A New Phase Space Analysis Algorithm for the Early Detection of Syncope during Head-Up Tilt Tests

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Abstract

In this study, we evaluate the ability to automatically predict syncope and differentiate between patients with positive response to head up tilt test (HUTT) and other with negative response, using only 12-min RR-interval time series for the supine position, preceding HUTT. An original method, based on the analysis of heart rate variability dynamics and a combination of phase space (PS) analysis and kernel support vector machine (KSVM), is proposed. The dynamic behavior of the RR-interval time series was analyzed using reconstructed phase space (RSP). Parameters computed from the phase space area such as the phase space density and indices derived from the recurrence quantification analysis were computed. Only parameters, displaying a statistical difference, are used for further classification using KSVM, to identify negative and positive patients. By applying a cross validation procedure repeated 10 times using 1/3 of the population in the training step, we determined the capability of correctly classifying positive patients. An optimal configuration maximizing the sensitivity for the early detection of positive response was found leading to 95% of sensitivity and 47% of specificity. RPS combined with KSVM demonstrate the interest to take into account the dynamics of the RR series and their capability to predict tilt test's outcome using only pre-HUTT data.

1. Introduction

Reflex syncope is a loss of consciousness defined as a response to a malfunction in the region of the nervous system responsible for the regulation of heart rate and blood pressure. Head-up tilt test (HUTT) is a medical procedure commonly used as a diagnostic test for reflex syncope. The duration of HUTT is usually between 45 to 60 minutes, which is unsuitable for patients who have physical weakness and cannot hold out to the end of the test. Moreover, minimizing this duration would help to optimize the time of clinical practitioners, and will reduce costs. These reasons have led to search for methods to minimize the duration of the test, by predicting the HUTT outcome using the cardiovascular signals recorded during the test. Several methods have been proposed for this purpose, such as the time and frequency-domain analyses of RR series extracted from ECG [1], the early response of heart rate (HR) to HUTT [2], the analysis of BP changes [3], the joint assessment of HR and blood pressure (BP) changes [4], or processing transthoracic impedance waveforms (TI) [5].

In the last years, the development of non linear dynamics methods have provided new tools to analyze the complex cardiovascular system and detect cardiac arrhythmias such as ventricular fibrillation. The reconstructed phase space (RPS) is one of the well-known techniques that can be applied to analyze the dynamics of non linear systems, by transforming time-lagged copies of the initial signal onto axes of a new high dimensional space. The use of RPSs has provided interesting results in different applications, such as in speech synthesis and recognition as well as in the biomedical field.

The aim of this study is to propose an original method, based on the analysis of heart rate variability dynamics and a combination of RPS analysis and kernel support vector machine (KSVM), to early differentiate between subjects who developed syncope during HUTT (positive response) and others who have negative response to the test. The rest of this paper is organized as follows. In the methods section; we present the clinical protocol, including the HUTT procedure, the database and signal acquisition and processing then the reconstructed phase space algorithm is described. The outcome of this work is displayed in the results section and is interpreted in the discussion section. Finally a conclusion summarizes the end-results.

2. Method

2.1. Clinical protocol

Tilt test was performed in the university hospital of Rennes-France, in 66 patients, 31 patients had a negative response to HUTT and 35 patients have developed syncope during the test (positive response). Subjects enrolled in the study are non smoker men from 18 to 35 years, they weren't taking cardioactive medication and they didn't have any other disorders.

Acquisitions were performed in a quiet room, without provocative drugs. Subjects underwent a familiarization 2 to 6 days before the HUTT. They were asked to avoid physical activity 24h before and exciting drinks 12h before (e.g. coffee), and to have a light or no breakfast. The HUTT started with 12 min of resting in a supine position, after that, the table (Sissel, Sautron, France), that had a foot-board support was tilted at 80° for 45 min. HUTT was considered as positive if the subject developed syncope or intolerable presyncope associated with significant arterial hypotension, in this case the table was immediately returned to its initial position, and the test was terminated.

During the test, patients were monitored by ECG and plethysmography using the Task Force Monitor. We acquired one lead ECG with sampling frequency 1000 Hz. Electrocardiogram signals were processed with a validated software DELICE (LTSI, UMR 1099, Rennes), which provides a fully automatic segmentation of all heart beats based on wavelet decomposition [6]. This algorithm offers the possibility to consistently extract a large number of ECG indicators (RR-interval, QT-interval, PR-segment, QRS duration …); The RR-interval (the time between the R-peaks in the ECG of two consecutive heart beats) has been explored to compute the RPS parameters for the 12-min of the supine position, preceding HUTT.

2.2. Reconstructed phase space algorithm

Given the RR signal as a time series: $x(1)$, $x(2)$ …$x(n)$ where n is the sample number, the reconstructed phase space vector can be represented as:

$$X_i = [x_i \ \ x_{i+\tau} \ \dots \ x_{i+(d-1)\tau}] \qquad i=1 \dots n-(d-1)\tau$$

with τ is the time delay between the points of the time series and where d is the embedding dimension which defines the number of phase space coordinates.

