Recurrence plot of heart rate variability signal in patients with vasovagal syncopeces

Jakub Schlenker a,*, Vladimír Socha b, Lucie Riedibauchová b, Tomáš Nedělka c, Anna Schlenker d, Veronika Potočková c, Šárka Malá c, Patrik Kutílek a

a Faculty of Biomedical Engineering, Czech Technical University, Nám. Siltá 3105, 272 01 Kladno, Czech Republic
b 2nd Faculty of Medicine of the Charles University and University Hospital Motol, Clinic of Cardiology, Department for Electrophysiology and Cardiac Pacing, V Úvalu 84, 150 06 Prague, Czech Republic
c 2nd Faculty of Medicine of the Charles University and University Hospital Motol, Department of Neurology, V Úvalu 84, 150 06 Prague, Czech Republic
d 1st Faculty of Medicine of the Charles University and General University Hospital, Institute of Hygiene and Epidemiology, Stadničkova 7, 128 06 Prague, Czech Republic

1. Introduction

Currently, the field of medicine is experiencing a rising tendency towards the use of nonlinear methods derived from chaos theory [1–3] that describe the dynamics of a system [4]. What makes nonlinear methods so widely used nowadays is their ability to describe certain ongoing processes in the organism more precisely than a range of other methods [5] that are currently used in medicine.

Every living organism shows signs of chaotic behaviour ranging from sub-cellular level to vital regulations, such as heart rate and blood pressure [4]. Since dysregulation of the latter may prove pathological and yields significant clinical consequences, measurement and evaluation of heart rate and blood pressure behaviour are particularly instrumental and important in clinical practice. Their dysregulation may be caused by abnormal autonomic
nervous system (ANS) regulation, as in the case of vasovagal syncopes [6]. Disregulated oscillation activity of ANS in vasovagal syncopes is related to hemodynamic changes that lead to sudden occurrence of bradycardia and hypotension resulting in loss of consciousness and collapse of a patient although there is no structural heart disease present. The most frequent provoking factor resulting in syncopes is orthostasis that leads to blood concentration in lower limb vessels in sensitive individuals. This blood redistribution in the vascular space causes lower blood filling of the heart with resulting activation of baroreceptors in the aortic arch and carotid sinus. Consequently, sympathetic division of ANS is activated, which results in increased heart rate and diastolic pressure [7]. However, in patients with vasovagal syncopes, no increase of sympathetic division activity occurs. Thus blood pressure decreases as a result of diminished ventricular filling and excessive activity of parasympathetics (the other part of ANS) causes bradycardia through mechanoreceptors in pulmonary artery, atrial walls and left ventricle [8]. In fact, vasovagal syncope is not a rare disease and falls among the most common causes of fainting, black-outs, sudden falls and short term loss of consciousness.

Autonomic nervous system, perceived as a fine example of nonlinear deterministic system [4,9,10], influences heart rate and blood pressure in order to secure proper functioning of all organs based on the state of the body. A constant and balanced tone between sympathetic and parasympathetic is responsible for adequate blood pressure and heart rate that reflects an actual hemodynamic need. Thus, ANS functioning can be partly studied using heart rate variability (HRV), an analysis of heart rate changes over time, which reflects the heart’s ability to react to the changes of ANS tone [11].

Clinical assumption on vasovagal aetiology of syncope is verified in a defined test that aims to de-mask presence of ANS dysfunction under the heading of so-called orthostatic test. There are two different methods of orthostatic testing, first is active standing and second is head-up tilt test (HUTT) [12,13].

