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Reduced short-term complexity of heart rate and blood pressure dynamics in patients with diabetes mellitus type 1: multiscale entropy analysis

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Abstract
Multiscale entropy (MSE) analysis provides information about complexity on various time scales. The aim of this study was to test whether MSE is able to detect autonomic dysregulation in young patients with diabetes mellitus (DM). We analyzed heart rate (HR) oscillations, systolic (SBP) and diastolic blood pressure (DBP) signals in 14 patients with DM type 1 and 14 age- and sex-matched healthy controls. SampEn values (scales 1–10) and linear measures were computed. HR: among the linear measures of heart rate variability significant differences between groups were only found for RMSSD ($p = 0.043$). MSE was significantly reduced on scales 2 and 3 in DM ($p = 0.023$ and 0.010, respectively). SBP and DBP: no significant differences were detected with linear measures. In contrast, MSE analysis revealed significantly lower SampEn values in DM on scale 3 ($p = 0.039$ for SBP; $p = 0.015$ for DBP). No significant correlations were found between MSE and linear measures. In conclusion, MSE analysis of HR, SBP and DBP oscillations is able to detect subtle abnormalities in cardiovascular control in young patients with DM and is independent of standard linear measures.

Keywords: diabetes mellitus, autonomic neuropathy, complexity, heart rate variability, blood pressure variability, multiscale entropy, sample entropy

1. Introduction

Variability in cardiovascular measures contains important information on the autonomic control of circulation. Quantifying these fluctuations in the supine position during rest provides

information on cardiovascular regulation without requiring stimuli, which may interfere with the measured parameters (Parati *et al* 2006). The reduction in heart rate variability (HRV) is well described in patients with diabetes mellitus (DM) and regarded as an early sign of its serious complication—cardiac autonomic neuropathy (CAN) (Ziegler 1994). In contrast, the analysis of spontaneous beat-to-beat oscillations in blood pressure (BP)—blood pressure variability (BPV)—shows inconsistent changes with DM (Bernardi *et al* 1997, Javorka *et al* 2005).

Heart rate (HR) and BP signals are traditionally analyzed by linear data analysis tools (time and frequency domain). However, these methods are not sufficient to characterize the complex dynamics of the cardiovascular system. Nonlinear control of heart rate and blood pressure is thought to possess physiological advantages, allowing them to adapt faster to changes in physiological needs than linear control mechanisms (Costa *et al* 2002). Analysis methods derived from nonlinear systems theory have opened up a new perspective for studying and understanding the characteristics of cardiovascular dynamics. Nonlinear measures describe qualitative features rather than the magnitude of the signal (Beckers *et al* 2006). The human body is a complex adaptive system and the complexity in its behavior allows for the broadest range of adaptive responses (Bornas *et al* 2006). Loss of complexity, therefore, has been proposed as a generic feature of pathologic dynamics (Goldberger *et al* 2002). Complexity can be defined as a 'meaningful structural richness' of a signal (Goldberger *et al* 2002).

From recently developed nonlinear methods, measures of short-term complexity (various entropy measures) have shown to be promising for analysis of both HR and blood pressure signals (Baumert *et al* 2004, Porta *et al* 2007, Wessel *et al* 2007). However, under healthy conditions, beat-to-beat R–R interval and BP time series have a complex temporal structure with correlations on multiple scales. Single-scale-based traditional entropy measures (e.g. sample entropy) may fail to account for the multiple time scales inherent in complex physiologic systems. Therefore, a meaningful measure of complexity should take into account multiple time scales. Recently, Costa *et al* (2002) introduced a new method to calculate entropy over multiple scales—multiscale entropy analysis (MSE).

The major aim of this study was to test whether MSE analysis provides information about heart rate/blood pressure dysregulation in young patients with DM according to the concept of complexity loss under pathological conditions.

