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Pulse Arrival Time as Surrogate for Systolic Blood Pressure Changes during Impending Neurally Mediated Syncope

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Abstract—**Blood pressure regulation failures cause neurally mediated syncope often resulting in a fall. A warning device might help to make patients aware of an impending critical event or even trigger the patient to perform countermeasures such as lying down or isometric exercises. We previously demonstrated that the Pulse Arrival Time (PAT) methodology is a potential approach to enable early detection of impending faints. The aim of the present study was to evaluate whether PAT can be used as an easy to measure beat-to-beat surrogate for systolic blood pressure (SBP) changes during a passive standing exercise (head-up tilt table testing (HUTT)). A significant PAT increase of more than 10 % was accompanied with a critical SBP decrease in syncope patients. Although PAT is in general not considered as a good measure of absolute blood pressure we found strong correlations (R>0.89, P<0.01) of SBP and PAT after PAT began to increase. Therefore, our data suggest that the pulse arrival time is useful to monitor blood pressure changes in patients with neurally mediated syncope. This might open up new avenues to prevent falls in these patients.**

I. Introduction

Neurally mediated Syncope (NMS) is a transient, self-limited loss of consciousness, usually leading to falling. It is a common disorder with a community lifetime cumulative incidence of about 40% [1]. It can have serious consequences, especially in elderly and is associated with injuries such as fractures, increased rates of hospitalization and loss of independence. Underlying root causes of faints vary a lot and might be due to structural heart diseases, dehydration, anxiety, psychological or physical stress or medication errors.

Although the treatment of NMS depends on the specific patho-physiology, it mainly includes education avoiding trigger-events, recognition of early symptoms as well as training of maneuvers to abort an episode e.g. by isometric counter pressure exercises or going into supine posture.

Warning devices to detect impending syncope due to regulation failures are not available yet, but might find applications to improve syncope training or as personal safe guard [4,5].

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Blood pressure (BP) could be a parameter to detect impending syncopes as demonstrated in a first feasibility study based on continuous blood pressure monitoring using the vascular unloading technique [6]. However, non-invasive continuous BP measurements offered by the volume clamp method or by tonometry might work in supervised settings, but commercial wearable devices are complex, heavy, prone to aretfacts and require trained personal to operate.

A promising surrogate to monitor BP changes is based on the pulse arrival time (PAT) methodology [7,8]. PAT is derived from an easy to acquire electrocardiogram (ECG) and photo-plethysmogram. PAT is actually the sum of the pre-ejection period (PEP) and pulse transit time (PTT). PTT has been accepted as a marker of BP changes due its well-defined relation to BP [7] and is based on pulse propagation in elastic arteries. However, PEP - the period of iso-volumetric contraction - can vary independent of BP as discussed e.g. in [9]. Therefore, some shortcomings of this technique have been shown for absolute BP tracking [9,10], but it might provide sufficient performance for our intended use case. We previously demonstrated the basic feasibility of using relative PAT changes for early detection of impending faints during a state-of-the-art diagnostic passive standing exercise (head-up tilt table testing [HUTT]) [3]. Here, a patient is asked to stand for a minimum of 20 min passively to trigger syncope during comprehensive hemodynamic monitoring. The aim of the present study was to evaluate whether PAT can be used as a surrogate for systolic blood pressure (SBP) changes during an impending syncope.

II. Experimental Setup and Clinical Protocol

A. Clinical Study Design

51 Patients scheduled for diagnostic HUTT because of a history of unexplained faints were enrolled in this study (NCT01262508). All patients gave written informed consent to participate.

After a resting period of at least 15 min in supine position, patients were tilted upright to 70° for a passive standing exercise. If syncope occurred during this phase, patients were immediately tilted back to the horizontal position and monitored for another 15 min. If syncope did not develop during the initial 20 minutes after tilt, 400 µg of glycerol trinitrate (GTN) were administered sublingually while the upright position was maintained for maximal additional 15 min. During HUTT the investigator annotated electronically

the patient's posture and symptoms such as dizziness, sweat, tremor, etc.

The test was considered positive (po) if the patients experienced syncope in the presence of bradycardia, hypotension, or both as it is defined by the European Society of Cardiology [1]. Data of 39 patients could be used for the objectives of this work. Their characteristics are summarized in Table I (BMI: Body Mass Index).

TABLE I
PATIENT CHARACTERISTICS

	Tilt positive (#19)	Tilt negative (#20)
Age [y]	54±20	57±22
Weight [kg]	85±15	72±14
BMI [kg/m2]	27.0±4.6	25±5
Male/female	11/8	7/13
GTN yes/no	18/1	14/6

Exclusion criteria of data not being considered in this work refer to syncope not related to BP regulation failures, strong arrhythmias and data quality issues in BP and PPG.

