A novel multi-parametric algorithm for faint prediction integrating indices of cardiac inotropy and vascular tone

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***Abstract*— Neurally medicated syncope (NMS) patients suffer from sudden loss of consciousness, which is associated with a high rate of falls and hospitalization. NMS negatively impacts a subject's quality of life and is a growing cost issue for the healthcare systems in particular since mainly elderly are at risk of NMS in our aging societies.**

In the present paper we present an algorithm for prediction of NMS, which is based on the analysis of the electrocardiogram (ECG) and photoplethysmogram (PPG) signals. Several parameters extracted from ECG and PPG, which have been associated in previous works with reflectory mechanisms underlying NMS, were combined in a single algorithm to detect impending syncope. The proposed algorithm was validated in 43 subjects using a 3-way data split scheme and achieved the following performance: sensitivity (SE) - 100%; specificity (SP) - 92%; positive predictive value (PPV) - 85%; false positive rate per hour (FPRh) - 0.146h^{-1} and; average prediction time (aPTime) - 217.58s.

I. INTRODUCTION

Syncope is a transient and self-limited loss of consciousness, resulting from a transient global cerebral hypoperfusion and is characterized by a rapid onset, short duration and spontaneous complete recovery [1]. Also referred to as vasovagal and neurocardiogenic syncope, NMS belongs to a broader group of syncope known as reflex syncope, responsible for 21% of syncope episodes [1].

In the latest Framingham Study [2] involving 7814 participants between 20 and 96 years old it was reported an incidence rate of 6.2 per 1000 person-years. Moreover, it was shown to increase with age, being the sharpest rise within the 70-79 and above 80 years old populations (11.1 and 19.5 per 1000 person-years, respectively. [2, 3]. Although the main causes of syncope are generally benign, it is associated with frequent hospitalizations and accounts for 1-3% of all emergency department (ED) visits, as well as 1-6% of all hospital admissions in general [2, 4]. Moreover, in U.S. approximately 4% of patients discharged from the ED with syncope experience severe adverse events within 72 hours, like readmission or death [4].

The recurrence of syncope episodes gains special emphasis in elderly populations, where morbidity is particularly high. Fear of falling often leads to reduced physical and social activity, which is associated with increased mental decline, incidence of medical conditions and subsequent institutionalization [1].

The main advances in syncope treatment and prevention focus on lifestyle modifications, which include the education of patients regarding the awareness and avoidance of triggers, the early recognition of prodromal symptoms, and performance of counter measures to abort the syncope episode [1]. Thus, the development of a non-invasive and non-intrusive, as well as cost-efficient personal p-health system to alert patients in case of an impending syncope might: 1) provide an opportunity for the patient to perform early counter-maneuvers and avoid or delay syncope, as well as 2) help in diagnostics of underlying pathophysiological mechanisms with better personalized treatment options.

Orthostatic intolerance is thought to be one of the most common triggers of reflex syncope [5]. Investigators believe that the abrupt and excessive amount of venous blood pooling during standing posture is responsible for a decrease in the venous blood return to the heart resulting in more vigorously ventricle contractions and excessive stimulation of the ventricular mechanoreceptors. As a result, a "paradoxical" withdrawal in sympathetic tone can occur i.e. cardioinhibition and vasodepression. This process is associated with a decrease in blood pressure and finally syncope [6]. Although the increase in parasympathetic activity (cardioinhibition) is commonly observed during NMS, hypotension due to vasodepression is considered as the primary mechanism leading to the loss of consciousness [7].

Several algorithms based on analysis of changes in heart rate and continuously measured systolic blood pressure (SBP) have been proposed to predict syncope events [8, 9]. However, current non-invasive blood pressure monitoring systems have several disadvantages. Most prominently their application is restricted by bulky and expensive hardware, as well as complicated handling with the need for frequent calibrations [10]. These limitations become critical in unsupervised environments such as at home or in ambulatory scenarios, where low cost and easy-to-use devices are essential. Recently, several authors focused on the analysis of the pulse arrival time (PAT) as a surrogate for SBP changes and consequently prediction of syncope [11-13]. In our previous work [13] we established and validated a method for syncope prediction using PAT. Additionally, in [14] we

This work was supported by EU projects HeartCycle (FP7-216695), CISUC (Center for Informatics and Systems of University of Coimbra), iCIS (CENTRO-07-ST24-FEDER-002003), Welcome (FP7-ICT-2013-10) and HeartSafe (PTDC-EEI-PRO-2857-2012).