2. Methods

2.1. Subjects

In this study we included a sample of 28 subjects subdivided into two groups. The first group consisted of 14 patients with type 1 DM (7 women, 7 men) aged 22.3 $\pm$ 1.2 years (mean $\pm$ SEM). The mean duration of DM was 12.5 $\pm$ 1.4 years. We used the subset of a previously published diabetic group ($n = 17$) (Javorka *et al* 2005). Out of these 17 subjects, 3 were omitted because of artifacts (drift) in the beat-to-beat blood pressure signal.

Based on anamnestic data, only one patient showed clinical symptoms of autonomic dysfunction (orthostatic intolerance). However, possible mechanisms other than CAN responsible for the patient's orthostatic intolerance could not be excluded. The Michigan Neuropathy Screening Instrument, composed of a history questionnaire and physical assessment (foot sensation), did not reveal neuropathy in any patient, although one subject showed borderline values of suspected neuropathy. Physical examination (predominantly foot inspection) showed excessively dry skin in one subject. No other abnormalities were observed. In addition, 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 another 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 ten separate places on both feet. All diabetic patients showed normal responses to these stimuli.

The second group consisted of 14 healthy gender- and age-matched probands (mean age: 21.8 ± 1.1 years). All subjects gave their informed consent prior to examination. Subjects were instructed not to use substances influencing the cardiovascular system activity (caffeine, alcohol) and moreover smokers (three probands in both control and DM groups) were also instructed not to smoke for 12 h prior to examination. None of the examined subjects used medicaments affecting cardiovascular functions. The only medication used was insulin in the DM group. The study was approved by the Ethics Committee of Jessenius Faculty of Medicine, Comenius University.

2.2. Procedures

All subjects were investigated in a quiet room from 8 am to 12 am. Recordings of R–R intervals, systolic (SBP) and diastolic blood pressure (DBP) lasting 60 minutes were obtained simultaneously and continuously under standardized conditions (supine position, rest, same time, same place) by means of a telemetric ECG system (VariaCardio TF4, Sima Media, Olomouc, Czech Republic) and the beat-to-beat blood pressure monitor Finapres (Ohmeda 2300, USA). The subjects were instructed to avoid voluntary movements and speaking. Intervals with excessive voluntary movements were excluded from the subsequent analysis. 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.

2.3. Data analysis

Analysis of HR, SBP and DBP oscillations was performed off-line on a recording segment consisting of 3200 beats using custom-made computer software. The analysis included linear (time domain) and complexity measures (multiscale entropy analysis).

2.3.1. Time domain parameters

- *HRV analysis*. For traditional time domain analysis of HRV we computed the three most commonly used measures: MeanNN—the mean beat-to-beat interval of normal heart beats; SDNN—standard deviation of NN intervals, reflecting the overall variability magnitude; and RMSSD—the root-mean-square of successive beat-to-beat differences, reflecting the average magnitude of changes between two consecutive beats and regarded as a marker of vagal heart rate control.
- *BPV analysis*. From SBP and DBP signals we computed the following linear measures:
  - For SBP: Mean SBP—mean systolic blood pressure value, SD SBP—standard deviation of systolic blood pressure values, RMSSD SBP—root-mean-square of successive differences of SBP values.
  - For DBP: Mean DBP—mean diastolic blood pressure value, SD DBP—standard deviation of diastolic blood pressure values, RMSSD DBP—root-mean-square of successive differences of DBP values.

  SD SBP and SD DBP measures reflect the overall magnitude of BPV, whereas RMSSD SBP and RMSSD DBP quantify the beat-to-beat variability of the respective signals.

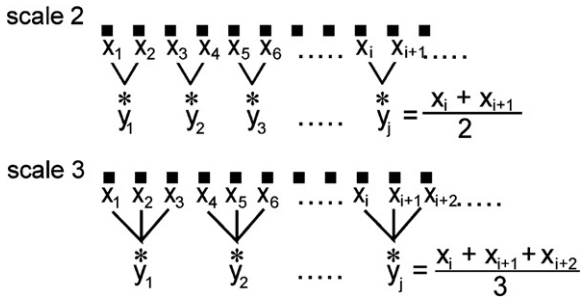

Figure 1. The scheme illustrating the coarse-graining of an original time series for scales $\tau = 2$ and $\tau = 3$. Original samples (R–R intervals or blood pressure values) measured on beat-to-beat basis (squares in this scheme) are transformed into coarse-grained time series (asterisks) by computing the arithmetic mean of two successive values for scale 2 (three successive values for scale 3) without overlapping. It follows that coarse-grained time series is composed of N/τ samples, where N is the number of samples (beats) in the original series.

