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Vascular reactivity characterized by PPG-derived pulse wave velocity

Pablo Armañac-Julián [a,b,*], Spyridon Kontaxis [a,b], Jesús Lázaro [a,b], Andrius Rapalis [c], Marius Brazaitis [d], Vaidotas Marozas [c], Pablo Laguna [a,b], Raquel Bailón [a,b], Eduardo Gil [a,b]

[a] Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina, Instituto de Salud Carlos III, Madrid, Spain
[b] Biomedical Signal Interpretation and Computational Simulation (BSICoS) Group, Aragón Institute of Engineering Research (I3A), Zaragoza, Spain
[c] Biomedical Engineering Institute and Electronics Engineering department, Kaunas University of Technology, Kaunas, Lithuania
[d] Lithuanian Sports University, Institute of Sports Science and Innovation, Kaunas, Lithuania

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ABSTRACT

Vascular reactivity is the capacity of the blood vessels to adapt under physiological and environmental stimuli. Heat stress causes changes at vascular level affecting pulse wave velocity (PWV), which can be non-invasively obtained using pulse photoplethysmography (PPG). The study aim is to characterize non-invasive and reliable PPG-derived PWV surrogates that are able to assess vascular reactivity, using data from fifteen healthy male volunteers under heat stress conditions. Pulse arrival time (PAT) is a recognized PWV surrogate measure, but our study explores further by including pulse transit time difference (PTTD) and pulse wave decomposition analysis (PDA). Our results indicate a significant linear decrease in PAT and PDA under heat stress, with an approximate 15% reduction compared to the relax phase, closely correlating with heart rate (HR) alterations. This correlation is likely influenced by factors such as the pre-ejection period or stroke volume changes. In contrast, PTTD demonstrates a distinct pattern: it exhibits significant and rapid changes during the initial exposure to heat stress, with an approximate 30% reduction, yet shows minimal intra-stage variations (around 0 ms/min compared to 2.5 ms/min in PAT). This suggests that PTTD, in measuring acute sympathetic activation responses, effectively minimizes the impact of HR-related phenomena that significantly influence PAT and PDA measurements. Our study highlights PTTD as an underexplored yet promising measure for accurately assessing vasoconstriction and vascular reactivity.

1. Introduction

Pulse wave velocity (PWV) is a widely accepted biomarker of arterial stiffness and predictor of cardiovascular morbidity and mortality [1]. PWV is defined as the speed of propagation of a blood pressure (BP) wave, originated at each heartbeat, through the arterial tree [2]. Carotid-femoral PWV is considered as a marker of arterial stiffness and endothelial dysfunction [3], and chronic-high PWV is associated with increased risk of cardiovascular diseases such as hypertension, stroke, and coronary heart disease [4].

PWV has been traditionally measured using invasive or cumbersome systems such as catheterization [5,6], or tonometry [7,8]. Nowadays, PWV measurements rely on electrocardiography (ECG) and peripheral detection of the pulse pressure by means of photoplethysmography (PPG) [9]. PPG is a non-invasive optical technique for detecting blood volume changes in the tissues [10]. It has been widely used in wearable devices [11], for estimating pulse rate, blood oxygen saturation, and BP [10]. For all these reasons, PPG has gained attention as a cost-effective and convenient monitoring system.

The most common non-invasive surrogate of PWV is the pulse arrival time (PAT), which is the time interval between the R-wave of the ECG and the pulse occurrence of the PPG at a peripheral artery [12]. However, the utility of PAT as PWV marker is limited since it includes the pre-ejection period (PEP) [13], also known as isovolumetric contraction, which is the time delay between the electrical heart depolarization, R-wave, and the actual blood ejection from the heart. The variability and regulation of PEP under different physiological conditions is still under research [14,15], and additional equipment such as a phonocardiogram, impedance cardiography, ballistocardiogram, or non-contact sensors based on video/micro waves are necessary to measure it [16]. This limitation, along with the challenge of accurately assessing the arterial path length in surrogate PWV measurements due to the arterial pathway's individual variability and complexity, affects the accuracy of PAT-based PWV measurements [17], and has lead to the search for alternative PWV surrogates: one is the pulse transit time

* Corresponding author at: Biomedical Signal Interpretation and Computational Simulation (BSICoS) Group, Aragón Institute of Engineering Research (I3A), Zaragoza, Spain.
E-mail address: parmanac@unizar.es (P. Armañac-Julián).

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difference (PTTD) [18], which only requires two PPG sensors and is a non-invasive surrogate of PWV not influenced by PEP [19], without the need of phonocardiogram.

Hemodynamic parameters such as BP and changes in arterial tone can be assessed by quantifying the time and amplitude relationship between the forward and the reflected waves, making this method another suitable alternative to measure PWV [20,21]. In addition, methods that decompose the PPG wave morphology, namely pulse decomposition analysis (PDA), are capable of obtaining vascular biomarkers requiring only one PPG sensor on the fingertip [22]. However, the influence of PEP on the biomarkers obtained with PDA is still unknown.

Heat is a common stressor that induces a complex physiological response, including peripheral vasodilation and sweating, intended to maintain the temperature of the core body [23,24]. Numerous studies have explored the role of autonomic nervous system regulation during passive heat stress (without exercise), using protocols such as immersion hydrotherapy, wet sauna, and dry sauna. Their findings show a significant increase of heart rate (HR) and sympathetic activity during the sauna session when compared to baseline measurements taken at ambient temperature, along with a decrease in total heart rate variability (HRV) [25–29].