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978-1-4244-7929-0/14/$26.00 ©2014 IEEE

evaluated the changes in several parameters, such as heart rate (HR) and left ventricular ejection time (LVET), in order to characterize the possible mechanisms underlying of NMS (e.g. chronotropic and inotropic changes).

In the present paper, we propose an algorithm for prediction of NMS by analyzing changes of several cardiovascular parameters that we previously suggested to characterize the chronotropic (HR), inotropic (LVET), vascular tone and blood pressure (PAT, stiffness index – SI – and reflection index - RI, respectively) changes. These parameters were extracted from the joint analysis of the electrocardiogram (ECG) and photoplethysmogram (PPG), which can be easily acquired with state-of-the-art equipment.

The remainder of the paper is organized as follows. In section II the data collection protocol and measurement protocol are described. The parameter extraction and syncope prediction algorithm are presented in section III. The main results are presented and discussed in section IV. In section V the main conclusions are presented.

II. Clinical Study

A. Study design and HUTT protocol

Data were acquired during scheduled diagnostic head-up tilt table tests (HUTT) from 55 patients with unexplained syncope. All patients gave written informed consent to participate in this study (NCT01262508).

HUTT consisted of four phases: 1) a initial resting period of at least 15 min in supine position; 2) a passive standing period of 20 min at a position of 70º 3) an additional standing period of 15 min, if no syncope occurred in (2), with sublingual administration of min 400 µg of glycerol trinitrate (GTN); 4) tilting back to the supine position. If syncope occurred at any time during the protocol the patient was brought back to the supine position immediately for recovery. Any prodromal symptoms such as dizziness, sweat, tremor, etc. during testing were documented.

Test outcome was classified as positive (po) or negative (ne) according to the guidelines of the European Society of Cardiology [2]. A positive result is characterized by occurrence of syncope or pre-syncope with the presence of bradycardia, hypotension, or both.

Data of 12 patients had to be removed due to BP regulation failures not caused by syncope, presences of arrhythmias and poor data quality in BP and PPG signals. The biometric characteristics of the 43 patients involved in the present study are summarized in Table I.

B. Experimental setup

ECG and PPG signals were acquired with a Philips MP50 patient monitor and stored on a laptop. Blood pressure was continuously measured (beat-to-beat) using a "Taskforce Monitor" [12]. Data coming from both systems were aligned in time via the synchronously detected ECG signals. Details of the acquisition system can be found in [14].

TABLE I. Patient characteristics (AVG± STD)

	Tilt positive (n=21)	Tilt negative (n=22)
Age [y]	57±18	63±17
Weight [kg]	86±15	74±13
BMI [kg/m2]	27.1±4.6	26±5
Male/female	13/8	10/12
GTN yes/no	15/6	15/7

III. Methods

The proposed algorithm consists of three steps: 1) Parameter extraction and post-processing; 2) Feature evaluation; 3) Syncope onset detection.

A. Parameter extraction and post-processing

Chronotropic and inotropic changes were assessed via HR and LVET. The HR was derived from the ECG and was defined as the time span between consecutive R-peaks. These peaks were detected using an algorithm similar to the approach discussed in [15]. The LVET was assessed from the PPG analysis using the algorithm proposed in [16].

To assess vascular and blood pressure changes, three highly pressure dependent parameters were also extracted [11-13, 17]. The SI is associated with the velocity of a pulse wave in large arteries [18] and correlates with pulse pressure [17]. In this work it was defined as time span between the forward (T1) and reflected waves (T2). The RI, associated with small artery stiffness [18], was defined as the ratio between the amplitudes of both waves (P1 and P2), as indicated in Figure 1. 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, which is known to correlate well with a decreasing BP in NMS [11]. Algorithms to detect characteristic points in the PPG are described in [16].