2.3.2. Multiscale entropy (MSE). MSE was computed according to the procedure published by Costa *et al* (2002). Given a one-dimensional discrete time series, $\{x_1, \ldots, x_i, \ldots, x_N\}$, we constructed consecutive coarse-grained time series $\{y^{(\tau)}\}$ determined by the scale factor τ, according to the equation

$$y_j^{(\tau)} = 1/\tau \sum_{i=(j-1)\tau+1}^{j\tau} x_i$$

where τ represents the scale factor and $1 \leqslant j \leqslant N/\tau$. In other words, coarse-grained time series for scale τ were obtained by taking arithmetic mean of τ neighboring original values without overlapping (figure 1). The length of each coarse-grained time series is N/τ. For scale 1, the coarse-grained time series is simply the original time series. We calculated sample entropy (SampEn) (Richman and Moorman 2000) for each of the coarse-grained time series and plotted the results considering the group means as a function of the scale factor.

SampEn is a refined version of traditionally used irregularity measure approximate entropy (ApEn) (Pincus 1995). Details of the SampEn algorithm are given in the appendix. Briefly, SampEn quantifies the irregularity of a time series. It reflects the conditional probability that two sequences of m consecutive data points, which are similar to each other (within given tolerance r), will remain similar when one consecutive point is included. The SampEn algorithm underlying the MSE computation requires to set two parameters: the tolerance level r and the pattern length m. According to previous studies, we have chosen a tolerance level of $r = 0.15\times$ standard deviation of the time series to avoid distortion of SampEn values by changes in signal magnitude. In addition to usual choice of the pattern length parameter $m = 2$, we tested the robustness of the MSE method by computing SampEn values also for $m = 1$. SampEn values were computed for scales τ up to 10, which corresponds to a minimal length of the coarse-grained time series equal to 320 beats—a length yet acceptable for a reliable estimate of SampEn (Richman and Moorman 2000).

2.4. Statistics

Nonparametric tests were used to take into account the possibly non-Gaussian distribution of the HRV and BPV parameters. Between-groups comparisons (DM versus control group) were performed with the Mann–Whitney U-test. Discriminative power of the measures was

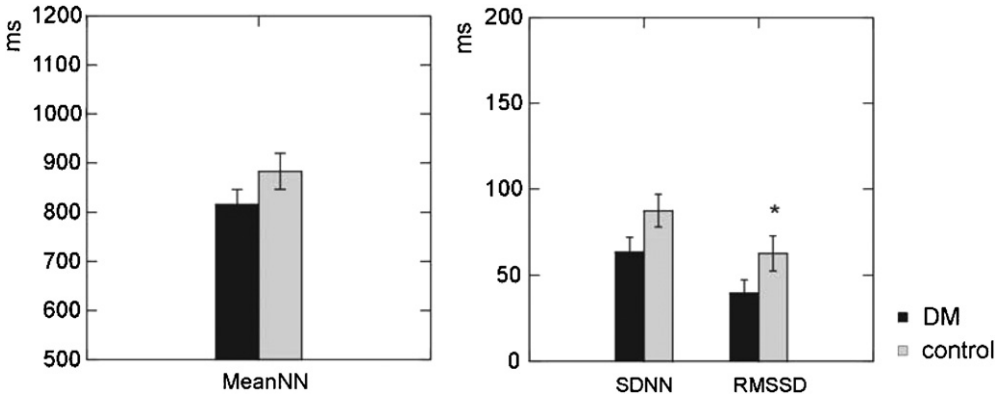

Figure 2. Linear time domain HRV measures. The parameters MeanNN and SDNN show no significant differences between young patients with type 1 diabetes mellitus (DM) and healthy gender- and age-matched controls (control). The parameter RMSSD, reflecting beat-to-beat variability, was significantly decreased in the DM group.

