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Characterization of Surrogate Parameters for Blood Pressure Regulation in Neurally-Mediated Syncope

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Abstract— **Neurally Mediated Syncope (NMS) is often cited as the most common cause of syncope. It can lead to severe consequences such as injuries, high rates of hospitalization and reduced quality of life, especially in elderly populations. Therefore, information about the syncope triggers and reflex mechanisms would be of a great value in the development of a cost-effective p-health system for the prediction of syncope episodes, by enhancing patients' quality of life and reducing the incidence of syncope related disorders/conditions.**

In the present paper we study the characterization of syncope reflex mechanisms and blood pressure changes from the analysis of several non-invasive modalities (ECG, ICG and PPG). Several parameters were extracted in order to characterize the chronotropic, inotropic and vascular tone changes. Thus, we evaluate the ability of parameters such as Heart Rate (HR), Pre-Ejection Period (PEP) and Left Ventricular Ejection Time (LVET) to characterize the physiological mechanisms behind the development of reflex syncope and their potential syncope prediction capability. The significant parameter changes (e.g. HR from 12.9% to -12.4%, PEP from 14.9% to -3.8% and LVET from -14.4% to 12.3%) found in the present work suggest the feasibility of these surrogates to characterize the blood pressure regulation mechanisms during impending syncope.

I. Introduction

Neurally Mediated Syncope (NMS) is a sudden, transient and self-limited loss of consciousness, resulting from a temporary reduction of cerebral blood flow. It is often cited as the most common cause of syncope and falls within a category of syncope known as reflex syncope.

Reflex Syncope has a high incidence among the general population. In the latest report of the Framingham Heart Study and the Framingham Offspring Study, 10% of 7814 participants (mean age 51 years, range 20 to 96) reported at least one episode of syncope during 17 years, corresponding to a cumulative lifetime incidence of approximately 42% (assuming an average life expectancy of 70 years and a constant incidence rate over time) [1]. In elderly populations (67-107 years), studies suggest that 23% of the elderly population will suffer syncope in the next ten years and such events can account for 5% of emergency visits and 3% of hospital visits for such patients [1].

The demographic aging of our population makes this issue gain special emphasis, since syncope episodes can lead to serious consequences, including injuries, high rates of hospitalization and reduced quality of life. Therefore, information about the syncope triggers and reflex mechanisms would be of a great value in the development of a cost-effective p-health system for the prediction of syncope episodes, by enhancing patients' quality of life and reducing the incidence of syncope related disorders/conditions.

Neurocardiogenic syncope, reflex vagal syndromes, and vasomotor instability refer to syncope that results from reflex mechanisms associated with inappropriate vasodilation and/or bradycardia. Investigators believe that sudden excessive amount of venous pooling during upright posture results in an abrupt decrease in venous return to the heart. With acute hypovolemia, vigorous contractions of an empty ventricle can excessively stimulate ventricular mechanoreceptors that would normally respond only to mechanical stretch, leading to "paradoxic" withdrawal in sympathetic tone. This mechanism, thought to mimic the conditions seen in hypertension, leads to paradoxical vasodilatation, bradycardia, hypotension and resultant syncope [2].

One of the most suitable modalities for the detection of impending syncope's could be blood pressure (BP) monitoring [3]. However, current methods for non-invasive continuous BP monitoring carry several disadvantages, especially in uncontrolled environments such as home care scenarios. Other authors focused on the evaluation of the Pulse Arrival Time as an appropriate surrogate for SBP changes in the prediction of impending syncope [4-6].

In the current paper, we propose the evaluation of several parameters for the characterization of the syncope reflex mechanisms and blood pressure changes that lead to cerebral hypoxia. These parameters were extracted from the analysis electrocardiogram (ECG), impedance cardiogram (ICG) and photoplethysmogram (PPG) bio-signals in order to characterize the chronotropic, inotropic and vascular tone changes. Additionally, parameters related to blood pressure changes were also evaluated. From the analysis of Heart Rate (HR), Pre-ejection Period (PEP) and Left ventricular Ejection Time (LVET) we were able to identify the principal response mechanisms resulting Blood Pressure decrease during impending syncope. Additionally, Pulse Arrival Time (PAT), Pulse Transit Time (PTT), Stiffness index and reflection index were found to be more closely associated with Blood Pressure decrease. Finally, Area Difference Ratio (ADR) and diastolic decay time (RC) have been associated with changes in the vascular tone.