It is well known that the PPG signal is prone to several sources of error (e.g. motion artifacts), which can be a serious obstacle in the reliable extraction of the derived parameters. In the current study, no special emphasis was given to the artifact removal problematic. Instead, an approach similar to [19] was used to remove outliers, where a boxplot analysis over a sliding window was adopted. However, here the sliding window is applied to the difference between each parameter and its correspondent smoothed version calculated using a 121 beat moving median filter. The rationale behind this approach is the detection of sporadic values that greatly differ from the parameter main trend.

Finally, parameter time series were linearly interpolated at a 2Hz frequency, which according to [13] is well above the

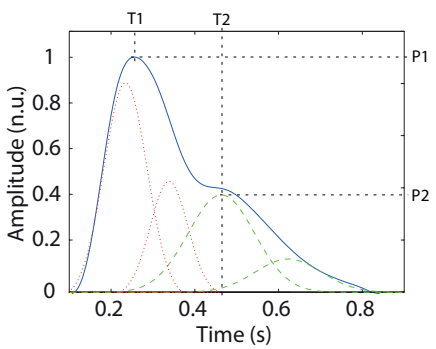

Figure 1. Representation of the PPG beat morphology and the extracted characteristic points used to assess stiffness and reflection indexes (SI and RI, respectively).

TABLE II. CORRESPONDENCE BETWEEN PARAMETERS/FEATURES INDEXES AND NAMES

Parameter name	Parameter index	Feature name (1st set)	Feature name (2nd set)
HR	PR_1	nHR	$n\Delta HR$
LVET	PR_2	$nLVET$	$n\Delta LVET$
SI	PR_3	nSI	$n\Delta SI$
RI	PR_4	nRI	$n\Delta RI$
PAT	PR_5	$nPAT$	$n\Delta PAT$

required minimal sample frequency. Additionally a Butterworth low-pass filter with a 0.05Hz cutoff frequency was used to reduce high frequency noise.

B. *Feature evaluation and selection*

To develop a robust prediction algorithm which is independent of a patient's specific characteristics the extracted parameters were normalized leading to a set of ten features in total, which are summarized in Table II. The first five features were defined as:

$$FT_i(t) = nPR_i = \frac{PR_i(t)}{PRref_i}, i = 1, \dots, 5 \quad (1)$$

where FT_i is the i[th] feature, PR_i is the i[th] parameter, $PRref_i$ is the average of each parameter during the second minute (reference window) after the patient was tilted to the upright position and t is the time instant. By selecting the reference window to be on the second minute, we ensure that the patient achieves orthostatic stabilization, which typically occurs within less than 1 minute [6].

Additionally, the normalized changes of the extracted parameters during the last 1.5 minutes - the minimum response time according to [13] - were also taken into account as:

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

The selection of the most appropriate features for syncope prediction was performed using the approach proposed in [20], where the features are selected based on a score metric (FSS) combining their relevance and redundancy, presented in eq. (3) . The relevance of each feature was assessed by the area under the curve (AUC) of the receiver operating characteristic (ROC) curve, while its redundancy was assessed by the spearman's rank correlation coefficient (RCC).

$$FSS_i = AUC(FT_i) - \frac{\left|\sum_{FT_j \in S} RCC(FT_i, FT_j)\right|}{|S|} \quad (3)$$

where S is the subset of selected features at each iteration and $|S|$ its cardinality. In sum, seven features were selected, which are presented in Table III.

C. *Syncope onset detection algorithm*

From the analysis of the extracted features instants before the onset of syncope, one observed the presence of significant changes in the majority of the tilt positive patients (Figure 2). The chronotropic and inotropic variations were observed in the substantial decrease of *nΔHR* and increase in *nΔLVET*. Moreover, significant blood pressure drop was observed by the substantial increase of *nSI*, *nPAT*, *nΔSI* and *nΔPAT*, and decrease of *nRI*.