assessed with linear discriminant analysis (stepwise backward variable selection; leaving-one-out cross-validation). Furthermore, we investigated the relationship between linear measures of HRV, SBPV and DBPV and SampEn values using Spearman correlation coefficients. A p value (two-tailed) < 0.05 was considered statistically significant. All values are presented as mean $\pm$ SEM.

3. Results

3.1. Time domain parameters—between-groups comparison

3.1.1. Time domain HRV analysis. No significant between-groups differences were found in MeanNN (control: 882.7 ± 35.5 ms, DM: 816 ± 28.6 ms; $p = 0.098$) and SDNN (control: 87.5 ± 9.0 ms, DM: 63.5 ± 8.3 ms; $p = 0.06$). A marginally significant reduction in RMSSD was found in DM patients, reflecting a loss in beat-to-beat variability (control group: 62.7 ± 9.8 ms, DM: 39.6 ± 7.4 ms; $p = 0.043$) (figure 2).

3.1.2. Time domain BPV analysis. For both, SBPV and DBPV, no significant between-groups differences were found in the linear measures reflecting overall (SD SBP, SD DBP) and beat-to-beat (RMSSD SBP, RMSSD DBP) variability (figure 3).

3.2. Multiscale entropy—between-groups comparison

3.2.1. MSE HR analysis. Computing MSE using a pattern length of $m = 2$, we found significantly reduced values of SampEn in DM patients on scales 2 and 3 ($p = 0.023$ and 0.010, respectively), but not on scale 1, which corresponds to original R–R intervals time series without coarse graining ($p = 0.520$) (figure 4, upper panel).

For a pattern length of $m = 1$ (figure 4, lower panel), we obtained MSE results similar to those for $m = 2$ although differences were less marked: on scale 1, the SampEn value was not statistically different between groups ($p = 0.408$). On scale 2, SampEn values were

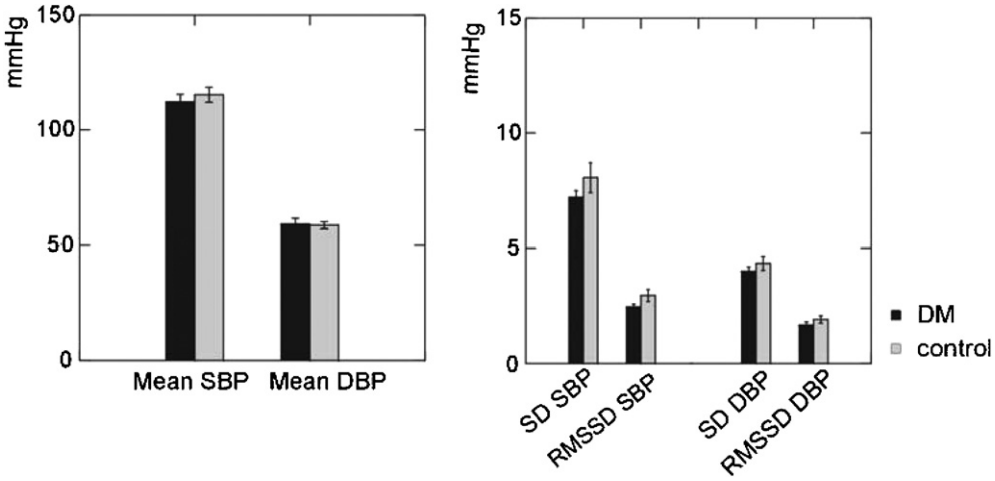

Figure 3. Linear time domain systolic blood pressure variability (SBPV) and diastolic blood pressure variability (DBPV) measures. No significant differences between controls and diabetic patients (DM) were found in the measures Mean SBP (systolic blood pressure) and Mean DBP (diastolic blood pressure), in the measures SD SBP and SD DBP (standard deviations of SBP and DBP, respectively) reflecting overall variability, nor in RMSSD SBP (root mean square of successive differences of SBP values) and RMSSD DBP (root mean square of successive differences of DBP values), reflecting beat-to-beat variability.

not significantly lower in DM patients ($p = 0.063$) and were significantly reduced on scale 3 ($p = 0.039$).