B. Experimental Setup and Data Analysis

During HUTT hemodynamic measures were monitored and logged with the "Taskforce Monitor" [11]. This device acquires two ECG leads (@1000 Hz), an Impedance Cardiography (ICG) signal (@50 Hz) as well as continuous non-invasive blood pressure BP (@50Hz). Based on these signals hemodynamic parameters using validated algorithms are provided such as systolic blood pressure (SBP), total peripheral resistance index (TPRI) and stroke volume (SV). A Philips MP50 [12] extended with a data logger functionality was used to acquire an additional ECG-II lead (@500 Hz) and a Plethwave signal (@126 Hz) with a standard SpO2 – sensor attached to the index-finger.

Data from both systems were synchronized in time via detected R-peaks in one of each ECG signals from the Taskforce and MP50 with an accuracy of less than 1 ms.

C. Data Analysis

Two different Pulse Arrival Time (PAT) measures were extracted from the ECG and Plethwave acquired with the Philips MP50. Two PAT are extracted as time intervals from the ECG-R-peak to 1.) the onset of each single PPG-pulse (PATfoot) and 2.) a robust measure close to the maximum of each PPG pulse (PATtop). Heart rate derived from ECG and both PAT were post-processed to remove artifacts via limitation to physiological ranges and consecutive time averaging using a 10 s window.

To characterize a HUTT, standardized time points have been defined from which 30 s averages have been calculated. These time points are: 1) "Baseline" at rest/lying: 1 minute before tilt, 2) "Early tilt": 1 minute after tilt and 3) "Late tilt": 1 minute before tilted back. Signal processing and data analysis was realized in MATLAB.

III. RESULTS

A. Blood pressure, pulse arrival time and heart rate during HUTT

Table II presents the average for HR, PATfoot, PATtop (mean±std) and SBP for these instances for tilt positive / negative separately. For tilt positive significant PAT increases are observed for Late tilt compared to Early tilt, which are associated with significant different average SBP and a critical SBP level of 88 mmHg for late tilt. Although for tilt negative a significant SBP difference of early vs. late tilt has been observed (no critical level reached for Late tilt), it is observed that PATfoot and PATtop are not significantly different to Early tilt.

TABLE II
HR, PATFOOT, PATTOP AND SBP DURING HUTT; * INDICATE A SIGNIFICANT DIFFERENCE ($P<0.05$) OF CONSECUTIVE TIME POINTS

Measure	HR [bpm]	PATfoot [ms]	PATtop [ms]	SBP [mmHg]
Baseline (po)	70±8	262±21	304±21	125±24
Early tilt (po)	74±10	268±23	309±25	143±23*
Late tilt (po)	75±22	299±35*	343±40*	88±21*
Baseline(ne)	69±11	269±26	323±38	126±20
Early tilt (ne)	73±12*	268±24	315±32	143±23*
Late tilt(ne)	82±13*	277±32	310±34	117±13*

B. Total peripheral resistance index, perfusion, and thoracal impedance and total fluid content during HUTT

Table III shows relevant additional measures such as total peripheral resistance index (TPRI), Perfusion derived from PPG [12], thorax impedance Z_0 and total fluid content (TFC) as (mean±std).

TABLE III
TPRI, PERFUSION, Z_0 AND TFC DURING HUTT

Measure	TPRI [dyne*s+m^2/cm^5]	Perfusion [a.u.]	Z_0 [Ohm]	TFC [1/kOhm]
Baseline(po)	2889±764	2.9±2.5	33.5±5.1	30.5±4.9
Early tilt(po)	3675±968	1.9±1.7	35.2±5.5	29.1±4.9
Late tilt (po)	2218±855	1.6±1.4	36.3±6.4	28.5±5.4
Baseline(ne)	2548±821	1.3±1.8	33.5±6.1	30.8±5.8
Early tilt (ne)	3186±1022	1.0±0.7	35.0±6.1	29.3±5.2
Late tilt(ne)	2499±676	1.7±1.3	36.8±6.1	27.9±4.8

A typical increase of Z_0 as well as an expected decrease in TFC is observed during HUTT when the patient posture changes from supine to standing. This Z_0 and TFC change of Baseline vs. Early Tilt relates to blood pooling to lower extremities because of a posture change. However, there are no significant differences between both patients. The perfusion index is during the resting phase a factor of 2 higher for patients who suffer from syncope compared to tilt negative patients. But both groups show the same Perfusion Index shortly before tilted back (Late tilt). Respiration rate was on average (17±4) bpm for both patient groups.