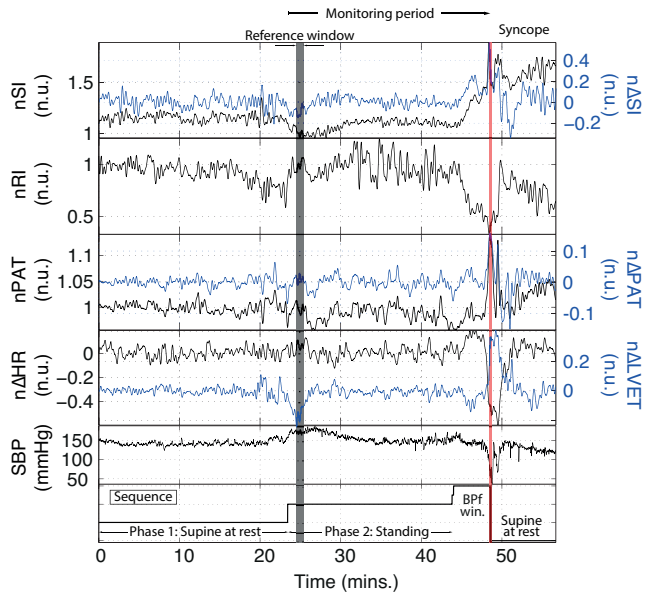

Figure 2. HUTT of a 50-year-old patient with syncope onset during GTN provocation. Representation of the seven most discriminant features assessed from the extracted parameters, SBP and HUTT sequence. BPf window corresponds time from the BP fall onset to the syncope episode.

In order to illustrate how the features vary in two patients (with/without NMS) during a HUTT, the first three principal components of a principal component analysis (PCA) are presented in Figure 3. In general, for HUTT po patient, the trajectory evolves away from the point corresponding to the orthostatic stable state, just before the onset of syncope. An example of this behavior is presented in Figure 3 (left) for a 69-year-old patient with manifested syncope and GTN provocation. Contrarily, on HUTT ne patients the trajectory remains closer to the orthostatic stable state as shown in Figure 3 (right) for a 78-year-old patient with no syncope after GTN administration.

Obviously distance metrics might be used as measure of a stable state or being at risk for an impending event. Therefore, the Minkowski distance was used to capture changes relative to a stable orthostatic reference at the beginning of the standing period (FTref), as calculated in (eq. (4)). The selection of the Minkowski distance order was performed using ROC analysis in a 5-fold cross-validation scheme. To eliminate feature variations that are not associated with NMS, and therefore might negatively affect the FD measure, *nSI* and *nPAT* values above unit and *nRI*

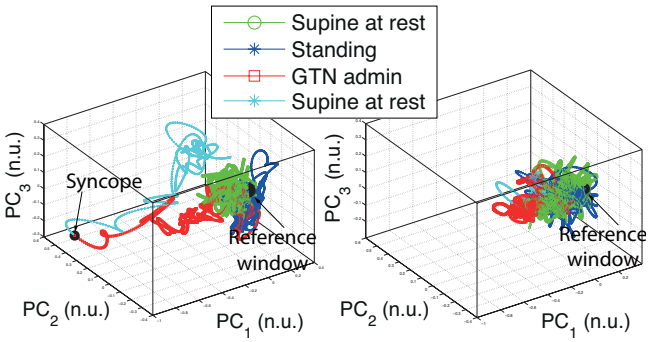

Figure 3. Illustration of the trajectory of the three principal components extracted from the most discriminative features, during HUTT procedure. Left: 69-year-old patient with manifested syncope and GTN provocation. Right: 78-year-old patient with no syncope and GTN provocation.

values below unit were set to one. Additionally, *nΔHR* values below zero and *nΔLVET, nΔSI* and *nΔPAT* values above zero were set to zero.

$$FD(t) = \left(\sum_{i=1}^{7} |FT_i(t) - FTref_i| \right)^{1/p}, p = 0.707 \quad (4)$$

where $FD(t)$ is the Minkowski distance at the time instant *t*.

Impending NMS was detected when FD crosses a predefined optimal threshold (TH_O=3.256). The SBP, FD and HUTT sequence are presented in Figure 4 for an example case of 69-year-old patient.

