

Heart rate turbulence in patients with poorly controlled diabetes mellitus type 2

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Abstract

Introduction: Cardiac autonomic neuropathy (CAN) causes substantial morbidity and increased mortality in patients with diabetes mellitus (DM). Besides heart rate variability (HRV), heart rate turbulence (HRT) is an important method of assessment of cardiac autonomic regulation. The aim of the study was to assess the correlation between HRT and diabetic control.

Material and methods: Fifty-nine patients met the inclusion criteria – 38 males and 21 females, age 64.4 ± 7.6 . The patients included had inadequately controlled DM type 2 defined as glycated haemoglobin (HbA_{1c}) $> 9\%$ (mean $11.8 \pm 2.7\%$). In all patients, intensive insulin treatment had been applied for 6 months. After 6 months, HbA_{1c} was measured. ECG Holter monitoring was performed before and after insulin treatment to evaluate the time domain HRV and HRT parameters (turbulence onset (TO) and turbulence slope (TS)).

Results: After 6 months of intensive insulin treatment, HbA_{1c} concentrations ranged from 6.3% (45 mmol/mol) to 11.2% (99 mmol/mol) – mean $8.5 \pm 3.8\%$ (69 ± 18 mmol/mol). Significant improvement of TO, TS and SDNN was observed. The TO and TS significantly correlated with HbA_{1c} ($r = 0.35$, $p = 0.006$ and $r = -0.31$, $p = 0.02$ respectively). Among analyzed HRV time domain parameters such as SDNN, rMSSD and pNN50, only SDNN correlated with HbA_{1c} ($r = -0.41$, $p = 0.001$). It was further concluded that intensive insulin therapy led to better glycemic control, resulting in improvement of HRT.

Conclusions: Heart rate turbulence may be useful in monitoring changes of the autonomic nervous system functions in patients with DM, similarly to HRV parameters.

Key words: diabetes mellitus, heart rate turbulence, diabetic autonomic neuropathy.

Introduction

Diabetic autonomic neuropathy causes substantial morbidity and increases mortality, more specifically if cardiovascular autonomic neuropathy (CAN) is present. A patient's history and physical examination are ineffective for early detection of CAN. Therefore noninvasive tests that have demonstrated efficacy are vital to diagnose and detect CAN earlier, rather than later [1]. Heart rate turbulence (HRT) has become an important method of assessment of cardiac autonomic regulation. It is a reliable indicator of baroreceptor sensitivity [2, 3]. Previous studies have revealed decreased HRT parameters in diabetes mellitus type 2, with and without cardiac autonomic neuropathy [4, 5]. Other studies have shown

that strict glycemic control leads to improvement of the autonomic nervous system [6, 7].

The aim of this study was to determine the influence of glycemic control on HRT.

Material and methods

Fifty-nine patients with poorly controlled diabetes mellitus type 2 met the criteria for inclusion in the study. Hemoglobin A_{1c} concentration (HbA_{1c}) was used to assess glycemic control. Patients with HbA_{1c} > 9% and with ventricular premature beats (VPBs) agreeing to HRT analysis were used in the study. All participants underwent a 24-hour Holter recording (SUPRIMA 12, DMS, USA) to assess time domain HRV and HRT components, turbulence onset (TO) and turbulence slope (TS). All Holter recordings were performed in an ambulatory setting. Recordings from digital 12-lead recorders (DMS 300-12, USA), with a sample rate of 1024 bps, were analyzed. The initial heart rhythm acceleration after ventricular premature beat is defined as TO and the ensuing deceleration as TS. Recordings lasting for ≥ 18 h containing at least 30 premature ventricular beats were included in the analysis. According to HRT consensus guidelines [8], sequences with at least 2 sinus rhythm R-R intervals before VPBs, and at least 15 subsequent sinus R-R intervals were included in the HRT analysis. Also analyzed VPBs were limited to VPBs with prematurity > 20% and a compensatory pause of > 120% of the mean of the last five sinus rhythm intervals preceding the VPB. After manual review of the Holter tracings, TO and TS were determined according to a previously published method [8]. In cases in which the criterion was not achieved, recordings were repeated – maximally three times. If Holter recordings were non-interpretable despite three rep-

etitions, the patient was excluded from the study. Coronary artery disease defined as > 70% narrowing in ≥ 1 coronary artery on a previous coronary angiogram, history of myocardial infarction, acute coronary syndrome, or typical angina pectoris, dilated or hypertrophic cardiomyopathy, nonsinus rhythm, hyper- or hypothyroidism, sustained or nonsustained ventricular tachycardia on Holter recording, hemodynamically significant valvular disease, and use of drugs that may influence HR variability and HR turbulence parameters, such as β-blockers and antiarrhythmic drugs, were excluded from the study. Subsequently intensive insulin therapy was started. All patients received subcutaneously short acting insulin (Insulin R) three times a day and long lasting insulin (Insulin N) at night. Insulin dosage was based on frequent – four times a day – glucose concentration measurement made by patients on a glucometer. In case of complications with insulin dosage by patient consultation, a diabetologist was available on-call.