C. Systolic BP and PAT: HUTT Example Measurements

Fig 1 shows heart rate, pulse arrival time (PATfoot) and SBP of a 72 year old patient during HUTT including GTN.

This patient fainted after 44 min. Heart rate at rest in supine was 55 bpm, SBP 150 mmHg and PATfoot 240 ms. Immediately after tilt at 19 min there is an obvious short term regulation process visible in PATfoot, which finally resulted in an PAT increase of about 20 ms.

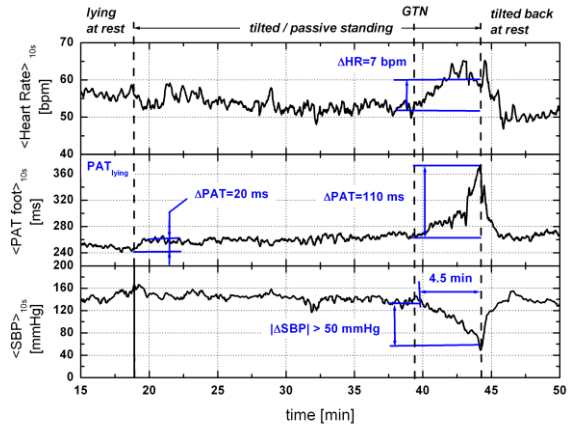

Fig. 1. HUTT of a 72 year old patient with manifested syncope (upper diagram: Heart rate, middle: PATfoot, low: SBP) including GTN provocation. The PATfoot increases synchronously with SBP during impending syncope.

During tilt at about 40 min, the SBP began to decrease, which finally manifested in a syncope after 4.5 min with |ΔSBP| > 50 mmHg. The patient was immediately tilted back to supine position. Parallel to the SBP drop, PATfoot increased in total by 110 ms compared to the average PATfoot of 260 ms 1 min after tilt. A similar behavior was observed for PATtop but is not presented here.

Figure 2 shows a second example of a HUTT of a 69 year old male. GTN was administrated during the procedure as well.

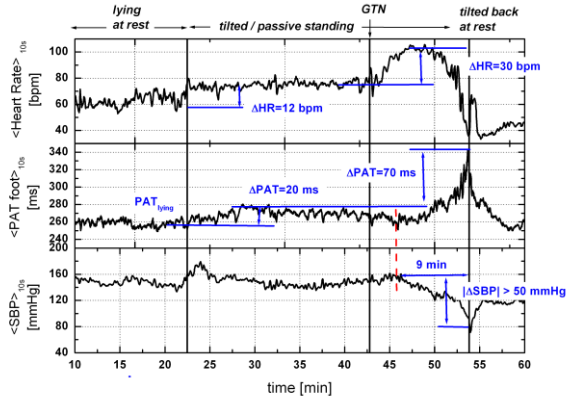

Fig. 2. HUTT of a 69 year old patient with GTN administration at 42.5 min / tilt positive (upper diagram: Heart rate, middle: PATfoot, low: SBP); GTU initiates a strong HR increase associated with a SBP decrease at 45.1 min.; there is a delay of about 3 min, before PATfoot starts to increase as well.

This patient had a SBP at rest in supine of 140-150 mmHg, a PATfoot of 260 ms and a HR of 62 bpm. After tilt (22.5 min), HR increased by 12 bpm as well as PATfoot by 20 ms within a period of 5 min. In contrast SBP showed a transition with a maximum of 180 mmHg, but reached after 2.5 min almost the same SBP as at the beginning of tilt. Obviously PATfoot didn't respond to this initial HR and SBP increase. After 20 min, GTN was administrated and triggered a strong HR increase (30 bpm maximum). At 45 min SBP began to decrease (red line) from 160 mmHg to less than 60 mmHg. However, PATfoot did not follow with a PAT increase immediately to this SBP decrease. There is an obvious delay of SBP and PATfoot response after GTN of about 2.5 min. Finally, there was a PATfoot increase of 70 ms before tilted back.

D. Relationship between SBP and PAT (ΔSBP < - 40 mmHg) during impending syncope

For patients with tilt positive and available continuous SBP reading the relation of PATfoot as well as PATtop was analyzed. A linear model SBP=A*PAT+B was applied on data extracted from the beginning of the PAT increase until a SBP of 80 mmHg was reached. 80 mmHg was chosen, since blood pressure readings below this value might be unreliable based on the vascular clamp method. Figure 2 shows data for SBP-PATfoot and SBP-PATtop for the measurement presented in figure 1.