ANS system dysfunction is believed to be present when blood pressure and/or heart rate suddenly decreases during stand-up phase of the test which is usually associated with manifestation of typical clinical symptoms/syncope. However, HRV analysis has proven to better identify and measure autonomic dysregulation responsible for heart rate and blood pressure changes before they manifest themselves in the form of a syncope. Actually, HRV has been known to be an effective tool for the prediction of cardiovascular morbidity and mortality [14–16]. For HRV evaluation, there are commonly used linear methods of analysis (based on time and frequency domain analysis) as well as nonlinear methods [14,17,3,18]. However, linear methods that are based on fast Fourier transform and autoregressive model proved to have a number of disadvantages [10]. Frequency domain also yields disadvantages such as long sessions of obtaining data, non-stationarity, lower sensitivity as well as high sensitivity to noise. On the other hand, recurrence analysis as a new and promising approach to HRV assessment seems to be able to tackle these obstacles relying on the observation that a healthy subject’s ANS immediately responds to impulses of the organism resulting in lower occurrence of the same or similar states. In contrast, since autonomic dysfunction causes a significant simplification of bodily functions control (including heart rate variability), similar states recur more frequently. Recurrence analysis seemed to be promising in pilot studies as an effective nonlinear technique capable of presenting discrete abnormalities in heart rate regulation in earlier stages of the autonomic dysfunction [9,19–23].

This work primarily aims to verify relevance of recurrence analysis in the detection of ANS regulation disorders that result in vasovagal syncopes.

### Table 1

<table>
<thead>
<tr>
<th>Study groups characteristics.</th>
<th>Control group</th>
<th>Syncope group</th>
<th>The significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>24.5 ± 3.2</td>
<td>23.7 ± 5.2</td>
<td>0.8493</td>
</tr>
<tr>
<td>Maximal age (years)</td>
<td>33</td>
<td>33</td>
<td>–</td>
</tr>
<tr>
<td>Minimal age (years)</td>
<td>20</td>
<td>15</td>
<td>–</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>9/9</td>
<td>2/16</td>
<td>0.0477</td>
</tr>
</tbody>
</table>

### 2. Methods

#### 2.1. Participants and measuring procedure

Two groups were formed with the total of 36 subjects. Eighteen patients, 16 women and 2 men, aged 15–33 years (mean age 23.7 ± 5.2 years), suffering from vasovagal syncope comprised the Syncope group. The second, Control group comprised of 18 healthy subjects, 9 women and 9 men, aged 20–33 years (mean age 24.5 ± 3.2 years), see Table 1. None of the subjects had history of cardiovascular disease or other disorders. All subjects participating in this study gave their informed consent with the examination.

Active standing test (including resting supine position phase lasting 5 min and standing position phase of the same duration) was used for this study. Subjects were instructed to avoid alcohol, caffeine and nicotine consumption for at least 12 h prior to examination. In our autonomic laboratory, heart rate variability recordings were assessed under standard conditions. We assessed short-term recordings between 10 a.m. and 12 a.m., and patients remained in supine rest 15 min before recording. Then the 5 min supine rest phase was recorded. For the standing phase, patients were instructed to stand up. To prevent artifacts from muscular contraction, the stand-up phase measurement was initiated after the patient was fully adapted to standing position (usually 10–15 s after standing up) and then the 5 min standing phase was recorded. We did not use paced breathing as it was considered less physiological than normal breathing, however, patients were instructed to breathe comfortably a without changing breathing frequency after changing the position of their body. According to literature [24,25], we absolutely agree that short term heart indices are subject to high variation and their reliability is still discussed in literature. We are trying to achieve similar conditions (i.e. time of examination, room temperature, humidity, absence of unwanted noise, etc.) to minimize those variations. During the entire test, ECG and blood pressure were recorded in both phases and sequence of R-R intervals (intervals between two consecutive heart beats) was subsequently derived from ECG recording. This series of R-R intervals was then analysed using Schwarzter FAN Study (FAN®, Schwarzter, Germany) system and HRV analysis was performed in accordance with standard measurement techniques and algorithms [26–28].