No significant differences in SampEn values between DM patients and controls were found on scales higher than 3, neither for $m = 1$ nor $m = 2$.

3.2.2. MSE SBP analysis. Computing MSE from the SBP signal using $m = 2$, we observed a significantly reduced SampEn on scale 3 in DM patients compared to the control group ($p = 0.039$). SampEn values on scales 2 and 4 were not significantly different in DM ($p = 0.077$ and $p = 0.066$, respectively). No differences were found on other scales (figure 4, upper panel).

No significant differences in SampEn of SBP time series were found for $m = 1$ (figure 4, lower panel).

3.2.3. MSE DBP analysis. Similar to the MSE SBP analysis results, the complexity was significantly reduced for $m = 2$ on scale 3 ($p = 0.015$) in patients with DM (figure 4, upper panel). For $m = 1$ no significant differences were observed (figure 4, lower panel).

3.3. Correlation analysis

Nonparametric correlation analysis was performed between time domain HRV, SBPV and DBPV measures and SampEn values of those scales that were significantly different between DM patients and control subjects (for $m = 2$).

HRV complexity measures based on MSE (SampEn values on scales 2 and 3 in the control and DM groups) showed neither in the DM patients nor in the control group significant correlations with standard time domain measures (table 1).

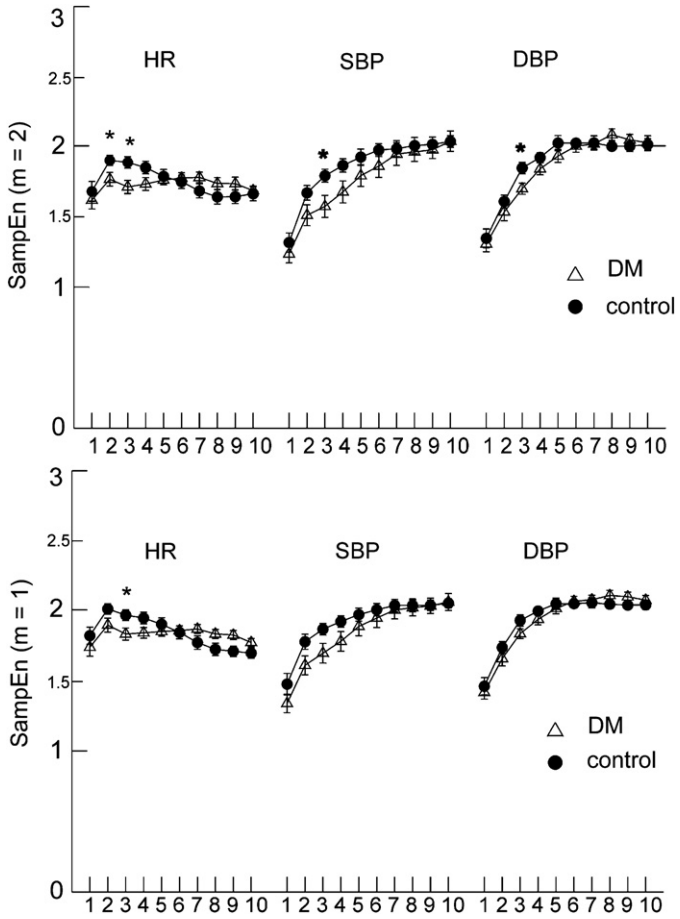

Figure 4. Multiscale entropy analysis (MSE) for different pattern lengths. Upper panel: MSE shows a significant reduction (asterisks) in complexity at small scales (scales 2 and 3 for heart rate (HR) signals, scale 3 for both systolic blood pressure (SBP) and diastolic blood pressure (DBP) signals) in young patients with type 1 diabetes mellitus (DM) compared to the control group (control) when SampEn values were computed for $m = 2$. Lower panel: although the MSE curves computed for $m = 1$ were similar in shape compared to the upper panel ($m = 2$), significant group differences were found only in HRV signals on scale 3.