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TABLE I
PATIENT CHARACTERISTICS

	Tilt positive (#21)	Tilt negative (#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

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

II. METHODS

A. Study design and HUTT protocol

In the current study (NCT01262508), 55 patients were enrolled for diagnostic head-upright tilt test (HUTT) because of unexplained faints. All patients gave written informed consent to participate.

During HUTT, the patients were positioned in a resting supine position for at least 15 mins, after which they were tilted upright to 70º for passive standing exercise. During this phase, if syncope occurred, patients were immediately tilted back to the supine position and monitored for at least more 15 mins. Otherwise, if syncope did not occur in the first 20 mins after tilt, 400 µg of glycerol trinitrate (GTN) were administered sublingually to the patients, which were maintained in the upright position for a maximum additional 15 mins. Patients posture and symptoms (e.g. dizziness, sweat, tremor, etc.) were electronically registered by an investigator during the whole test.

The test was considered positive (po) if patients experienced syncope in the presence of bradycardia, hypotension, or both, as defined by the European Society of Cardiology [1]. Otherwise, the test was considered negative (ne).

The collected data was analyzed to verify if it fulfilled the objectives of the present work, leading to the exclusion of 12 patients. The exclusion criteria refer to syncope not related to BP regulation failures, strong arrhythmias and data quality issues in BP and PPG. The biometric characteristics of the 43 patients involved in the present study are summarized in Table I.

B. Experimental setup

During the HUTT protocol, a simultaneous collection of various bio-signals and hemodynamic parameters was performed using two measurement systems. Using a "Taskforce Monitor" [7] it was possible to perform the simultaneous acquisition of two ECG leads (@ 500 Hz), an Impedance Cardiography (ICG) signal (@50 Hz) as well as continuous non-invasive blood pressure BP (@50Hz). Additionally, this system also provides several hemodynamic parameters, such as systolic blood pressure (SBP), total peripheral resistance index (TPRI) and stroke volume (SV). Using a Philips MP50 [8] extended with a data logger functionality, we were able to acquire an additional ECG-II lead (@ 500 Hz) and a Photoplethysmographic signal (@126 Hz) with a standard SpO2 – sensor attached to the index-finger.

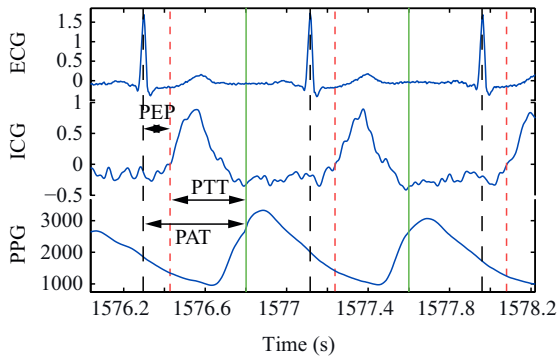

Figure 1: Representation of the HR, PEP, LVET, PAT and PTT parameters extracted from the joint analysis of ECG, ICG and PPG waveforms.

The data from both systems was synchronized in time using the R-peaks detected in the ECG signals from Taskforce and MP50 systems, with an accuracy bellow 1 ms.

C. Parameter Extraction

Nine different parameters were extracted from the analysis of ECG, ICG and PPG waveforms.

The primary reflex mechanism in impending syncope is the increase in HR resulting from the increase of the sympathetic tone. The HR was extracted from the analysis of the ECG signal, i.e., the time span between consecutive R-peaks.

