Algorithm for Real-time Prediction of Neurally Mediated Syncope Integrating Indexes of Autonomic Modulation

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Abstract

Neurally mediated syncope (NMS) is a transient and self-limited loss of consciousness that affects all ages and is associated with high rates of falls and hospitalizations.

In this study we propose a new algorithm for real-time prediction of NMS that integrates indexes of autonomic modulation among other parameters, which is based on the analysis of the electrocardiogram (ECG) and photoplethysmogram (PPG) alone.

ECG and PPG signals were acquired from 43 patients with suspected NMS, during scheduled diagnostic head-up tilt table (HUTT) tests.

Heart rate variability (HRV) indexes were integrated in a NMS prediction algorithm comprising surrogates of chronotropic, inotropic, blood pressure and vascular tone changes.

The proposed algorithm was validated using a three-way data split approach. HRV indexes improved the algorithm performance in both the train/validation phase and the test phase, showing the importance of autonomic modulation indexes in real-time prediction of NMS.

1. Introduction

Syncope is defined by a transient and self-limited loss of consciousness, which is characterized by a rapid onset, short duration and spontaneous complete recovery [1].

Syncope is associated with high rate of falls and hospitalizations, accounting for 1-3% of all emergency department (ED) visits and 1-6% of all hospital admissions in general [2, 3]. It is responsible for lifestyle quality reduction and is often associated with the appearance of medical complications, especially in elderly were its incidence rises up to 30.6 incidents per 1000 person-years [2]. With an annual cost of $1.7-2.4 billion, the costs of hospitalizations related to syncope are equivalent to conditions such as asthma, HIV and chronic obstructive pulmonary disease [4]. Therefore, the development of a warning system, capable of informing patients for the need of taking appropriate counter measures and avoid potential injuries is essential.

Although there are many syndromes of reflex syncope, they all share the same mechanism, composed by a trigger (the afferent pathway) and a response (the efferent pathway. In these neurally mediated syncopes (NMS), the Bezold-Jarisch reflex is thought to have a primary role in the development of loss of consciousness. The overstimulation of the left ventricular wall leads to an over-response of the hypersensitive autonomic nervous system, which is responsible for inducing a vagal mediated suppression of sympathetic activity, in order to protect the myocardium. The result is bradycardia, vasodilation, and consequently hypotension and syncope.

NMS prediction has been tackled over the last years from several perspectives, which differ in the objectives, methods and sensing modalities. The most common approach is the early prediction of the HUTT outcome based on an analysis of heart rate (HR) and blood pressure (BP) variability, using time, frequency domain techniques, or both. Contrarily, real time prediction approaches focus on assessment of the risk of an impending syncope episode. In this area, authors focused on the analysis of changes in HR and BP [5] and also pulse arrival time (PAT) as a surrogate for systolic BP changes [6]. However, to our knowledge, the integration of autonomic modulation indexes in a real time perspective still lacks proper analysis.

In the present paper, we propose the integration and analysis of heart rate variability (HRV) indexes, extracted from time and frequency domain analysis, into a previously proposed algorithm [7], for real time prediction of NMS.

2. Study design and experimental setup

Data from 55 patients with unexplained syncope was

collected during scheduled diagnostic HUTT. All the patients gave a written informed consent to participate in the study (NCT01262508).

The HUTT protocol consisted of four phases. In the 1st phase (initial resting period) the patient lies for at least 15 min in supine position. Next, in the 2nd phase (passive standing period), the patient stands for a period of 20 minutes in a 70º position. If no syncope occurs during the previous phase, the patient remains in a passive standing position and it is administrated sublingually a min 400 µg of glycerol trinitrate (GTN). In the last phase (final recovery period), the patient is tilted back to the supine position for recovery. If the patient experienced syncope during any of the protocol phases, it was immediately returned to the supine position for recovery. A technician documented prodromal symptoms (e.g. dizziness, sweat, tremor) during the whole protocol.

The HUTT outcome was classified as positive (po) or negative (ne) according to the European Society of Cardiology [2] guidelines. The occurrence of syncope or pre-syncope in the presence of cardioinhibitory, vasodepressor, or mixed responses, was considered a positive result.

The data collected in this study was recorded using a Philips MP50 patient monitor extended with data logger functionality (ECG @500 Hz and PPG @126 Hz) and a "Taskforce Monitor" (continuous BP @50 Hz, two ECG leads @1000Hz, among other signals). The recorded data were synchronized using the RR interval time series extracted from the ECGs of both systems.

Due to BP regulation failures not caused by syncope, arrhythmias and poor data quality in BP and PPG signals, data recorded from 12 patients have been removed. The biometric characteristics of the study population (21 po / 22 ne) are (mean ± std):

- Age: 57 ± 18 (po) and □□±17 (ne) years
- BMI: 27.1 ± 4.6 (po) and 26 ± 5 (ne) Kg/m2
- GTN admin. (yes/no): 15/6 (po) and 15/7 (ne)

3. Methods

The main steps of the proposed algorithm are: 1) Detection of motion artifacts; 2) Parameter extraction and post-processing; 3) Feature evaluation and; 4) Syncope prediction.