Similarly, SampEn values of SBP signals (scale 3) showed no significant correlation with overall (SD SBP) or beat-to-beat (RMSSD SBP) variability measures in the control group. In the DM group, SampEn values on that scale correlated positively with RMSSD SBP ($p = 0.006$) (table 2).

For DBP signals, SampEn values on scale 3 showed no significant correlation with standard time domain measures (table 3).

3.4. Linear discriminant analysis

Based on linear HRV measures linear discriminant analysis resulted in a correct classification rate of 61% after cross-validation (selected variable SDNN). If MSE values were allowed to be selected into the discriminant function the correct classification rate increased to 89% (selected variables: SampEn at scales 1, 4, 7, 10).

Table 1. Spearman correlation coefficients between heart rate variability (HRV) measures and SampEn ($m = 2$) for scales, that were significantly altered in patients with diabetes mellitus (DM). The coefficients were separately computed for the healthy control group and for diabetic patients. MSE(2) and MSE(3) denote a SampEn value for scales 2 and 3, respectively, within multiscale entropy (MSE) analysis.

	MeanNN	SDNN	RMSSD
	Control group		
MSE(2)	0.231	0.385	0.446
MSE(3)	−0.213	0.200	−0.200
	DM		
MSE(2)	0.033	0.099	0.095
MSE(3)	0.319	0.270	0.103

Table 2. Spearman correlation coefficients between systolic blood pressure variability (SBPV) measures and SampEn ($m = 2$) for the scale that was significantly altered in patients with diabetes mellitus (DM). The coefficients were separately computed for the healthy control group and for diabetic patients. MSE(3) denotes a SampEn value for scale 3 within multiscale entropy (MSE) analysis. Asterisk denotes the correlation significant at 0.05.

	Mean SBP	SD SBP	RMSSD SBP
	Control group		
MSE(3)	0.398	−0.007	0.248
	DM		
MSE(3)	0.526	0.189	0.690*

Table 3. Spearman correlation coefficients between diastolic blood pressure variability (DBPV) measures and SampEn ($m = 2$) for the scale that was significantly altered in patients with diabetes mellitus (DM). The coefficients were separately computed for the healthy control group and for diabetic patients. MSE(3) denotes a SampEn value for scale 3 within multiscale entropy (MSE) analysis.

	Mean DBP	SD DBP	RMSSD DBP
	Control group		
MSE(3)	−0.064	0.176	0.506
	DM		
MSE(3)	−0.200	0.174	0.428

Based on linear SBP and DBP measures, respectively, discriminant analysis resulted in a correct classification rate of 61% for each signal (selected variables: RMSSD SBP and RMSSD DBP, respectively). If MSE values were allowed to be selected, the correct classification rate increased to 79% and 86%, respectively (selected variables for SBP: RMSSD SBP, SampEn at scales 4 and 7; for DBP: SampEn at scales 3 and 8).

4. Discussion

The major finding of our study is that multiscale entropy (MSE) analysis of HR/BP signals allows a better discrimination between patients with type 1 diabetes mellitus and healthy

subjects than linear time domain analysis. Further, MSE values are statistically independent from linear measures and relatively robust against the choice of the pattern length m.