The secondary reflex mechanism is the increase in the inotropic state of the heart (myocardial contractility), which can be characterized by the Pre-Ejection Period (PEP) and Left Ventricular Ejection Time (LVET) [9]. The PEP was calculated as the time span between the ECG R-peak and the onset of the left ventricular ejection, i.e., the ICG B-point. The ICG B-point was defined using a zero-crossing algorithm proposed by Ono et al. [10], while LVET parameter was calculated using an algorithm proposed by Couceiro et al. [11].

To characterize blood pressures changes, Pulse Arrival Time ($PAT_{80\%}$) and Pulse Transit Time ($PTT_{80\%}$) were extracted from the joint analysis of ECG, ICG and PPG waveforms. $PAT_{80\%}$ was defined as the time span between the ECG R-peak and 80% of the PPG pulse amplitude after its onset, while $PTT_{80\%}$ parameter was defined as the time span between the onset of the left ventricular ejection (ICG

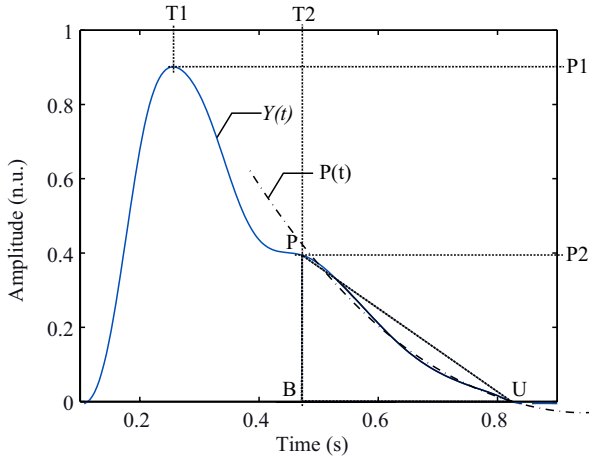

Figure 2: Representation of the PPG beat morphology and extracted parameters: Stiffness and Reflection indexes, ADR and RC decay time.

TABLE II

HR, REFLECTION AND STIFFENESS INDEX, PEP, LVET, PAT, PTT, ADR AND RC DURING HUTT; *INDICATE A SIGNIFICANT DIFFERENCE (P<0.05) BETWEEN TWO TIME CONSECUTIVE INSTANTS; † INDICATE A SIGNIFICANT DIFFERENCE (P<0.05) BETWEEN TILT POSITIVE AND NEGATIVE DATA POINTS AT THE SAME TIME INSTANT