#### 2.2. Data analysis

Specifically, sequence of R-R intervals has been analysed using standard time and frequency domain analysis. In addition, recurrence analysis was subsequently performed. In case of the former, following parameters were calculated: mean R-R, mean heart rate (HR), standard deviation for R-R intervals (SDNN), standard deviation for heart rate (SDHR), root mean square of the successive differences for R-R intervals (RMSDD), the sum of all R-R intervals occurring more than 50 ms from each other (NN50), percental representation of NN50 occurrence in the total sum of R-R intervals (pNN50). Parameters derived from geometric methods (Triangular interpolation of N-N intervals and HRV triangular index) were not evaluated, as they are not suitable for short-term 5-min records [14,29].
For direct evaluation of sympathovagal activity, spectral analysis of measured R-R intervals was selected. Kubios® software was used with this regard [30]. This type of analysis distinguishes between three basic bands, which describe the behaviour of the autonomic nervous system. There is the very low frequency (VLF) band (0.0033–0.04 Hz) indicating the overall activity of various slow sympathetic functional mechanisms, the low frequency (LF) band (0.04–0.15 Hz) reflecting both the activity of sympathetic and that of parasympathetic (but generally being a major indicator of sympathetic activity), and the high frequency (HF) band (0.15–0.40Hz) which on the other hand reflects vagal activity (i.e. parasympathetic) [14,31–33]. Power values in individual bands were calculated by integrating respective sequences. Parameters used for further evaluation include power values in LF, HF and LF/HF ratio which indicates balance between sympathetics and parasympathetics. These parameters were used in previous studies focused on vasovagal syncope evaluation [34,29,35].

The same sequence of R-R interval was then analysed using recurrent analysis, methodology of which is described in detail below.

2.2.1. Phase space reconstruction

Recurrence analysis starts with phase space reconstruction, for which the length of R-R intervals was used as an input signal. Every given point in the space phase represents a certain state of the system. The most commonly used method for phase space reconstruction is time delay embedding based on Takens’ theorem [2,26,37].

State variables can be used to describe the state of a system. They form vectors which represent a trajectory in phase space, which is N-dimensional for N state variables. On one hand, it is often impossible to observe more than one state variable of a system [2], since they are either unknown or difficult to measure. Using the Takens’ theorem [2], however enables us to reconstruct a phase space trajectory from a single observation:

\[ x_i = (y_{i}, y_{i+\tau}, \ldots, y_{i+(m-1)\tau})^T, \]

in which m is the embedding dimension, \( \tau \) is the time delay and \( y_i \) is a single observation, \( T \) is period.

Literature offers a range of various approaches when choosing time delay and dimension [36]. To describe system dynamics fully using phase space reconstruction, an accurate set of these parameters is required [36].

The distance between neighboring elements is given by the time delay. Small state difference is determined by a small time delay, and vice versa, large time delays represent states which can be evaluated as independent. Autocorrelation function is one of the older methods for choosing time delay [38,36], however the possibility of nonlinear processes is not taken into account by this method. The accurate criterion for choosing time delay, as latest studies suggest, is mutual information function [36,38,39], which enables to measure mutual dependence of two random variables. The most suitable way for choosing time delay for space portraits is the first minimum of mutual information [39]. Using entropy, the mutual information of two variables can be defined as follows [39]:

\[ I(A, B) = H(A) + H(B) - H(A, B), \]

in which \( H(A) \) and \( H(B) \) are the entropies and \( H(A, B) \) is the joint entropy of \( A \) and \( B \).

An optimal embedding dimension is required right after the selection of an optimal time delay. It reflects number of the reconstructed shape space dimensions [36]. False nearest neighbor method represents one of the methods used to set optimal embedding dimension, and it proceeds from an observation that the selection of low embedding dimension results in crossing of phase space trajectory [36], representing a situation when points which are distant from each other in original phase space become closer in reconstructed phase space [40]. Modified false nearest neighbour method was introduced by Cao [40,36,41].

A custom designed MATLAB script (MATLAB R2013a, MathWorks, Inc., Natick, MA, USA) was used in this study. Cao’s modified method of false nearest neighbour [40], and method of first minimum of mutual information function [39] (to obtain optimal time delay) were used in this work as well.

