Recurrences in heart rate dynamics are changed in patients with diabetes mellitus
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Summary
Detection of subclinical autonomic dysfunction in patients with diabetes mellitus (DM) is of vital importance for risk stratification and subsequent management. Heart rate variability (HRV) analysis is a sensitive tool for assessment of cardiovascular autonomic dysfunction. As the heart is controlled by non-linear deterministic system, the non-linear dynamics measures should be preferred. Recurrence plot (RP) is able to analyse recurrences within system dynamics. The aim of the study was to detect heart rate dysregulation in DM by RP and to ascertain which of the recurrence quantification analysis (RQA) measures are changed in patients with DM compared to control group. We analysed HRV recordings from 17 young patients with type 1 DM and 17 healthy matched control subjects. RQA was performed on RPs with a fixed value of recurrence points percentage. From RQA measures based on diagonal lines, we have found higher percentage of determinism in DM group (P = 0.038). Trapping time measure was also higher in DM (P = 0.022). RQA revealed changes in dynamics recurrences with reduced complexity of heart rate control in young diabetic patients. As RQA parameters are independent of overall HRV, parameters of RP should be used together with linear HRV parameters for better description of heart rate dysregulation in patients with diabetics.

Introduction
Diabetic autonomic neuropathy is a common complication of diabetes mellitus (DM) and is among the least recognized and understood complications of this chronic disease (Vinik & Erbas, 2001). Cardiac autonomic neuropathy (CAN) is the most clinically important form of the diabetic autonomic neuropathy (Vinik et al., 2003) – early detection of subclinical autonomic dysfunction in diabetic patients is of vital importance for risk stratification and subsequent management for the prevention of serious adverse consequences (Schroeder et al., 2005).

The diagnosis of neuropathy was usually performed by Ewing tests, including Valsalva manoeuvre, deep breathing test, orthostatic test and isometric handgrip test. However, these tests require active patient participation and cooperation, are time-consuming, difficult to standardize and carry a potential risk of adverse effects (Takase et al., 2002; Vinik et al., 2003).

One of the early signs of CAN is the reduction of spontaneous heart rate variability (HRV). Therefore, the analysis of HRV is a rapid sensitive non-invasive and reproducible tool for the assessment of cardiovascular autonomic dysfunction (Makimattila et al., 2000; Burger et al., 2002). The traditional linear techniques of data analysis in time and frequency domain are rather simple but they are not sufficient to characterize the complex dynamics of heart rhythm modulation. Usually, the linear measures are strongly mutually dependent and their values markedly overlap between healthy and pathological groups. Therefore, new parameters able to quantify additional information (independent of HRV magnitude) hidden in the HRV signal are needed. As the heart is controlled by a non-linear deterministic system, measures derived from non-linear systems theory are increasingly used in HRV analysis. However, the application of traditionally used non-linear methods (e.g. correlation dimension, largest Lyapunov exponent) is limited only to long stationary signals – a condition that is only rarely met in biology (Schreiber, 1999). New methods with applicability to real biological signals are continuously developed – recurrence plot (RP) with its subsequent quantitative analysis is one of them.

Recurrence is a basic feature of many dynamical systems – it is defined as a repeated occurrence of a given state of the system in time. RP is a graphical representation of the recurrences in dynamical system (Marwan et al., 2007). The structures inside RP can be described quantitatively by the recurrence quantification analysis (RQA) (Webber & Zbilut, 1994; Marwan et al., 2002).
The aim of this study was to detect heart rate dysregulation using RP analysis and to ascertain which of the RQA parameters are different in young patients with DM compared to control group.

**Methods**

**Subjects**

A total of 34 subjects divided into two groups participated in this study. The first group (DM) consisted of 17 patients with type 1 DM (10 women, 7 men) aged 12.9–31.5 years (mean ± SEM: 22.4 ± 1.0 years). The mean duration of disease was 12.4 ± 1.2 years. The second group (control group) consisted of 17 healthy gender and age-matched subjects (mean age: 21.9 ± 0.9 years). All subjects gave their informed consent prior to examination. Subjects were instructed to avoid substances influencing cardiovascular system activity (caffeine, alcohol) and smoking for 12 h before examination. The study groups characteristics are given in Table 1.