Time	HR % (avg ± std) beats/min.	STIFF. INDEX % (avg ± std) ms	REF. INDEX % (avg ± std) %	PEP % (avg ± std) ms	LVET % (avg ± std) ms	PAT % (avg ± std) ms	PTT % (avg ± std) ms	ADR % (avg ± std) %	RC % (avg ± std) s.	SBP % (avg ± std) mmHg
0% (po)	0% (76,2±14,4)	0% (162,5±40,6)	0% (44,3±11,3)	0% (108,7±35,8)	0% (242,1±29,1)	0% (467,3±58,6)	0% (358,5±35,7)	0% (5,8±7,5)	0% (0,6±0,5)	0% (144,2±15)
5% (po)	0,8% (76,8±12,1)	2,2% (166,2±40,4)	4% (46±12,4)	-4,2% (104,1±20)	-0,8% (240,1±29,6)	-0,9% (462,8±46,3)	0% (358,7±35,5)	10,1% (6,4±9,8)	5,3% (0,7±0,5)	-0,7% (143,1±15,8)
20% (po)	2,6% (78,1±14,7)	4,7% (170,1±46,9)	-0,6% (44±10)	3,5% (112,6±40,2)	-3,6% † (233,3±35,1)*	0,1% (467,8±69)	-0,9% (355,2±40)	7,8% (6,3±8,8)	-1,7% (0,6±0,4)	-9% (131,3±14,9)*
50% (po)	12,9% † (86±18,8)*	13,3% † (184,1±44,6)	-17% (36,8±9,8)*	2,4% (111,4±31,5)	-10,2% † (217,5±36,9)*	-1,2% (461,5±49,2)	-2,3% (350,2±38,9)	-70,3% (1,7±10,1)*	17,3% (0,7±0,6)	-15,9% (121,2±21)*
80% (po)	6,9% (81,4±21,3)	36% † (221±39,5)*	-27,5% (32,1±11,5)*	14,9% † (124,9±43,4)*	-14,4% (207,3±47,8)	0% † (467,2±52,5)	-4,5% (342,3±77,1)	-135% (-2±9,4)	49,1% † (0,9±0,6)	-30,7% † (100±23,8)*
100% (po)	-12,5% (66,6±14,7)*	49,7% † (243,3±69,6)	-34% † (29,2±12,3)	3,9% (113±35,8)	12,3% † (271,9±40,9)*	12,6% † (526±82,5)*	9,8% † (393,8±44,3)*	-128,5% (-1,7±8,6)	37,8% † (0,9±0,8)	-42,3% † (83,2±20,8)*
0% (ne)	0% (80,2±13,6)	0% (167,5±33,9)	0% (43,8±14,8)	0% (119,5±31)	0% (218,3±34,9)	0% (446,9±54,4)	0% (327,4±61,1)	0% (5,2±9,1)	0% (0,6±0,4)	0% (129,6±19,1)
5% (ne)	-0,3% (80±14,4)	-0,6% (166,5±33,3)	-3% (42,4±12,7)	-0,9% (118,4±34,2)	2,8% (224,5±35,5)	0,1% (447,2±55,3)	0% (327,3±68,2)	25,5% (6,6±9,8)	-7,6% (0,6±0,4)	-1,2% (128±17,9)
20% (ne)	-0,2% (80±14,4)	1,2% (169,5±34)	-7,6% (40,4±10,9)	2,6% (122,6±40,2)	1,7% (222,1±31,8)	1,2% (452,4±55,1)	0,3% (328,3±72,8)	35,1% (7,1±10,9)	-7,2% (0,6±0,5)	-4,8% (123,3±18,7)*
50% (ne)	-0,1% (80,1±14,4)	3,1% (172,7±36)	-10% (39,4±11,8)	1,1% (120,8±41,5)	0,4% (219,2±45,9)	0% (446,7±51,4)	0,8% (330,2±68,4)	12,2% (5,9±9,6)	1,7% (0,6±0,5)	-10,3% (116,2±18,8)*
80% (ne)	-0,2% (80±14,2)	0,6% (168,5±32,5)	-12% (38,5±9,4)	-0,6% (118,7±33,6)	-3,6% (210,6±30,5)	-0,3% (445,7±51,3)	-0,1% (327,1±52,1)	47,5% (7,7±9,5)	-12,5% (0,5±0,4)	-13,8% (111,7±15,1)
100% (ne)	-1,5% (79±11,4)	1,6% (170,1±37,9)	-7,7% (40,4±9,2)	-2,2% (116,8±25,1)	5% (229,3±37)*	-0,7% (443,7±54)	-0,2% (326,8±55,5)	37,9% (7,2±7,8)	-23,2% (0,5±0,3)	-13,5% (112,1±18,4)

B-point) and 80% of the PPG pulse amplitude, that is, the difference between PAT and PEP (i.e., *PTT = PAT - PEP*). These parameters are illustrated in Figure 1.

Additionally, two other highly pressure dependent parameters were also extracted from the analysis of PPG beats morphology, which are the stiffness and reflection indexes [12]. The stiffness index was defined as the time span between the forward (T1) and reflected (T2) waves, while the reflection index was calculated as the ratio between the amplitude of the reflected (P2) and forward (P1) waves (see Figure 2).

To assess vascular tone changes (vasodilatation/ vasoconstriction), the Area Difference Ratio (ADR) and exponential diatolic decay time constant (RC) were calculated from the morphological analysis of the PPG beats.