2.2.2. Recurrence analysis

The objective of recurrence analysis is the comparison of all possible states in the phase space trajectory. It primarily uses recurrence plot (RP), which is able to represent recurrences in a dynamic system graphically (see Fig. 1). RPs are used both to identify interrelations between different systems and to find transitions between different states [2]. This can be described by the following formula:

\[ R_{ij} = \Theta (\epsilon - ||x_i - x_j||), \quad \text{for} \quad i, j = 1, 2, \ldots, N, \]

in which \( N \) is the number of states \( x_i \), \( \epsilon \) is a threshold distance, \( || \cdot || \) a norm and \( \Theta(\cdot) \) the Heaviside function.

The most important parameter in recurrence analysis is the threshold distance. It points out that we can assume an occurrence of the recurrence point in case when the trajectory between two states is smaller than the threshold. A number of studies [42,9,21] focused on the choice of threshold distance \( \epsilon \), which can be set to e.g. 10% of mean space diameter, 25% of standard deviation, 5–6% of maximal space diameter or to fixed percentage or recurrence points (basically ranged from 1.5% to 15% [43]). The above-mentioned settings are standardly used and we selected the method of fixed percentage of recurrence points \%RR = 2.5% for this study, being one of the most frequently used method (see also [9,19]).

Graphic representation of multidimensional phase space in 2D graph (see Fig. 1), immunity to noise and nonstationarity, and recording chaotic properties without extensive data collection represent the greatest advantage of RP. Another feature of RP are recurrence points, diagonal lines as well as vertical and horizontal lines. Sequences of recurrent states are represented by diagonal lines, whereas the duration of a non-changing, or slowly changing states are reflected by vertical and horizontal lines. Rare states are represented by single isolated recurrence points [38].

Finally, structures formed by points and lines yielded by RPs comprise a basis for recurrence quantification analysis (RQA), introduced by Zbilut and Webber [44], which allow quantitative evaluation of RPs.

The following measures are standardly derived from RP: Percentage of recurrence points (\%R) which form RP. This measure corresponds to the probability that concrete state will recur [38]. Higher recurrence means lower system variability. However we use such a threshold distance which ensures 2.5% of recurrence points.

\[ RR = \frac{1}{N^2} \sum_{i,j=1}^{N} R_{ij}. \]

Determinism (DET) is the percentage of recurrence points that form diagonal lines [38]. This parameter corresponds to system predictability [38]:

\[ DET = \frac{\sum_{i,j} IP(l)}{\sum_{i,j} R_{ij}}, \]

in which \( P(l) \) is the histogram of the lengths of the diagonal lines (l).
Divergence (DIV) is related with the Kolmogorov–Sinai entropy of the system [38]:

\[ \text{DIV} = \frac{1}{l_{\text{max}}} \]

Laminarity (LAM), percentage of points which forms vertical lines. This parameter helps to detect laminar states (states that do not change at all or that change very slowly) [38]:

\[ \text{LAM} = \frac{\sum_{i=1}^{N} vP(v)}{\sum_{i=1}^{N} vP(v)} \]

in which \( P(v) \) is the histogram of the lengths of the vertical lines \( v \).

Ratio between DET and RR (RATIO), can be used to discover transitions [38]:

\[ \text{RATIO} = \frac{\sum_{i=1}^{N} lP(l)}{\sum_{i=1}^{N} lP(l)} \]

The DET and RR ratio (RATIO) are used to identify hidden transitions [38].

Trapping time (TT), the average length of vertical lines. This parameter informs us for how long is the system trapped in a specific state [38]. It represents frequency and length of laminar states. Low values of LAM and TT indicate high complexity of a system [9].

\[ \text{TT} = \frac{\sum_{i=1}^{N} vP(v)}{\sum_{i=1}^{N} P(v)} \]

Longest diagonal line (LMAX) [38]:

\[ L_{\text{max}} = \max(|l_i; i = 1 \ldots N|) \]

Maximum length of a diagonal line LMAX and its reciprocal value DIV might be related to the largest positive Lyapunov exponent [38].