Based on anamnestic data, only one patient showed clinical symptoms of autonomic dysfunction (orthostatic intolerance). The Michigan Neuropathy Screening Instrument, composed of a history questionnaire and physical assessment (foot sensation), did not reveal neuropathy in any patient. In addition, the vibration sensation was tested using a graduated tuning fork (128 Hz) applied to the dorsum of the patient’s great toe. A reduced vibration sensation was found in one subject. Ankle reflexes were bilaterally present in all subjects. At the end of physical examination, standard monofilament sensation testing was performed at a pressure of 10 g on 10 separate places on both feet. All diabetic patients showed correct responses to these stimuli.

All subjects were examined in a quiet room from 8 to 12 AM. The VariaCardio TF4 device (Sima Media, Olomouc, Czech Republic) was used for continuous beat-to-beat heart rate monitoring represented by R–R intervals (sampling frequency 1000 Hz). During measurement, subjects were under standard-monitoring represented by R–R intervals (sampling frequency 1 min. We have asked the probands to avoid voluntary

**Table 1** Study groups characteristics (control group – C, group of patients with type 1 diabetes mellitus – DM).

<table>
<thead>
<tr>
<th>C/DM/P</th>
<th>C</th>
<th>DM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>21.9 ± 0.9</td>
<td>22.4 ± 1.0</td>
<td>0.617</td>
</tr>
<tr>
<td>Body mass index (kg m⁻²)</td>
<td>21.2 ± 0.7</td>
<td>23.1 ± 0.7</td>
<td>0.033*</td>
</tr>
<tr>
<td>Plasma glucose (mmol l⁻¹)</td>
<td>4.8 ± 0.1</td>
<td>10.2 ± 1.4</td>
<td>0.001*</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>4.8 ± 0.1</td>
<td>9.6 ± 0.4</td>
<td>0.001*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>123 ± 3</td>
<td>117 ± 3</td>
<td>0.326</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>72 ± 2</td>
<td>73 ± 2</td>
<td>0.836</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>67.5 ± 10.0</td>
<td>74.8 ± 10.3</td>
<td>0.046*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SEM and P-values were obtained using Mann–Whitney U-test. *Significant (P<0.05) between-group difference.

The subjects were resting for 20 min before the actual recording started allowing the cardiovascular system to reach equilibrium, i.e. a quasi-stationary condition.

**Data analysis**

The HRV analysis was performed off-line using special software on one time segment of R–R interval time series – this segment consisted of 1000 normal R–R intervals starting from 30th minute of supine rest.

First, a multidimensional state space has to be reconstructed from recorded time series that is one-dimensional. It can be performed by the method of time delay embedding (Takens, 1981). Each point in the reconstructed phase space represents the state of the system in a given time. This point is determined by m coordinates (embedding dimension). The values of these coordinates are the values from original time series delayed by selected time interval τ (time delay). Based on the modified false nearest neighbours method for computing of the minimum embedding dimension applicable on short time series (Cao, 1997) (we found saturation of E1 values for individual recordings in the embedding dimensions range of 7–10), and in accordance with previous studies (Dabire et al., 1998; Gonzalez et al., 2000; Mestivier et al., 2001), we have chosen embedding dimension m = 10. Time delay (τ) for embedding was set as the first minimum of the mutual information function (Fraser & Swinney, 1986) individually for each recording to reduce a relatively strong autocorrelation present in the heart rate signal. Next, the distances between individual points (a point in 10-dimensional space corresponds to a state of the system in given time) in times i and j were calculated using an Euclidean norm. When the distance of points was lower than given threshold (tolerance) – a recurrence point in RP with coordinates [i, j] was plotted (Fig. 1) (Webber & Zbilut, 1994; Marwan et al., 2007). The tolerance level was selected individually for each recording (for further details, see the last paragraphs of this section).