The ADR parameter in a single beat [13], as illustrated in Figure 2, was calculated as the difference between the area of the triangle ΔPUB (S_t) and the area under the curve of the pulse *Y(t)*, but above the horizontal line BU (S_p) divided by S_t:

$$ADR = \frac{S_t - S_p}{S_t} \quad (1)$$

The diastolic portion of the PPG beat, defined by *Y(t)* from B to U (Figure 2) was fitted by a exponential function $P(t) = ae^{bt} + c$ and the RC decay time was defined using equation (2).

$$RC = -\frac{1}{b} \quad (2)$$

The extracted parameters were post-processed to remove artifacts, by limitation to the physiological ranges and applying a 10 s window average filter.

D. Measurements protocol

To evaluate the extracted parameters during HUTT, various time instants were defined from the beginning of the Systolic Blood Pressure break down (0%) to the time when syncope occurs and/or the time when the patient is tilted back to the supine position (100%). These time instants, illustrated in Figure 3, were defined as 5%, 20%, 50% and 80% of the aforementioned total time span corresponding to the SBP decrease. 30-sec averages were calculated around each time instant for each parameter.

The rationale behind this measurement protocol is to define enough time instants that enable an extensive description of the mechanisms leading to the syncope during the SBP break down.

III. RESULTS AND DISCUSSION

Table II presents the average and standard deviation (avg±std) for HR, Reflection index, Stiffness index, PEP, LVET, PAT, PTT, ADR and RC parameters, in the time instants defined by the measurement protocol (Figure 3), for tilt positive (po) / negative (ne) volunteers separately.

Additionally, the rate of change of the aforementioned parameters (*PT*) was evaluated as the ratio between the mean

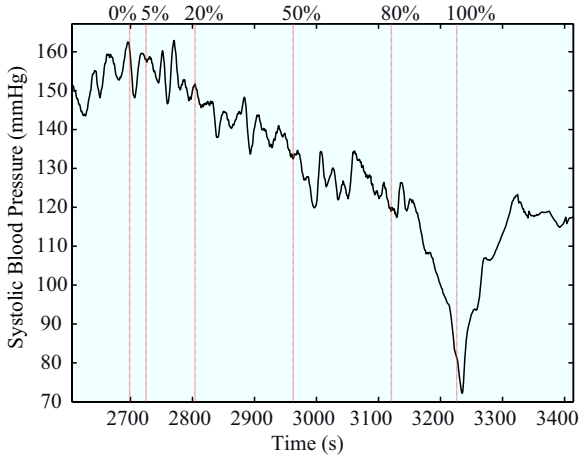

Figure 3: Definition of the time instants (5%, 20%, 50% and 80%) used for parameter extraction from the beginning of the blood pressure decrease (0%) to the occurrence of syncope and/or the time when the patient is tilted back to the supine position (100%).

value in each time instant and the reference time instant (0%), using the following equation:

$$PT(t,i) = \frac{Par(t,i) - Par(0,i)}{Par(0,i)} \times 100 \qquad (3)$$

where *Par(i,t)* refers to the measured parameter *i* at the time instant *t*.

The difference between parameter data points measured at consecutive time instants was tested for Gaussianity using the Kolmogorov–Smirnov test. Accordingly, statistical analysis was performed using the paired Student test and the two-sided Wilcoxon signed rank test. The difference between the rate of change of tilt positive and tilt negative patients at similar time instants was tested using unpaired Student test and Mann-Whitney U-test.

From Table II, in tilt positive patients, it is observed that:

1) From the 0% time instant to the 50% time instant there is a significant increase in HR of approximately 12.9%, corresponding to the primary compensation mechanism to SBP decrease. Additionally, PEP parameter remains approximately unchanged ([-4.2,3.5]%).
2) At the 80% time instant, there is a significant increase of PEP (14.9%). Additionally, there steady decrease of LVET parameter until 80% time instant (-14.4%). This is the secondary response mechanism, the increase of the left ventricular contractility resultant from the lack of blood return to the heart.
3) There is a significant decrease of HR (-12.5%), a decrease in PEP (-3.8%) and a significant increase in LVET (12.3%), until the 100% time instant. These trends reflect the third mechanism, which is a response to the excessive activation of the ventricular mechanoreceptors.