The PPG signal is prone to several sources of error, which can represent a serious obstacle to the reliable extraction of cardiovascular parameters. In the present algorithm motion artifacts were detected using the algorithm proposed in [8], which is based on the time and period domain analysis of the PPG signal.

3.1. Parameter extraction

The chronotropic and inotropic changes were assessed from the analysis of the HR and left ventricular ejection time (LVET). The HR was extracted from the analysis of the ECG signal and defined as the time span between consecutive R-peaks, while the LVET was extracted from the analysis of the PPG signal using the algorithm proposed in [9].

Vascular tone and BP changes were assessed by three highly pressure dependent parameters: the stiffness index (SI); the reflection index (RI) and the pulse arrival time (PAT). The SI was defined as time span between the forward (T1) and reflected waves (T2), while the RI was defined as the ratio between the amplitudes of both waves (P1 and P2). Finally, $PAT_{80\%}$ was defined as the time span between the ECG R-peak and the moment in time corresponding to 80% of the PPG pulse amplitude after its onset. More details about the extraction of these parameters can be found in [9].

3.2. HRV analysis

The sympathetic and parasympathetic activity was assessed using both time and frequency domain HRV analysis in a 180 sec sliding window, shifted by 5 sec increments.

From the time domain analysis five parameters have been extracted: 1) SDNN - standard deviation of normal-to-normal (NN) intervals; 2) SDSD - standard deviation of successive differences between adjacent NNs; 3) RMSSD – square root of the mean squared differences between adjacent NN intervals; 4) NN50 - number of interval differences of successive NN intervals greater than 50 ms and; 5) pNN50 – ratio between NN50 and the total number of NN intervals.

Additionally, the autoregressive power spectral density estimate was evaluated using Burg's method and three frequency domain parameters were extracted: 1) aLF - normalized area of the spectra low frequency (LF) band (0.04-0.15 Hz); 2) aHF – normalized area of the spectra high frequency (HF) band (0.15-0.4 Hz) and; 3) aLH - ratio between aLF and aHF. While the HF component is commonly accepted as a marker of parasympathetic activity, the LF component is considered as a primary indicator of sympathetic modulation. However, the influence of the sympathetic and parasympathetic systems on the LF component is still controversial. The LF/HF ratio is commonly defined as a marker of sympatho-vagal balance [10].

3.3. Feature evaluation

The extracted parameters are comprised within different ranges, which change depending on the patients' physiological characteristics and status. Therefore, to develop a robust algorithm it is essential to define a set of features independent from such factors. To that end, the extracted parameters were normalized according to (1)

leading to the definition of the first set of 13 features.

$$n[PR_i(t)] = \frac{PR_i(t)}{PRref_i}, i = 1, \dots, 13 \quad (1)$$

where FT_i is the i[th] feature, PR_i is the i[th] parameter (e.g. PR_1 = HR, …, PR_6 = SDNN, …, PR_{11} = aLF, etc.), $PRref_i$ is the average of each parameter during the second minute after the patient was tilted to the upright position (reference window corresponding to orthostatic stabilization) and t is the time instant.

Furthermore, a set of five features was also defined as the normalized changes (of the first five parameters) over the previous 1.5 minutes (the minimum response time according to [6]) according to:

$$n\Delta[PR_i(t)] = \frac{PR_i(t) - PR_i(t - 1.5)}{PRref_i}, i = 1, \dots, 5 \quad (2)$$

To select the best features for syncope prediction we used a score metric (FSS) proposed in [11], which combines the feature relevance (the area under the curve - AUC) and redundancy (spearman's rank correlation coefficient - RCC). In sum, ten features were selected corresponding to the highest features selection scores.

3.4. Syncope prediction

To evaluate the risk of an impending syncope event a threshold based approached was used, resorting on the evaluation of the changes relative to a stable orthostatic reference at the beginning of the standing period (FTref). To evaluate these changes several distance metrics were tested and the Minkowski distance metric ($p=2^{-0.5}$) was selected.

One of the limitations of distance metrics is that they don't take into account the direction of the evolving trajectory. Therefore, it is necessary to suppress feature variations that are known a priori not being associated with the physiological mechanisms underlying NMS. To this matter, the *n[SI]* and *n[PAT]* and *n[SDNN]* values below unit, and *n[RI]* values above unit were set to one. Additionally, *nΔ[HR]* values above zero, and *nΔ[LVET], nΔ[SI]* and *nΔ[PAT]* values below zero were set to zero.

Impending NMS was detected when the Minkowski distance crosses a predefined optimal threshold.