Longest vertical line (MAXV) [38]:

\[ \text{MAXV} = \max(v_i; i = 1 \ldots N_v) \]

Average length of diagonal line (AVDL) reflects average time when there are two segments of the trajectory in phase space close to each other [38]:

\[ \text{AVDL} = \frac{\sum_{i=1}^{N} lP(l)}{\sum_{i=1}^{N} P(l)} \]
Shannon entropy (ENTR) reflects the complexity of system dynamics [38]:

\[ \text{ENTR} = - \sum_{l=\text{min}}^{N} p(l) \ln p(l). \]  

(13)

For more details with regard to RQA measures, see also [38].

2.3. Statistical analysis

Parameters of time and frequency domain analysis and RQA measures were calculated for each subject and each phase of measurement. Kolmogorov-Smirnov test was used to verify the normality of parameters in each group. The assumption of normal data distribution in the observed participant samples was not proven in any of the cases and the normal data distribution hypothesis was rejected at significance level \( p = 0.05 \).

Therefore, non-parametric Wilcoxon test was used to compare statistical significance in the two observed groups. Testing was realized using significance level \( p = 0.05 \), and results \( p < 0.05 \) were considered significant. The results and observed differences in the measured parameters between the two groups were visualized as box-plots representing median, the first and third quartile, maximum, minimum and extreme values of the obtained statistic samples. The statistical analysis was performed in MATLAB environment (MATLAB R2013a, MathWorks, Inc., Natick, MA, USA).

3. Results

According to an earlier study by Pietrucha et al. [45], syncope was induced in similar proportion of women and men. Also, there was no significant relation between gender and orthostatic test results [45].
Time domain evaluation of R-R interval analysis revealed a significant drop in the values of SDNN ($p=0.0111$), mean HR ($p=0.0018$), NN50 ($p=0.0031$), pNN50 ($p=0.0042$) parameters, and a significant rise in the value of Mean RR ($p=0.002$) parameter in patients with syncope during the second phase of the active standing test in contrast to the first phase where a significant difference was found only in RMSSD ($p=0.0421$) parameter, see Figs. 2 and 3.

On the other hand, spectral analysis of R-R intervals did not identify any significant differences between the groups during the second phase of the active standing test, see Fig. 4. These two groups differed only in the significantly lower occurrence of LF ($p=0.0032$) in the syncopal group in the first phase of the test (Fig. 4).

Results of recurrence analysis are depicted in Fig. 1, 5 and 6 and in Tables 2 and 3.

Fig. 1 demonstrates examples of findings in a healthy subject (Fig. 1a) with significant shortening of R-R intervals after standing-up (resting phase on the left, stand-up phase on the right of appropriate graphs in Fig. 1a and b) and with two distinctly separated parts in the recurrence plot. On the other hand, in a syncopal patient (Fig. 1b), no clear heart rate change after stand-up was apparent and both phases of the tests overlap in the recurrence plot.

No significant change was found in RQA measures during the first phase of the orthostatic test (resting in supine position) between both groups. Wilcoxon test showed, that medians of the examined RQA measures were not significantly different (Fig. 5). Table 2 summarizes mean values of all RQA measures in the resting phase of the orthostatic test.

On the contrary, significant differences were found in most RQA measures between patients and the control group in the standing phase of the orthostatic test (Fig. 6). Significantly lower divergence (DIV) and significantly higher proportion of points forming diagonal lines (DET), length of the longest diagonal line (LMAX), points forming vertical lines (LAM), the average length of diagonal lines (AVDL), RATIO, the average length of vertical lines (TT) and maximal length of vertical line (MAXV) were found in Syncope group.
Fig. 4. Box-plots illustrating the comparison of frequency domain parameters between patients with syncope and control group during laying phase (Phase 1) and standing phase (Phase 2) of the active standing test.