After 6 months of intensive insulin treatment, concentrations of HbA_{1c} were analyzed and all participants underwent a 24-hour Holter recording to assess time domain HRV and HRT.

Statistical analysis

Analysis of the results was performed using Stat Direct software v.1.9.8. Nominal variables were presented as number of cases with percentage and continuous variables as mean ± SD. After testing for normal distribution using the Shapiro-Wilk test, nonparametric Mann-Whitney *U* test was used for comparison between groups and Wilcoxon's signed ranks test for analysis of the same group. Correlations were performed using Spearman's correlation tests. A *p* value < 0.05 was considered statistically significant.

Results

Characteristics of studied patients are listed in Table I.

In the study group, baseline HbA_{1c} concentration was 11.8 ± 2.7% (105 ± 13 mmol/mol). After 6 months of intensive insulin treatment, mean HbA_{1c} concentration was 8.5 ± 3.8% (69 ± 18 mmol/mol). Significant improvement of TO, TS and standard deviation of all normal-normal intervals (SDNN) were also observed, as presented in Table II. Examples of HRT parameter changes in the single patient are shown in Figures 1 and 2.

At the end of the study, the HRT parameters TO and TS correlated with HbA_{1c} ($r = 0.35, p = 0.006$ and $r = -0.31, p = 0.02$ respectively) (Figures 3 and 4).

Among the analyzed HRV time domain parameters SDNN, square root of the mean of the squares of differences between adjacent normal-normal

Table I. Baseline characteristics of patients included in the study

Parameter	Results
Number of patients	59
Sex (male/female)	38/21 (64%/36%)
Age, mean ± SD [years]	64.4 ± 7.6
Body mass index, mean ± SD [kg/m ²]	30.3 ± 4.5
Duration of diabetes, mean ± SD [years]	5.0 ± 1.3
Baseline HbA _{1c} , mean ± SD [%, mmol/mol]	11.8 ± 2.7, 105 ± 13
Insulin therapy, <i>n</i> (%)	15 (25)
Oral antidiabetic drugs, <i>n</i> (%)	35 (59)
Insulin + oral antidiabetic drug, <i>n</i> (%)	5 (8)
No diabetes treatment or diet only, <i>n</i> (%)	4 (7)

Table II. Changes of HRT and HRV after intensive insulin treatment

Parameter	Before intensive insulin therapy	After intensive insulin therapy	Value of <i>p</i>
TO (%)	-1.1 ±1.4	-1.6 ±1.4	0.001
TS [ms/RR]	12.1 ±9.5	13.8 ±6.7	0.01
SDNN [ms]	113.7 ±16.2	119.5 ±14.9	0.001
rMSSD [ms]	22.9 ±8.8	23.4 ±8.5	NS
pNN50 (%)	3.5 ±1.4	3.6 ±1.5	NS

TO – turbulence onset, TS – turbulence slope, SDNN – standard deviation of all normal-normal intervals, rMSSD – square root of the mean of the squares of differences between adjacent normal-normal intervals, pNN50 – percentage of differences between adjacent normal-normal intervals greater than 50 ms.

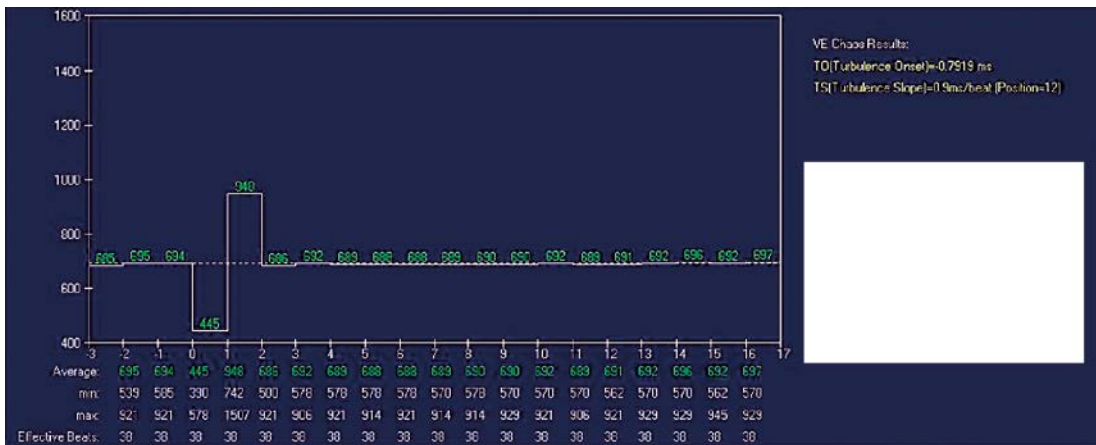


Figure 1. Example of heart rate turbulence (HRT) analysis in a patient before intensive insulin treatment. Turbulence onset (TO) = 0.7919 ms, turbulence slope (TS) = 0.9 ms/RR