4.1. Complexity analysis

Integrated biological systems are characterized by various interacting subsystems and feedback loops processing internal and external inputs. This complex organization results in a dynamical complexity that may be quantified by the analysis of the time course of systemic variables (e.g. heart rate, systolic blood pressure). Cardiovascular regulation in the healthy human body is mediated by a variety of neural, hormonal, genetic and external interactions that operate across multiple time scales. Output variables of the system exhibit complex fluctuations—the measured output signal is characterized by great complexity. A wide range of diseases as well as aging appear to reduce this complexity, hereby reducing the adaptive capacity of the individual's regulatory system. Loss of complexity has been proposed as a general feature of pathological dynamics (Porta *et al* 2007, Costa *et al* 2008). Cardiovascular variability analysis (HRV and BPV) provides important information on the autonomic control of circulation (Parati *et al* 2006). Since HRV originates predominantly from oscillations in parasympathetic nervous traffic and blood vessels are predominantly under sympathetic nervous system control, beat-to-beat analysis of simultaneously obtained heart rate and blood pressure signals may provide information about both branches of cardiovascular control (Laitinen *et al* 1999, Eckberg 2000). Numerous studies have suggested that the quantification of complexity is of importance for the understanding as well as for the classification of HR oscillations (Baumert *et al* 2005, Batchinsky *et al* 2007). In contrast, complexity analyses of blood pressure fluctuations have only been performed rarely.

4.2. Heart rate complexity

Using the original single time scale approach, several authors observed reduced entropy values in the HR signal after parasympathetic withdrawal upon standing, in the course of aging and during mental stress (Javorka *et al* 2002, Vuksanovic and Gal 2005, Batchinsky *et al* 2007). This is in accordance with the fact that heart rate is predominantly under parasympathetic nervous control. However, comparing diabetics with control subjects Bettermann *et al* (2001) did not find significant difference in the ApEn parameter despite a lower HRV magnitude. Our results are in line with this observation, showing no significant group differences for scale 1 (original time series; for $m = 2$ as well as for $m = 1$). This might be explained by the fact that ApEn values of truly complex systems (healthy) are similar to those of random systems (markedly reduced beat-to-beat variability in DM patients resembles white noise).

Multiscale entropy analysis proposed by Costa *et al* (2002) is a new tool that considers multiple time scales. The main advantage of MSE over other analysis techniques is its ability to measure complexity according to the concept of complexity defined as 'a meaningful structural richness' (Costa *et al* 2008). In our study we observed significantly reduced values of SampEn in DM patients on coarse-grained signals (scales 2 and 3). Our results suggest that complexity is mostly reduced on scales covering respiratory sinus arrhythmia, which is in accordance with parasympathetic dysfunction in DM (Javorka *et al* 2005).

4.3. Blood pressure complexity

To our knowledge, this is the first study to investigate the complexity of beat-to-beat blood pressure fluctuations in patients with DM. No significant differences in SBPV or DBPV could

be detected using linear time domain measures. Frequency domain analysis in the same group of patients showed nonsignificant changes of BPV (Javorka *et al* 2005). This is in line with a previous study on BPV in DM (Chau *et al* 1994). MSE analysis, however, revealed subtle abnormalities in both SBP and DBP dynamics in diabetic patients, emphasizing the high sensitivity of the MSE method compared to standard time domain techniques. MSE analysis might allow an earlier detection of sympathetic dysfunction in DM, which is thought to be mainly responsible for short-term blood pressure fluctuations (Laitinen *et al* 1999). On the other hand, indirect haemodynamic effects mediated by the heart might play a role.

4.4. Methodological issues

Our results obtained with MSE analysis of both HR and BP oscillations point to a relative robustness of the SampEn algorithm against the choice of m (see figure 4). However, based on statistical results, the choice of $m = 2$ is superior to $m = 1$ because it allows more detailed reconstruction of the process dynamics according to nonlinear dynamics theory (Pincus and Goldberger 1994)—MSE analysis for $m = 2$ was associated with lower p values. Moreover, correlation analysis showed that SampEn values computed for $m = 2$ are less correlated with time domain measures than for $m = 1$ (correlation analysis results not shown). We speculate that the choice of m higher than 2 might increase the information present in the given pattern and therefore improve the discrimination between both groups. However, the proper application of the SampEn algorithm for higher m values requires a substantially increased number of data samples (beats)—a situation in which the stationarity presumptions are usually violated by living biological systems (Richman and Moorman 2000).