The most important structures in RP are diagonals and verticals. Diagonals reflect the repetitive occurrence of similar sequences of states in the system dynamics. The diagonals express the similarity of system behaviour in two distinct time sequences. Verticals result from a persistence of one state during some time interval. Theoretically, these linear structures would not occur in random (stochastic) as opposed to deterministic process (Marwan et al., 2007).

Webber & Zbilut (1994) developed quantitative descriptors of the RP pattern – RQA measures. In our study, we analysed diagonal lines occurrence using measure %Det (percentage of determinism) computed as the percentage of recurrence points forming diagonals from all recurrence points. As the diagonals are a reflection of the repeating of states sequences, this parameter is a measure of the determinism and regularity of the system dynamics over time. The next parameter based on diagonal lines is Lmax – maximal length of a diagonal. We have also analysed parameters derived from vertical lines: trapping
time (TT) – mean length of the vertical lines, and laminarity (Lam) – percentage of recurrence points forming verticals (Marwan et al., 2002). These measures were proposed as complexity measures. Simply said, the lower TT and Lam means the higher complexity of the system dynamics, because the state of the system stays for longer time in a state similar to previously occurring state.

For proper RQA measures evaluation, it is very important to properly set the tolerance level for recurrence points detection. The tolerance value should be selected so that percentage of recurrence points (%Rec) gives values between 0-1% and 2-0%. Larger tolerance values up to 5% may be necessary to obtain reliable values for %Lam and TT (Webber & Zbilut, 2005; Webber, 2007). Higher percentage of recurrence points in RP (higher %Rec) can itself cause higher probability of diagonals and verticals occurrence only by chance (in extreme situation, when %Rec = 100, all points in RP will form diagonals and verticals) and therefore almost all RQA parameters are usually dependent on %Rec value (the higher %Rec – the higher %Det, \( L_{\text{max}} \), TT, etc.). Therefore, to detect fine changes in structures of system dynamics recurrences, it is proper to construct RP with fixed %Rec. This procedure also minimizes the influence of HRV magnitude on RQA parameters. We used individually chosen tolerance level giving the fixed %Rec = 5%.

Frequently, relatively strong autocorrelation is present in the heart rate signal – i.e. the length of two neighbouring R–R intervals is usually similar. As a consequence, the distance of two points in the phase space reconstructed from R–R intervals, that are close in time, is usually small. Therefore, in RP, a lot of recurrence points in the vicinity of the main diagonal can be found purely as a consequence of above-mentioned strong autocorrelation. To avoid the autocorrelation influence, Theiler window (Theiler, 1986) was applied and set to the value of time delay \( \tau \) – i.e. only points more distant than \( \tau \) from central diagonal \( j > i + \tau \) were considered for subsequent computation of RQA measures.

**Statistics**

Given the Gaussian distribution of parameters %Det, \( L_{\text{max}} \) and %Lam, between-group comparisons were performed by two-sample t-test. Because of non-Gaussian distribution of variable TT and study groups characteristics, between-group comparisons were performed by non-parametric Mann–Whitney U-test for these variables. Values \( P<0.05 \) were considered statistically significant.

**Results**

In Fig. 1, an example of RQA analysis with corresponding RP is shown.

From RQA measures based on diagonal lines, we have found significantly higher percentage of points forming diagonals – %Det (Fig. 2; \( P=0.038 \)) in DM. There was no significant
difference in $L_{\text{max}}$ (Fig. 3; $P = 0.760$) between these two groups.

Using RQA measures derived from vertical lines, significant difference in TT was detected – TT was higher in DM subjects (Fig. 4; $P = 0.022$). Other measure based on vertical lines – Lam (Fig. 5) – was not significantly different between groups ($P = 0.084$).

Discussion

The major findings of our study are significant changes in measures derived from RP in diabetic patients. Higher percentage of points forming diagonals (%Det) and higher values of TT point towards complexity loss and simplification of heart rate dynamics in pathological conditions.