Eckman et al have proposed a method to visualize the recurrence of states in phase space [7]. This representation is called *recurrence plot (RP)* and can be mathematically expressed as:

$$R_{i,j} = \Theta(\varepsilon_i - \|x_i - x_j\|), \qquad x_i \in \mathbb{R}^m,\ i,j=1 \dots N$$

With Θ (.) is the Heaviside function, $\mathcal{E}_i$ is a threshold distance and N is the number of states x_i. The recurrence quantification analysis quantifies the number and duration of recurrences presented in the phase space of the time series.

To predict the outcome of the HUTT (positive or negative) two methods were evaluated. The first one requires the normalization of the reconstructed phase space to have all values within the range [0,1], divides it into 1000 equal sized cells [8] and then estimates the distribution of points in each cell. In the rest of this paper each cell is mentioned by an attributed number according to its bounds in the 3 axes (*i.e.* the bounds of cells number 1 and 2 are 0-0.1 in the 1st axis; 0-0.1 in the 2nd axis and respectively 0-0.1 and 0-0.2 in the 3rd axis). The second method computes new measures of complexity based on RP extended by [9] and summarized in figure 1.

Measure	Definition
Recurrence rate *RR*	The percentage of recurrence points in an RP: $RR = \frac{1}{N^2}\sum_{i,j=1}^{N} \mathbf{R}_{i,j}$
Determinism *DET*	The percentage of recurrence points which form diagonal lines: $DET = \frac{\sum_{l=lmin}^{N} l\,P(l)}{\sum_{i,j}^{N} \mathbf{R}_{i,j}}$ *P(l)* is the histogram of the lengths *l* of the diagonal lines.
Laminarity *LAM*	The percentage of recurrence points which form vertical lines: $LAM = \frac{\sum_{v=v_{min}}^{N} vP(v)}{\sum_{v=1}^{N} vP(v)}$ *P(v)* is the histogram of the lengths *v* of the vertical lines.
Ratio *RATIO*	The ratio between *DET* and *RR*: $RATIO = N^2 \frac{\sum_{l=l_{min}}^{N} l\,P(l)}{(\sum_{l=1}^{N} l\,P(l))^2}$
Longest diagonal line L_{max}	The length of the longest diagonal line: $L_{max} = \max(\{l_i; i = 1 \dots N_l\})$
Divergence *DIV*	The inverse of L_{max} : $DIV = \frac{1}{L_{max}}$ Related with the sum of the positive Lyapunov exponents.
Entropy *ENTR*	The Shannon entropy of the probability distribution of the diagonal line lengths *p(l)*: $ENTR = -\sum_{l=l_{min}}^{N} p(l) \ln p(l)$

Figure 1. Recurrences quantification analysis measures, RQA.

3. Results

3.1. RPS parameter adjustment

The delay τ was estimated as the first minimum of the average mutual information measure and d is chosen as the value that minimizes the false neighbor's percentage using the false nearest neighbor algorithm. Based on these measures, we found that d=3 and τ =3 are the best values for these 2 parameters. Figure 2 shows examples of the RR time series and its RPS for negative and positive subjects during supine position.

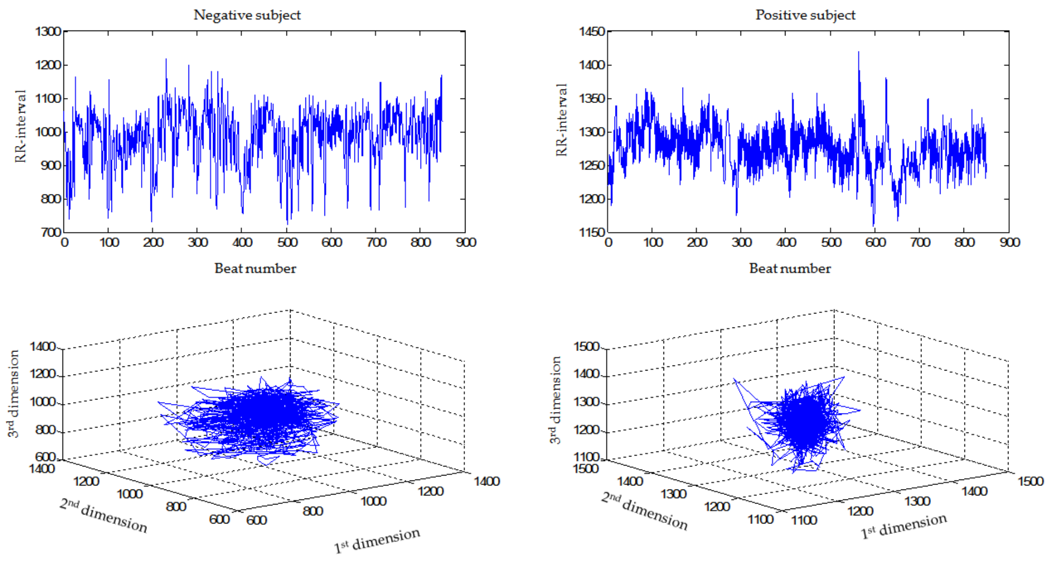

Figure 2. RR time series and its RPS for negative (left panel) and positive (right panel) subject with d=3 and τ=3 during supine position.

