perceived Exertion scale, which uses the subjective feelings of intensity of the individual, instead in heart rate and oxygen consumption. Patients with lower HRV parameters had lower scale scores and lower exercise tolerance.

Orthostatic hypotension correlates with HRV ( $r = 0.66$ ) and heart rate ( $r = -0.71$ ), but only a minority of the total group had symptomatic orthostatic hypotension. OH is associated with sympathetic nervous dysfunction and is a relatively late complication [11].

### Conclusion

It is important that autonomic dysfunction can be detected at the time of diagnosis, correlates with poor glycemic control; there is a long period of time in which patients are asymptomatic but the disease progress; this so called subclinical autonomic neuropathy could and should be detected using autonomic function tests, including 24-hour Holter monitoring. Waiting for symptoms to appear is not recommended, as clinical signs and symptoms not always progress, so are not reliable tools in early diagnosis risk stratification.

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