Table 2
Overview results: the medians of RQA measures during first phase of active standing test.

<table>
<thead>
<tr>
<th>RQA measure</th>
<th>Control group</th>
<th>Syncope group</th>
<th>The significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25th</td>
<td>50th</td>
<td>75th</td>
</tr>
<tr>
<td>DET</td>
<td>0.1676</td>
<td>0.2547</td>
<td>0.3191</td>
</tr>
<tr>
<td>DIV</td>
<td>0.0852</td>
<td>0.0955</td>
<td>0.1607</td>
</tr>
<tr>
<td>LAM</td>
<td>0.1624</td>
<td>0.3508</td>
<td>0.4646</td>
</tr>
<tr>
<td>RATIO</td>
<td>6.6927</td>
<td>10.1700</td>
<td>12.7252</td>
</tr>
<tr>
<td>TT</td>
<td>2.0364</td>
<td>2.3160</td>
<td>2.4785</td>
</tr>
<tr>
<td>AVDL</td>
<td>2.2603</td>
<td>2.4914</td>
<td>2.7799</td>
</tr>
<tr>
<td>MAXV</td>
<td>3.0000</td>
<td>6.5000</td>
<td>7.7500</td>
</tr>
<tr>
<td>LMAX</td>
<td>6.2500</td>
<td>10.5000</td>
<td>11.7500</td>
</tr>
<tr>
<td>ENTR</td>
<td>0.5836</td>
<td>0.8407</td>
<td>0.9955</td>
</tr>
</tbody>
</table>

25th: 1st quartile/25th percentile; 50th: median/2nd quartile; 75th: 3rd quartile/75th percentile.

Table 3
Overview results: the medians of RQA measures during second phase of active standing test.

<table>
<thead>
<tr>
<th>RQA measure</th>
<th>Control group</th>
<th>Syncope group</th>
<th>The significance level</th>
</tr>
</thead>
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<tr>
<td></td>
<td>25th</td>
<td>50th</td>
<td>75th</td>
</tr>
<tr>
<td>DET</td>
<td>0.4178</td>
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<td>0.6511</td>
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<td>0.0171</td>
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<td>LAM</td>
<td>0.5632</td>
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<tr>
<td>TT</td>
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<td>3.1141</td>
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<td>2.9780</td>
</tr>
<tr>
<td>MAXV</td>
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<td>9.0000</td>
<td>12.7500</td>
</tr>
<tr>
<td>LMAX</td>
<td>17.2500</td>
<td>35.5000</td>
<td>58.5000</td>
</tr>
<tr>
<td>ENTR</td>
<td>0.9889</td>
<td>1.0721</td>
<td>1.2326</td>
</tr>
</tbody>
</table>

25th: 1st quartile/25th percentile; 50th: median/2nd quartile; 75th: 3rd quartile/75th percentile.

Significant values (p < 0.05) are in bold.
Higher values of $DET$ reflect more frequent return of the system into the previous state reflecting the system’s predictability. Significant differences in $TT$ and $MAXV$ were also identified, see Table 3.

4. Discussion

It is well known that the rigidity of sinus rhythm, i.e. a decrease in HRV is a negative prognostic marker [46,14].

The results of time domain analysis showed significant differences between the groups in the second phase of the active standing test. These findings correspond to results presented in previous studies, e.g. Lagi et al. [47] despite the fact that the analysed record was 24 h long in their study. On the other hand, results yielded by frequency domain analysis did not point to any significant differences between the groups in any phase of the test. Based on our results, it is not possible to verify the claim [29,35] that HRV analysis is capable of identifying differences between patients and the control group, with respect to autonomic nervous system activation as a reaction to orthostasis, or of reflecting changes in the autonomic nervous system related to the onset of vasovagal episodes. In any case, the measuring protocol is partly divided in our study, with the main focus on the total test duration of 10 minutes without using tilt table. With regard to spectral analysis, it is also necessary to take into account a significant interindividual variability [31], which may significantly distort the results with errors.