The major advantage of RPs is their applicability to short and non-stationary physiological time series. The power of the RQA also resides in its independence from constraining assumptions and limitations plaguing other analyses. Because recurrence structures are simply tallied within the signal, there is no need to precondition the data by filtering, linear detrending or transforming the data to conform to any particular statistical distribution. For these reasons, RQA has proven to be ideally suited for the study of numerous real-world systems (Marwan et al., 2007).

When applied to HRV time series, Dabire et al. (1998) and Gonzalez et al. (2000) observed significant increase of %Det and $L_{\text{max}}$ after parasympathetic blockade by atropine in rats. Similar results were obtained after the administration of prazosine ($\alpha_1$-blockade) (Mestivier et al., 2001). These results suggest reduced complexity and better predictability of heart rate control after pharmacological simplification of the control system. Similar changes (higher %Det and lower $L_{\text{max}}$) were found in an animal model of DM – in streptozotocin-induced diabetic rats (Giudice et al., 2002).

However, these results concerning the quantification of RP pattern should be taken with caution due to several reasons: too dense plots were sometimes applied (%Rec up to 50%) and all these changes in %Det and $L_{\text{max}}$ were accompanied by significantly higher %Rec in RP. Higher %Rec in RP increases a probability of diagonal and vertical lines occurrence (and also increases their length) only by chance even in the stochastic signals (Thiel et al., 2002; Marwan et al., 2007). Concomitant increase of %Det and $L_{\text{max}}$ can be just a result of increased %Rec. In addition, too high %Rec can hide fine structures in RP. Therefore, we used fixed %Rec = 5% in accordance with a suggestion of Webber (2007).
Even after this adjustment, we have found an increase of %Det in young patients with DM, but parameter $I_{\text{max}}$ was not different in DM patients compared to control group. The difference between our results and results of above-mentioned authors can be caused by using non-fixed %Rec in their studies. Nevertheless, our results point towards increased repeatability of heart rate patterns in diabetic patients, suggesting reduced complexity of their heart control system.

RQA was traditionally focussed on diagonal lines in RPs, but additional information can be obtained from vertical lines’ characteristics. The vertical lines reflect the persistence of a given state of the system for some time interval (Marwan et al., 2007). In this study, we have shown that this phenomenon is more typical for DM patients compared to healthy control subjects. We suggest that this fact is the reflection of the reduction in heart rate complexity in diabetic patients.

The human body is a complex adaptive system and the complexity in its behaviour allows for broadest range of adaptive responses. Loss of complexity, therefore, has been proposed as a generic feature of pathologic dynamics (Goldberger et al., 2002). Cardiovascular regulation in the healthy human body is mediated by a variety of neural, hormonal, genetic and external interactions. Output variables of that system exhibit complex fluctuations – the measured output signal is characterized by great complexity. A wide class of various disease states as well as aging appear to reduce this complexity, hereby reducing the adaptive capacity of the individual. Therefore, the loss of complexity was proposed as a general feature of pathological dynamics (Baumert et al., 2004, 2005; Costa et al., 2008). The results of our study (increased %Det and TT) are also in line with this concept of pathologically reduced heart rate complexity.

We suggest that, as heart rate is predominantly under parasympathetic nervous control (Hayano et al., 1991), the changes in heart rate dynamics recurrences are probably caused by parasympathetic dysfunction. Interestingly, none of analysed RQA measures correlated significantly with the overall HRV magnitude as expressed by standard deviation of R–R intervals (results not shown) in both groups. This finding suggests the importance of RQA parameters as the indices that are independent on the magnitude of HRV. These measures can provide novel information regarding heart rate dysregulation in DM patients.

The major limitation of this pilot study is the relatively small number of patients. We took this into consideration by the selection of age and gender-matched control group. However, we could not perform the analysis of RP measures’ relation to the degree of neuropathy in diabetic patients. Therefore, future studies on this issue are needed.

**Conclusion**

We detected the reduced complexity of heart rate control even in young diabetic patients using RP with fixed %Rec. As RQA parameters are independent of overall HRV (in contrast to linear measures), these parameters should be used together with other HRV parameters for better description of heart rate dysregulation in diabetic patients with potential diagnostic and prognostic value.

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