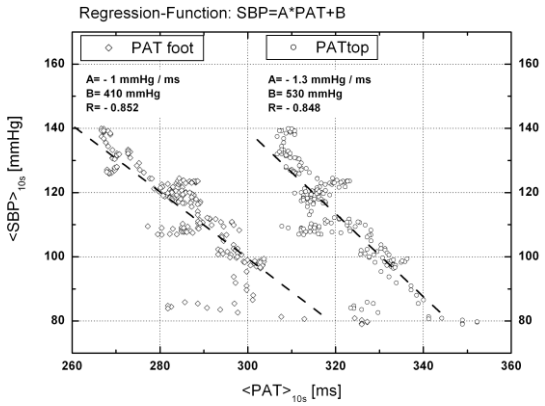

Fig. 2. SBP vs. PAT foot / PATtop extracted from the measurement shown in Fig 1 till 80 mmHg have been reached. A linear regression have been applied with a correlation of R= - 0.85 for both PAT. The sensitivity factor A is 1 mmHg/ms (PAT foot) and -1.3 mmHg/ms in this example.

There is a strong linear relation of SBP and both PATs with a person-correlation coefficient of about -0.85. PATfoot shows a slope of -1 mmHg/ms whereas PATfoot has a sensitivity factor A of -1.3 mmHg/ms.

The average results for A, B and the correlation Pearson-coefficient for PATfoot and for all patients are presented in Table IV.

TABLE IV
LINEAR REGRESSION BETWEEN
SYSTOLIC BLOOD PRESSURE AND PAT FOOT

Measure	Average	Span
A [mmHg/ms]	-1.01±0.46	[-0.3 … -1.9]
B [mmHg]	392±125	[202 … 660]
Regression R	-0.89±0.11	[-0.99 … -0.6]

The sensitivity is about 1 mmHg/ms with a large inter-patient difference ranging from -1.9 to -0.3 mmHg/ms. The average correlation coefficient was -0.89 because of a strong linear and consistent relation of SBP and PATfoot. Similar results have been observed for PATtop with no significant

differences expect for the parameter B with (427±145) mmHg and a range of [202 … 760] mmHg.

IV. Discussion

The present data show: (1.) PAT and SBP has a complex relation during HUTT (see example measurements). (2.) PAT strongly correlates with SBP changes during an impending NMS.

A. PAT as hemodynamic surrogate for BP decrease

Upright tilts trigger blood pressure regulation mechanisms due to fluid shifts to the lower body herein documented as thoracic total fluid content decrease being associated with a typical HR increase. However, accompanied responses of PAT and SBP can vary a lot as we found in our study population. It is also observed that both PATfoot and PATtop respond to HR changes not necessarily associated with SBP changes. Therefore, no simple relation of SBP-PAT exists in general.

These observations might be –partially- explained by the pre-ejection period (PEP) as additive contributor to PAT, which can behave independent to blood pressure e.g. due to medication or posture effects. PEP effects due to posture changes are discussed e.g. by [8,9,10,14], which have been partially verified in this study as well. Our findings strengthen the observations that PAT is an unreliable BP surrogates for absolute BP inference.

B. SBP-PAT relation during impending syncope

Consistent increases of PATfoot and PATtop accompanied with critical SBP decreases could be found shortly before syncope manifests. There is on average a PAT increase by about 10 % for "Late tilt" compared to PAT at "Early tilt" not being observed for tilt negative patients. HR responses vary a lot during this process independently of PAT and SBP. Strong linear negative correlation coefficients between SBP-PAT were obtained as well. However, significant inter-patient differences of the sensitivity parameter A and the absolute term B derived from linear regression had to be recognized. The parameter A can differ between patients up to a factor 6.

These findings confirm the predictive value of our risk score defined in [4] to detect an impending faint as well as our results on using HR-PAT plots with 1) a high risk of syncope, when a relative PAT increase is detected and 2) a low risk, when PAT is constant or decreases both independent of HR [15].

This consistent PAT response suggests a well-defined response of PEP during impending faint. In our particular setting of a HUTT, it is reasonable to assume that the PEP increases during impending faint because contractility, stroke volume, and central venous volume decrease prior to syncope.

V. Conclusion and Next Steps

We could show that a pertinent relation of PAT measures with SBP in a well-defined HUTT setting can be observed shortly before syncope, when PAT starts constantly to increase. This might explain the previously recognized predictive power of PAT to detect critical events related to BP regulation failures based on this simple and easy measure. However, PAT has in general a complex relation to SBP and HR that are rather difficult to interpret unless detailed context information is available such in a HUTT protocol. Current research focuses on more robust feature extraction approaches, since PPG signals are prone to artifacts. In addition, a more in-depth understanding of the interplay of PAT and HR is needed. Another aspect we have been working is taking into account PPG morphology features towards a better characterization of the patient status.

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