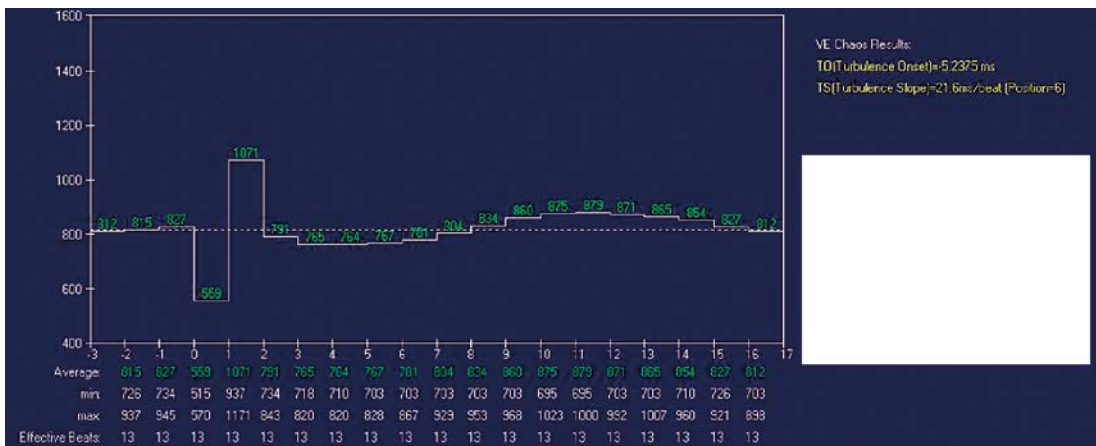


Figure 2. Example of heart rate turbulence (HRT) analysis in the same patient as presented at Figure 1, after intensive insulin treatment. Turbulence onset (TO) = -5.2375 ms, turbulence slope (TS) = 21.6 ms/RR

intervals (rMSSD) and percentage of differences between adjacent normal-normal intervals greater than 50 ms (pNN50), only SDNN correlated with HbA_{1c} ($r = -0.41, p = 0.001$) (Figure 5).

Discussion

The main finding of this study is that improvement of glycemic control leads to improvement of HRT parameters. Heart rate turbulence is an indirect measurement of baroreflex sensitivity depen-

dent on autonomic nervous system function. The metabolic disorder of diabetes leads to damage of peripheral and autonomic nerves. Clinical manifestations of autonomic dysfunction frequently occur concurrently but not in consistent patterns. Therefore, it can be suspected that a patient diagnosed with diabetes mellitus type 2 should have at least subclinical disturbances of the autonomic nervous system [9]. Cardiovascular autonomic neuropathy has been linked to cardiac arrhythmias, postural hypotension, exercise intolerance,

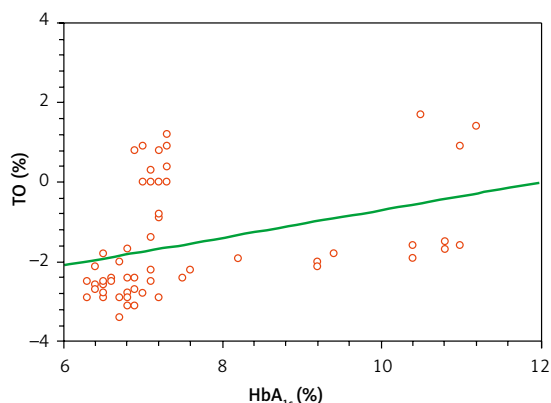


Figure 3. Correlation between TO (turbulence onset) and HbA_{1c} concentration ($r = 0.35, p = 0.006$)

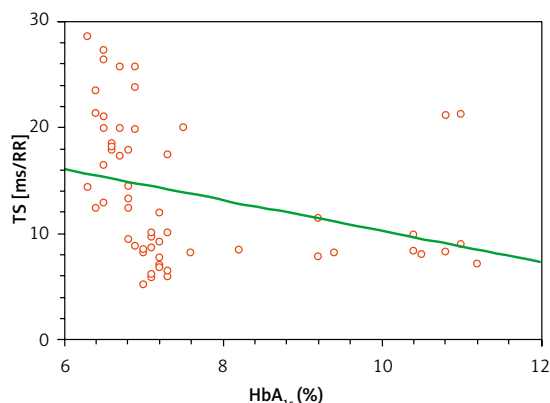


Figure 4. Correlation between TS (turbulence slope) and HbA_{1c} concentration ($r = -0.31, p = 0.02$)