IV. Results and Discussion

To evaluate the performance of the proposed algorithm a three-way data split approach was adopted. The dataset was randomly partitioned into a training/validation (30 patients) and test (13 patients) subsets. The train/validation subset was used to select the best features, evaluate the performance of the proposed algorithm and select the optimal threshold for syncope prediction. In this phase, the algorithm performance and optimal threshold were evaluated using a 5-fold cross validation (5f-CV) approach (repeated 20 times). The optimal threshold was defined as the average of the thresholds evaluated at each fold/iterations. The test subset was used to validate the final solution, and test the real algorithms' performance.

The proposed methodology was evaluated using the following metrics: F-measure (F-m), sensitivity (SE) and specificity (SP), positive predictive value (PPV), false positive rate per hour (FPRh), prediction time average (aPTime) and standard deviation (sPTime). The performance of the algorithm was assessed in each 5-fold CV iteration and the average was computed. After repeating this process 20 times, the average and standard deviation (avg ± std) of the aforementioned metrics was evaluated.

The detection result was considered a true positive (TP) if an alarm is generated within the time window corresponding to the time between the start of BP fall and the syncope episode (BPf window). Otherwise, the detection result was considered a false positive (FP). A true negative (TN) was assigned if no alarm is generated outside the BPf window, whereas a false negative (FN) is considered if alarms are generated in this period. The FPRh was defined as the number of false positives divided by the sum of all non-BPf windows (in hours) of all patients. The PTime was defined as the time span between the first alarm and the syncope episode.

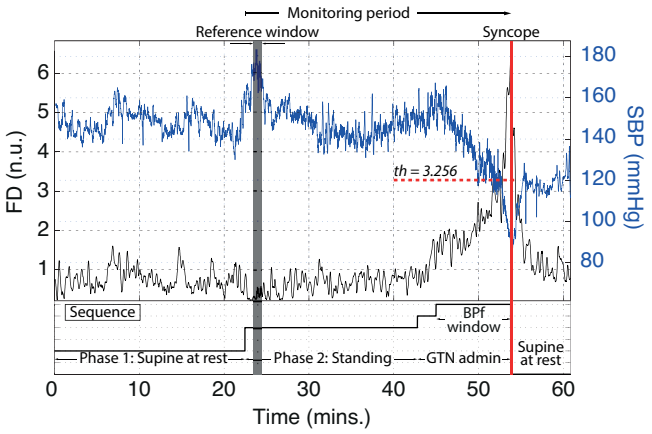

Figure 4. HUTT of a 69-year-old patient with manifested syncope and GTN provocation. Top diagram: SBP (blue) and FD (black) time series during HUTT. Bottom diagram: Phases of HUTT. Reference window represented as a black bar, corresponds to the second minute of phase 2. BPf window is time from the start of BP fall to onset of the syncope.

A. Feature selection

The feature selection results are presented in Table III. It is observed that the feature presenting the highest FSS refer to PAT parameter (*nPAT*), followed by *nSI* and *nΔSI*, related to SI. The remaining selected features correspond the normalized changes of HR (*nΔHR*) over a 1.5 minutes window and to the change of RI relatively to the reference window (*nRI*). It is also evident that between the 7th and 8th features (separated by a thick red line in Table III) there is a huge gap in the FSS score (≈11.4%). This performance decrease led to the exclusion of the last three features. In summary, seven features were selected from a total of ten extracted features. Although the best feature (*nPAT*) extracted from the analysis of the PAT parameter present the highest FSS, it is worth noting that it presents lower SP (90%) and PPV (83.3%), when compared to *nSI* (SP: 96.7% and PPV: 92.3%). Additionally, this feature presents a high FPRh (1.7 h^{-1}) when compared to the selected features, and particularly *nSI* (0.81h^{-1}).

The selected features with the highest prediction time (aPTime) also derive from the analysis of SI (*nSI*: 125.2s), followed by *nRI* (113.2s) and *nPAT* (101s). The aPTime of the remaining features ranges from 60.8s (*nΔHR*) to 90.2s (*nΔLVET*).

B. Syncope detection

The results achieved by the proposed syncope prediction algorithm in the training/validation and testing phases are presented in Table III (*FDval* and *FDts* respectively).