4. Results and discussion

The selection of the best features, best distance metric and optimal threshold was performed on the train/validation subset (30 patients), while the test subset (13 patients) was independently used to validate the algorithm. The optimal threshold was defined as the average of the thresholds assessed at each fold/iterations during a 5-fold cross validation (5f-CV), repeated 20 times.

Table 1. Performance of the best 10 features

Feature	FSS(%)	SE(%)	SP(%)	PPV(%)
n[PAT]	92,1	92,1	100	90
n[SI]	89,1	89,8	80	96,7
n[SDNN]	80,2	86,2	93,3	73,3
nΔ[HR]	74,9	82,9	80	86,7
nΔ[SI]	72,6	88,9	80	93,3
nΔ[PAT]	72,3	90,3	80	93,3
n[RI]	72,3	86,6	86,7	83,3
nΔ[LVET]	68	80	80	73,3
n[aHF]	67	75,4	66,7	86,7
n[aLF]	60,7	73,9	66,7	86,7

4.1. Feature selection

The features prediction ability is presented in Table 1. One observes that all the selected features present an FSS above 60%, being the best associated with the changes of BP and vascular tone: *n[PAT] and n[SI]*. From the ten selected features, three features were selected from the HRV analysis: *n[SDNN]*, *n[aHF]* and *n[aLF]*. The *n[SDNN]* presented the best score within the HRV features, while the *n[aHF]* and *n[aLF]* were the last selected features, presenting the lowest FSS within the selected feature set.

In Figure 1 it is possible to observe an abrupt increase in the SDNN parameter and the trend of both aLF and aHF towards zero, preceding the onset of syncope. This trend mainly results from the increase of the very low frequency (VLF) oscillations, which have been recently associated with the increase of vagal activity, known as the last mechanism leading to syncope. This observation was found in 17 out of 21 patients with a positive test.

4.2. Syncope prediction

In Table 2 we compare the results achieved by the proposed algorithm with and without HRV indexes.

In the validation phase, our algorithm achieved a high

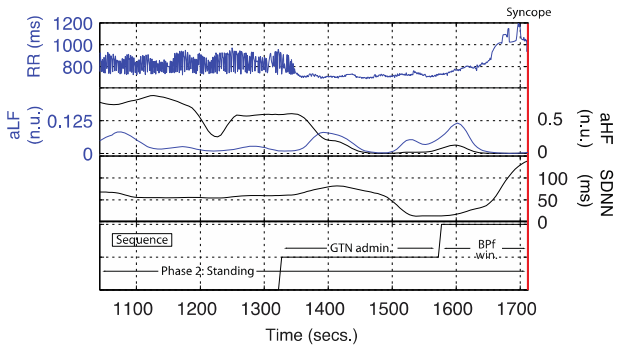

Figure 1. Representation of the RR, HRV selected parameters during a positive HUTT.

Table 2 – Results achieved by the proposed algorithm with and without HRV indexes

Algorithm	Phase	SE (%)	SP (%)	PPV(%)	FPRh (h-1)	PreTime (s)
With HRV	Train/Validation	93.3	100	100	0	56.1±36.8
indexes	Test	100	92.3	85.7	0.15	256.7±239.4
Without HRV	Train/Validation	93.3	96.7	94.8	0.15	61.0±38.6
indexes	Test	100	92.3	85.7	0.15	243.3±242.5

sensitivity (SE) of 93.3%, associated with high specificity (SP) and positive predictive value (PPV: 100%). During this phase no false alarms have been detected (FPRh:0 h^{-1}) and a good prediction time was achieved (56.1±36.8s).

In the testing phase, there was an increase in the algorithm prediction capability, reflected by the high SE (100%). Although, the SP and PPV remained elevated in this phase (above 85%) we observed a decrease when compared to the train/validation phase. The achieved FPRh was low (0.15 h^{-1}) and a good prediction time was achieved (prediction time (PreTime): 256.7±239,4).

Visibly, the integration of HRV indexes increased the performance of the proposed algorithm in both train/validation and test phases. In the validation phase, the HRV indexes enabled the enhancement of both SP PPV and FPRh, followed by a minor decrease in the prediction time (ΔPreTime: -4.9s). In the test phase, the HRV indexes did not produce such enhancements, leading to similar results. An exception was observed in the prediction time, which increased by approximately 13 sec.

5. Conclusions

In the current paper we investigated the possibility of integrating autonomic modulation indexes in an algorithm for syncope prediction. The prediction capability of several HRV time and frequency domain indexes was evaluated and compared with features associated chronotropic (HR), inotropic (LVET) and vascular tone (SI, RI and PAT) changes. From the eight HRV features investigated, three features (*n[SDNN]*, *n[aHF]* and *n[aLF]*) presented a prediction capability above the established selection criterion and were integrated in a set of ten features, which were combined into a single distance measure and a threshold-based approach to detect impending NMS. Our results show that the integration of HRV features enhanced the performance of the proposed algorithm, highlighting the importance of autonomic modulation indexes in real-time prediction of NMS.

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