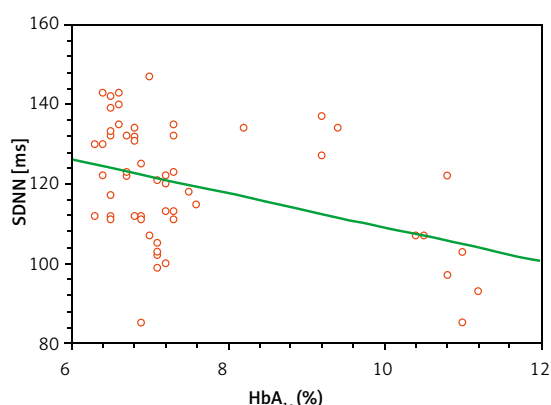


Figure 5. Correlation between SDNN and HbA_{1c} concentration ($r = -0.41, p = 0.001$)

increased incidence of asymptomatic ischemia, myocardial infarction, and decreased likelihood of survival after myocardial infarction [10–12]. The autonomic nervous system closely integrates vital processes such as heart rate, blood pressure and myocardial contractility and as a consequence plays a pivotal role in the regulation of the cardiovascular system. Summarized data of nine studies showed that after 5.8 years, mortality in diabetic patients with CAN was 29%, while it was 6% in those without CAN [7]. Myocardial infarction is the primary cause of death among diabetic patients. A large longitudinal study proved the initial evidence that HRV was a powerful predictor of cardiac mortality after myocardial infarction [13]. The vagus nerve plays a crucial role in the mediation of HRV. The ability to augment vagal activity can be quantified by baroreflex sensitivity. The ATRAMI study (Autonomic Tone and Reflexes After Myocardial Infarction) confirmed that after myocardial infarction, the analysis of baroreflex sensitivity has significant prognostic value independently of left ventricular ejection fraction and ventricular dysrhythmia. It significantly adds to the prognostic value of HRV [14]. It has also been shown by analyzing HRV and baroreflex sensitivity that

cardiovascular adaptation mechanisms are severely impaired in patients with long-term type 1 diabetes [15]. Baroreflex can be evaluated using HRT, which is a relatively new and simple method, representing a reliable indicator of baroreceptor sensitivity [2, 3]. Our study revealed that both HRT parameters – TO and TS – were found to be significantly improved in patients with better glycemic control. This observation is consistent with other studies stating that glycemic control is an important factor in the pathogenesis of CAN [16–19].

Ewing’s battery tests are reliable tests commonly used to detect CAN [20], though their application is limited, because they are very time consuming and require patient compliance, and they are another method of measurement of HRV. A decrease in HRV is the earliest sign of CAN; therefore a beat-to-beat HRV is suggested as a useful diagnostic test by the American Diabetes Association [1].

In our study, HRT was used for assessing the autonomic nervous system in DM instead of HRV. There are several papers presenting changes of HRV in diabetic patients. Also, Ewing’s battery tests are based on RR variability. On the other hand, there are many different HRV parameters that can be analyzed in the time domain (e.g. SDNN, SDANN, SDNNI, pNN50, RMSDD) and in the frequency domain (e.g. LF, HF, HF/LF ratio). Until now, there is no consensus in which HRV parameters and cut-off values should be used for clinical practice. In this study, only SDNN significantly correlated with HbA_{1c}. According to our knowledge, using HRT may be as useful as HRV analysis. Konduracka *et al.* [5] found significantly decreased TS but essentially similar TO values in type 1 diabetic patients in comparison with healthy controls. Balcioglu *et al.* [4] also reported decreased TS but similar TO values in type 2 DM with and without CAN. In our study, we did not assess the presence of CAN, but only used HRT for monitoring changes of autonomic nervous system function during

intensive insulin therapy. HRT tests are not standardized for detection of CAN and have no cut-off values for diagnosis of CAN; for that reason HRT parameters may be particularly useful in monitoring changes of baroreceptor sensitivity in patients with DM. Heart rate turbulence may be useful in monitoring changes of autonomic nervous system functions in patients with DM instead of HRV parameters or Ewing's tests. This finding needs to be verified by larger studies.

The major limitation concerning the measurement of HRT is that sinus rhythm and the presence of ventricular premature beats are mandatory for its evaluation. Another limitation is the small study group.

In conclusion, intensive insulin therapy, leading to better glycemic control, results in improvement of HRT. Heart rate turbulence parameters may be a useful monitoring tool for the function of the autonomic nervous system in patients with diabetes mellitus.

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