This pilot study identified significant differences between results obtained from vasovagal syncope patients and healthy subjects using recurrence analysis. Our study demonstrated that the
RQA measures did not differ significantly in the two groups in the first phase of the orthostatic test (resting phase). This finding was predictable, since the activity of ANS between vasovagal syncope patients and healthy population does not differ in resting position [48].

In the second phase of active standing test, expected clinical symptoms typical for syncope patients took place [48]. At the same time, changes occurred in the RQA measures. The Syncope group yielded higher \( \text{DET}, \text{LAM}, \text{MAXV}, \text{TT}, \text{AVDL}, \text{RATIO} \) and \( \text{LMAX} \) and lower \( \text{DIV} \) values reflecting lower heart rate variability, which imply pathological conditions.

Increase in \( \text{DET} \) values generally points out to a more frequent return of the system (sinus rhythm) to previous states [49] and at the same time, increase in \( \text{LAM} \) values reflects higher rate of laminar phases in the system [49], and thus an increased intermittence.

An increase in \( \text{MAXV} \) value in patients with syncope points out to the fact that sinus rhythm remains in its previous phase longer [49]. Additional data to \( \text{MAXV} \) is \( \text{TT} \), which represents the time span of a specific state in the system [49]. Higher values of \( \text{AVDL} \) levels in patients with syncope also reflect lower variability. An average length of an \( \text{AVDL} \) diagonal line represents a state when the trajectory in the phase space runs directly into another segment of the phase space, also called mean prediction time [38].

The significant differences observed between these parameters in healthy subjects and in patients with syncope after verticalization reflect lower HRV. This means that increase in the parameters implies a higher predictability of the system [50].

The aforementioned observation is caused by the fact that physiological circumstances activate the regulatory function of ANS in terms of the adaptation to the given situation either by increased...
activity of sympathetic or parasympathetic, to preserve balanced system and to avoid the occurrence of pathological states. These changes in the activation of the two parts of ANS at the same time cause significant deviations in heart rate. However, in the case of syncpe, with disorders in regulatory function of ANS (decreased activity of sympathetics), these mechanisms cannot take place, and thus apparent influence of ANS on heart activity in terms of heart beat variability are not as significant.

5. Conclusions

In our study, recurrence analysis was applied for evaluation of HRV with the aim to identify ANS dysfunction that is responsible for orthostatic syncopes in patients. Results from recurrence analysis were compared with the standard HRV analysis that is based on time-domain and frequency domain analysis. Our results suggest that recurrence analysis may be useful tool for identifying patients with autonomic dysfunction that present with orthostatic syncope and that this method may be more sensitive in detecting ANS dysfunction than the measures of HRV derived from time and frequency domain analysis. Since these standard methods of HRV analysis have been demonstrated to be useful in the assessment and identification of high-risk patients with cardiovascular diseases connected to heart attack [15,16,46] or diabetic neuropathy [27,28], recurrence analysis with its possibly higher sensitivity to detect ANS dysfunction may help in the risk-stratification of these patients in the future.

However, since recurrence analysis represents a new method, some questions related to optimal set of input parameters (especially the threshold distance) remain open and widely discussed [42,43]. Moreover, this study represents a pilot project and the demonstrated findings should be perceived in this light as a relatively small number of subjects in both groups and the lack of gender-matched control group pose certain limitations. Therefore, future studies in this area would be appreciated.

Acknowledgement

This work was supported by the Grant Agency of the Czech Technical University in Prague, grant no. SGS14/169/OKH4/2T/17 and grant no. SGS14/170/OKH4/2T/17. The authors would also like to thank Andrej Madorin, BA, for the translation of this paper.

References