Linear parameters are usually correlated with each other and thus provide only limited additional diagnostic information. In contrast, MSE shows predominantly nonsignificant correlations with time domain measures for both HRV and BPV. Thus, complexity analysis using MSE may be a potential source for additional diagnostic information and a useful tool for a better discrimination between different physiological and pathophysiological signals.

For both HR and BP recordings, we obtained the best discrimination between patients and control subjects on MSE scale 3. In contrast, Costa *et al* (2002) found the best discrimination between pathological (chronic heart failure) and healthy HR signals on scale 5. In addition, different MSE values were recently found for BP in patients with chronic heart failure compared to control subjects (Angelini *et al* 2007)—the only application of the MSE method to BP signals so far. These results suggest that the scale optimal for discriminating pathological from physiological cardiovascular signals might vary with the type and stage of disease. Despite the analytical advantages of MSE its physiological meaning is not well understood. Furthermore, MSE analysis requires longer recording durations than conventional HRV/BPV analyses.

A limitation of our study is the relatively small number of patients. We took this into consideration by using an age- and gender-matched control group. Furthermore, we performed multiple statistical comparisons, in particular with the MSE measures, increasing the risk of type 1 errors. However, since MSE showed significant differences on scale 3 in the heart rate, systolic as well as diastolic BP signals they are unlikely to be random.

5. Conclusion

We conclude that MSE analysis of spontaneous HR and BP oscillations is able to detect subtle abnormalities in cardiovascular control in young patients with DM, supporting the concept of

complexity loss. MSE is statistically independent from conventional methods and may provide a better discrimination between DM and control groups than linear time domain measures.

Acknowledgments

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Appendix. Algorithm for SampEn computing

For computation of sample entropy (SampEn), three input parameters m, r and N have to be fixed. For a time series of N points, $\{u(j) : 1 \leqslant j \leqslant N\}$ forms $N - m$ vectors $\boldsymbol{x}_m(i)$ for $\{i \,|1 \leqslant i \leqslant N - m\}$, where $\boldsymbol{x}_m(i) = \{u(i+k) : 0 \leqslant k \leqslant m-1\}$ is the vector of m consecutive data points. The distance between two such vectors is defined to be $d[\boldsymbol{x}_m(i), \boldsymbol{x}_m(j)] = \max\{|u(i+k) - u(j+k)| : 0 \leqslant k \leqslant m-1\}$, i.e. the maximum difference of their corresponding scalar components. The whole class of vector sequences $\boldsymbol{x}_m(1), \boldsymbol{x}_m(2), \ldots, \boldsymbol{x}_m(N-m)$ is stepwise used to calculate values $B_i^m(r)$ as $(N-m-1)^{-1}$ times the number of vectors $\boldsymbol{x}_m(j)$ within r of $\boldsymbol{x}_m(i)$, where j ranges from 1 to $N-m$, and $j \neq i$ to exclude self-matches. $B^m(r)$ is then defined as

$$B^m(r) = (N-m)^{-1} \sum_{i=1}^{N-m} B_i^m(r).$$

Similarly, $A_i^m(r)$ is defined as $(N-m-1)^{-1}$ times the number of vectors $\boldsymbol{x}_{m+1}(j)$ within r of $\boldsymbol{x}_{m+1}(i)$, where j ranges from 1 to $N-m$ ($j \neq i$), and set

$$A^m(r) = (N-m)^{-1} \sum_{i=1}^{N-m} A_i^m(r).$$

$B^m(r)$ is then the probability that two sequences will match for m points, whereas $A^m(r)$ is the probability that two sequences will match for $m+1$ points. The parameter SampEn(m, r) is then defined as

$$\text{SampEn}(m, r) = \lim_{N \to \infty} \{-\ln[A^m(r)/B^m(r)]\},$$

which is estimated by the statistic

$$\text{SampEn}(m, r, N) = -\ln[A^m(r)/B^m(r)].$$

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