From the analysis of the PAT and PTT, one observes that these parameters remain almost unchanged until the time instant when syncope occurs, where there is a significant increase in these parameters (PAT: 12.6% and PTT: 9.8%). The stiffness and reflection indexes trends present an increase/decrease from 0% to 100% time instants (49.7%/-34%, respectively). In ADR parameter it is observed a small increase from 0 to 20% time instants (10.1%), followed by a significant decrease until the 50% time instant (-70.3%). Contrarily, it was observed a decrease in the RC parameter from 0 to 20% time instants, followed by an increase until the 80% time instant (49%).

In the tilt negative volunteers, there aren't significant

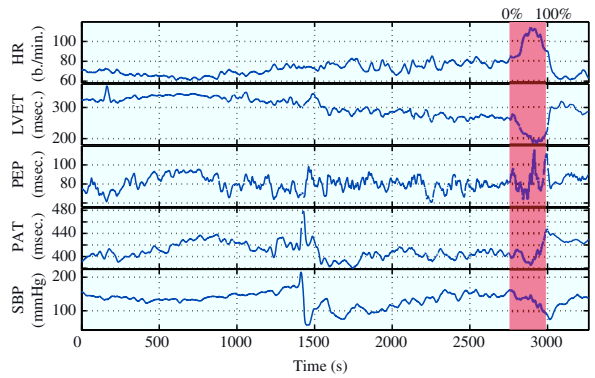

Figure 5: HUTT of a 66-year-old patient with manifested syncope including GTN provocation. Representation of the HR, LVET, PEP, PAT and SBP waveforms during the HUTT protocol.

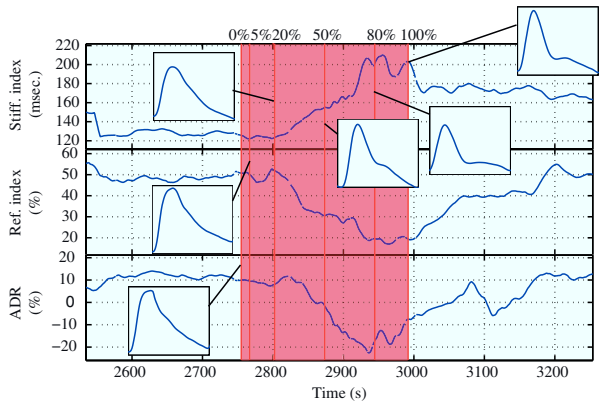

Figure 4: HUTT of a 66-year-old patient with manifested syncope including GTN provocation. Representation of Stiffness and reflection indexes and ADR parameter and correspondent PPG beat morphological changes during impending syncope SBP drop.

changes in the parameter trends. The rate of change of the HR, Stiffness and Reflection indexes, PEP, LVET, PAT and PTT parameters is clearly lower during the 100% time window, when compared to the tilt positive volunteers. Additionally, there is an inversion in the ADR and RC parameters trends when compared to the tilt positive volunteers (although not significant). In tilt positive patients ADR decreases during SBP break down, while in tilt negative volunteers there is an increase in ADR. Moreover, one can observe that the standard deviation of the ADR and RC parameters is clearly high.

When comparing the tilt positive and tilt negative parameters rate of change at similar time instants, it is possible to observe a significant difference in the HR at the 50% time instant, in Reflection index and PTT at the 100% time instant and in PEP at 80% time instant. Additionally, it was also observed a significant difference in LVET parameter from 20% to 50% and 100% time instants, in Stiffness index from 50% to 100% time instants, and in PAT and RC parameters from 80% to 100%.