3.2. Classification performance

As regard to the density distribution in cells, the parameters that displayed a statistical difference (p-value <0.05 using Mann-Whitney test) are: the density of points in the cells number 588, 589, 859, 969 (with p-value respectively: 0.004; 0.0065; 0.0013 and 0.0036), details about these cells is reported in table 1. Examples of histograms based on the distribution of points in each cell are presented in figure 3 and clearly show the difference during the rest position between negative and positive subjects.

Table 1. The bounds of the significant cells.

Cell number	Bounds in 1st axis	Bounds in 2nd axis	Bounds in 3rd axis
588	0.5-0.6	0.8-0.9	0.7-0.8
589	0.5-0.6	0.8-0.9	0.8-0.9
859	0.8-0.9	0.5-0.6	0.8-0.9
969	0.9-1	0.6-0.7	0.8-0.9

Moreover none of the RQA parameters have shown significant differences between the two groups (see table 2 with RTE is the recurrence time entropy). Parameters showing statistical difference between the two groups were used to participate in the non-linear classification tests using kernel support vector machine (KSVM) with Gaussian radial basis kernel as kernel function.

An exhaustive search for all possible combinations of these parameters was done to find an optimal performance with zero error of classification of subjects with positive response.

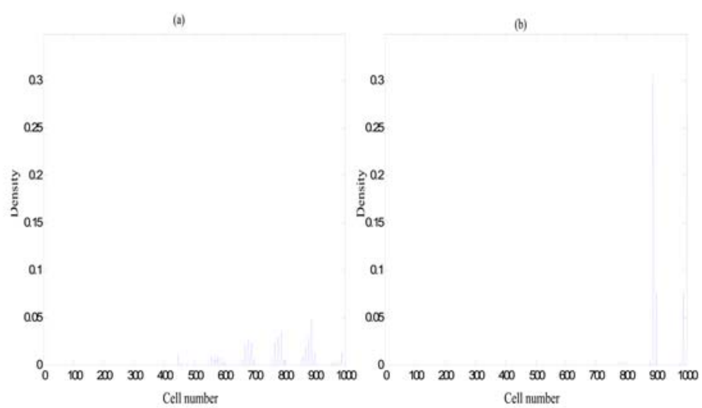

Figure 3. Phase space density plot of negative (a) and positive subject (b).

Table 2. Mean and standard deviation of RQA parameters.

	Negative	Positive	*p*-value
R_eR_a	0,002±0,0014	0,002±0,0013	0,06068
DET	0,034±0,031	0,039±0,041	0,657575
Lmax	3,322±2,344	4,171±4,409	0,513159
ENTR	0,146±0,209	0,193±0,227	0,354328
LAM	0,027±0,025	0,049±0,061	0,136084
RTE	0,789±0,043	0,782±0,0371	0,126284

Kernel parameter (σ) was varied from 0.01 to 4 using 0.01 as step size. With σ>4, the error of classification was generally large, this is why we decided to stop at σ=4. By applying a cross validation procedure repeated 10 times using 1/3 of the population in the training step, we determined the capability of correctly classifying the majority of positive patients. A sensitivity of 95% with specificity of 47% was observed using the density of points in the 4 cells showing statistical difference between the two groups when the σ is equal to 0.5. Table 3 shows the confusion matrix obtained from the average result of the 10 iterations.

Table 3. Matrix representing the average result of the 10 iterations.

	Classified as	
	Negative	**Positive**
Negative	9.4	10.6
Positive	1.3	23.7

4. Discussion

In the present work, a novel method is proposed to distinguish between patients with negative and positive response to head up tilt test, using parameters extracted from the reconstructed phase space of RR-interval time series. Applying these proposed parameters, we achieved to correctly classify most of the positive patients. Although the obtained specificity is not very high, our findings are interesting in terms of sensitivity leading to predict the occurrence of syncope from the supine position. The phase space reconstruction combined with KSVM demonstrates the interest to take into account the dynamics of the RR series and their capability to predict tilt test's outcome using only pre-HUTT data. These findings can induce to a significant reduction of HUTT duration which is usually from 45 to 60 min and to improve the efficiency of syncope management units in hospitals.

5. Conclusion

The applied phase space reconstruction technique to evaluate the dynamic behavior of the RR time series provides useful information to early predict the outcome of HUTT. The proposed phase space analysis parameters combined with KSVM classification has been shown to be effective for correctly classify most of subjects with positive response with a specificity of 47% during the 12 min of supine position, allowing the reduction of the examination time in the clinical domain.

It is worthwhile to note that in this analysis only the supine position before table inclination is used. To our knowledge, and compared to the results reported in the literature, the new tool used in this application provides promising results that may be seen complementary to those using nonlinear parameters during the 15 min following the tilt position [10].

Further work is in progress to apply this method on different time series extracted from other cardiovascular signals (*i.e.* blood pressure signal) and to evaluate the capability of other dynamic analysis tools, such as the hidden semi-markovian model, to early predict the outcome of HUTT.

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