In the validation phase, the proposed algorithm achieved a SE of 89%, associated with high specificity (SP: 96.7%) and positive predictive value (PPV: 94.42%). Moreover, the number of false positives per hour is low (FPRh: 0.18h^{-1}) and a good prediction time was achieved (65.37 ± 40.6s).

In the testing phase, the proposed algorithm predicted

TABLE III. Performance of the extrated features ($FT_{1,\ldots,10}$), and the proposed algorithm in the validation (*FDVAL*) and test (*FDTS*) phases

Feature	Score (%)	SE (%)	SP (%)	PPV (%)	FPRh (h^{-1})	aPTime (s)	sPTime (s)
nPAT	94.6*	100.0	90.0	83.3	1.7	101.0	85.4
nSI	89.6*	80.0	96.7	92.3	0.8	125.2	121.3
nΔHR	75.8*	80.0	86.7	75.0	2.4	60.8	72.3
nRI	71.0*	86.7	83.3	72.2	2.0	113.2	94.2
nΔPAT	70.7*	80.0	93.3	85.7	0.8	76.4	143.0
nΔSI	68.3*	80.0	93.3	85.7	0.3	84.5	84.3
nΔLVET	67.4*	80.0	73.3	60.0	4.1	90.2	80.6
nLVET	56.0*	93.3	60.0	53.8	5.2	201.6	130.2
nHR	49.0*	73.3	90.0	78.6	1.2	77.0	142.7
nΔRI	35.9*	100.0	10.0	35.7	11.3	206.7	141.8
FDval‡	91.8±2†	89±3.3	96.7±0	94.42±0.82	0.18±0.05	65.37±2.6	40.6±5.08
FDts	92.3†	100	92.3	85.7	0.146	217.58	197.45

* Feature selection score (FSS). † F-measure (F-m). ‡Average ± standard deviation

syncope episodes with a high SE of 100%, without compromising both specificity (SP: 92.3%) and positive predictive value (PPV: 85.7%). Moreover, the number of false positives per hour is low (FPRh: 0.146 h^{-1}) and a good prediction time was achieved (PTime: 217.58 ± 197.45s), ranging from 62.5 to 569s. The detection of impending syncope was always after the onset of the prodomi symptoms (from approximately 0.5 to 3 minutes), with exception to patient #36, where syncope was predicted before the appearance of symptoms.

An important characteristic of the proposed algorithm is the compromise between the high performance, supported by the high values of SE, SP and PPV (above 85%), and the low false positive rate per hour, in both validation and testing phases. Here, an essential improvement could be achieved of utmost importance to avoid false alarms limiting the use in p-health scenarios by mistrust in a monitoring solution. Moreover, the observed prediction times can give patients the ability to act appropriately, e.g. by performing physical counterpressure maneuvers (PCMs). According to [21], the effects of PCMs such as hand grip maneuver were evident after the first 10s and showed significant BP increases after a 2 min. Our results suggest that the achieved prediction times (ranging from 1 to 9 minutes) might be helpful in an early execution of PCMs and therefore could facilitate the timely administration of effective interventions to prevent or delay NMS.

V. Conclusions and Future Work

In the current paper an algorithm for syncope prediction based on the evaluation of chronotropic (HR), inotropic (LVET) and vascular tone (SI, RI and PAT) changes is presented. The extracted features resulted from the analysis of ECG and PPG signals and were combined into a single distance measure and a threshold-based approach was used to detect NMS. The proposed methodology was trained and tested on 43 patients using a three-way data split scheme. Our results highlight the potential importance of a combined analysis of the extracted parameters in the prediction of impending NMS. Additionally, we demonstrate the robustness of the algorithm approach against artifacts, which might prove to be a key feature in the translation of this method in to ambulatory p-health settings.

Future work will focus on the implementation of a classification model such as Support Vector Machine to identify patterns during impending syncope combined with a threshold-based approach for early NMS detection.

Acknowledgment

We thank the medical and nursing staff of the Neurocardiology Unit, Division of Cardiology, Pneumology and Angiology, University Düsseldorf, for supporting this study. We thank especially Sandy Gläser for excellent technical support.

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