From the analysis of the HR, PEP and LVET trends in tilt positive volunteers, one can observe that HR increase (0-50% time instants) is the first mechanism that acts as a response to the SBP decrease. This mechanism is the primary response to regulate blood pressure, i.e., to increase the SBP to "regular" values. This is followed (80% time instant) by a HR decrease and a simultaneous decrease/increase in LVET/PEP parameters. This is the second compensation mechanism to the SBP decrease, which reflects the increase in the left ventricle contractility and consequent attempt of the heart muscle to pump blood to the circulation (attempt to increase Cardiac Output) in response to SBP break down. At last, from 80% to 100% time instants, there is a clear failure of the first and second compensation mechanisms, showed by the significant HR decrease, and simultaneous LVET increase and PEP decrease. The sudden increase in sympathetic output as a consequence of vigorous ventricular contractions result in a peripheral sympathetic inhibition and vasodilatation. The reduction in the sympathetic activity is observed in the failure of the primary chronotropic and inotropic responses [2].

Contrarily to the abovementioned parameters, the PAT and PTT parameters are more closely associated to the SBP changes. One can observe that these parameters remain almost unchanged until the abrupt SBP break down.

Additionally, the stiffness/reflection indexes start to increase/decrease from the beginning of SBP decrease, in tilt positive volunteers, while in tilt negative patients, these parameters remain almost unchanged during the whole analysis window.

From the analysis of the ADR and RC parameters, one observes that there is a clear and reversed trend between tilt positive and negative volunteers. The decrease of ADR in tilt positive volunteers suggests the inability of these patients to decrease the pooling of venous blood in the lower extremities and abdomen and to increase peripheral arterial resistance, which results in the SBP break down. Contrarily, in tilt negative volunteers, there is an inversion in the ADR trend, which suggests the ability to increase the vasculature peripheral resistance and regulation of SBP.

Figure 5 shows the HR, PEP, LVET, PAT and SBP of a 66-year-old patient during HUTT including GTN, where the patient fainted after approximately 50 min. Heart rate at rest in supine position was 70 bpm, LVET 324 ms, PEP 75 ms, PAT 391 ms and SBP 154 mmHg. At the beginning of the SBP break down (160 mmHg), the Heart rate was 82 bpm, LVET 264 ms, PEP 89 ms and PAT 404 ms. At the 50% time instant Heart Rate increased to 107 bpm, followed by the decrease in contractility, i.e., decrease of LVET to 185 ms and increase of PEP to 115ms. This reflex mechanisms lead to bradycardia, and simultaneous decrease in the left ventricle contractility, and resultant syncope. During this process until syncope occurs, it is possible to observe a significant increase of PAT (to 447 ms), reflecting changes in SBP.

Figure 4 shows the Stiffness and Reflection indexes, and ADR parameter for the aforementioned patient. It is possible to observe a significant increase in the Stiffness index (from 0% to 80%: 125 ms to 209 ms) and simultaneous decrease of the reflection index (51% to 19%) and ADR parameter (9.8% to -12%). The morphological changes in the PPG beats during the blood pressure break down are also presented.

IV. Conclusion and Future Work

In the present study we proposed the characterization of syncope reflex mechanisms and blood pressure changes from the analysis of several non-invasive modalities (ECG, ICG and PPG). Several parameters were extracted in order to characterize the chronotropic, inotropic and vascular tone changes. Firstly, there is a significant increase in the Heart Rate as a response to excessive amount of venous pooling. The lack in blood return to the heart, forces it to pump harder in order to eject more blood to the circulation. This phenomenon was captured in the increase in PEP and simultaneous decrease in LVET, assessed from ECG and ICG, and PPG, respectively. The excessive stimulation of ventricular mechanoreceptors mimics the conditions seen in hypertension leading to a paradoxical vasodilation observed in the significant change of the ADR parameter. Consequently, it was observed bradycardia (from the ECG HR), hypotension and resultant syncope. The abrupt decrease of SBP could be observed in the significant increase of PAT, PTT and Stiffness index and decrease in Reflection index instants before the occurrence of syncope, suggesting the suitability of these parameters as blood pressure surrogates during impending syncope.

Future work will focus on the development of a novel methodology capable of identifying the reflex mechanisms present during impending syncope. By correctly detecting these mechanisms along with blood pressure changes using the proposed surrogates, it is believed that a novel methodology capable of predicting impending syncope can be proposed.

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