Elevated body temperature induces cutaneous vasodilation, redirecting blood volume from internal organs to peripheral regions, in order to enhance heat dissipation via sweating [30]. In addition, as response to the sympathetic nervous system (SNS) activation, there is a generalized vasoconstriction of the great vessels to further increase the blood volume pumped towards the skin, leading to an increase of PWV [30]. Therefore, since PWV has been shown to be a reliable indicator of vascular reactivity, the use of novel PWV surrogates may be a valuable tool for assessing the cardiovascular regulation of changes induced by heat stress, that cannot be measured using only ECG sensors and HRV indices.

In this study, we aim to characterize vascular reactivity in a heat stress test database. We hypothesize that PWV and vascular reactivity are altered during heat stress, and that these alterations can be detected using PPG-based methods. By non-invasively assessing these parameters, we could gain insight into the effects of heat stress on cardiovascular function and identify potential markers of cardiovascular status. We also aim to provide some reference values for PTTD when measured with different setups and during relax but also stress.

2. Materials and methods

We analyze PPG signals collected from healthy participants during a heat stress test, to calculate PWV and vascular reactivity surrogates using established methods: the PWV obtained using PAT-based measurements will be compared with those obtained using PTTD and PDA.

2.1. Heat stress data

The data comes from fifteen young (26 ± 2 years), healthy male volunteers [29]. The original study aimed to determine whether the exposure to total 36-hr sleep deprivation would suppress the autonomic response to whole-body uncompensable passive heat stress in traditional Finnish sauna (air temperature of 80–90 °C, relative humidity of 30%). The biosignals were synchronously recorded at a sampling rate, F_s, of 1000 Hz, including the lead-II of the ECG and three PPG signals at red wavelength, with transmission PPG from the middle finger of the right hand (PPG_F), reflection PPG from the forehead above the right eyebrow (PPG_H), and transmission PPG from the right earlobe (PPG_E). Thus, all PPG signals were recorded on the same side of the body. The fifteen sauna sessions included in this study comes from the control session, i.e., when the fifteen subjects had normal sleep (8 h of sleep), before sauna session. All the sauna sessions were collected between 7:00 and 11:00 p.m.

Each sauna session consists of a heat stress protocol with four repetitive exposures to uncompensable heat in the sauna [27]. Before and after 15-min stage of heat stress in the sauna at 80–90 °C, namely stress stages, participants were instructed to rest in a semi-Fowler's position in a room at ambient temperature (25 °C) for around 20-min, namely rest stages. The heat stress protocol lasted around 2 h and 20 min. The signals were acquired with the physiological recording system Nautilus1 (Biomedical Engineering Institute of Kaunas University of Technology, Lithuania). All the procedures were approved by the Human Research Ethics Committee and they were conducted according to the guidelines of the Declaration of Helsinki. The volunteers signed the informed consent, and self-reported good health, which was confirmed by their medical history and physical examinations. Further details have been previously published in [27,29].

2.2. ECG and PPG delineation

The R-wave is detected for each heartbeat by means of a wavelet-based method [31]. The time instants of each R-wave are denoted as n_R and expressed in samples. The time between two successive R-waves defines the RR interval. The inverse of the RR intervals is used to calculate the HR, in beats per minute (bpm). Ectopic beats and miss-detections are corrected as described in [32]. The exclusion of non-normal RR intervals, results in the normal-to-normal interval series, from which the HR is derived.

PPG signals are band-pass filtered between 0.3 and 15 Hz with a 4-th order Chebyshev type II filter, in order to eliminate the baseline contamination and high frequency noise [33]. Forward-backward zero-phase filtering is applied for preserving signal morphology. Following PPG filtering, motion artifacts are removed before PPG delineation using a energy-based method described in [34]. PPG pulses are detected by an algorithm that determines the maximum up-slope instant of each PPG pulse based on a low pass differentiator filter and a time-varying threshold [35]. The instant in time when the pulse is at basal level, n_B, is delineated for each PPG detected pulse (see Fig. 1(a)) and denoted as n_B^X where $X \in \{F, H, E\}$ for finger, forehead and earlobe, respectively. PPG pulses detected as ectopic beats are also eliminated from the n_B series, as described in [32].

2.3. HR estimation

Given a particular beat time occurrence, the instantaneous HR time series are estimated as:

$$d^u_{HR}(n) = \sum_i \frac{60 \cdot F_s}{n_{R_i} - n_{R_{i-1}}} \cdot \delta(n - n_{R_i}), \quad (1)$$

where "i" represents the index for each heartbeat, $\delta(\cdot)$ denotes the Kronecker delta function and the superscript "u" denotes that the signals are unevenly sampled, since heartbeats occur unevenly in time. Units are beats per minute (bpm).

2.4. Pulse wave velocity surrogates

In this section, we explain the three different methodologies we used to obtain PWV surrogates.

First, PAT measures the time a BP wave takes to travel from the heart to peripheral arteries (see Fig. 1(a)), generating the $d^u_{PAT}(n)$ series, which can be particularize at finger ($d^u_{PAT_F}(n)$ series), forehead ($d^u_{PAT_H}(n)$), and earlobe ($d^u_{PAT_E}(n)$) [36]:

$$d^u_{PAT}(n) = \frac{1000}{F_s} \sum_i [n_{B_i} - n_{R_i}] \cdot \delta(n - n_{R_i}), \quad (2)$$

expressed in [ms].

Second, PTTD is the time difference between arrival times from two PPG pulses occurrence at two different sites of the arterial tree (see Fig. 1(a)). With three PPG signals at finger, forehead and earlobe, we can thus calculate three PTTD signals denoted [19]: $d^u_{PTTD_{EF}}(n)$,

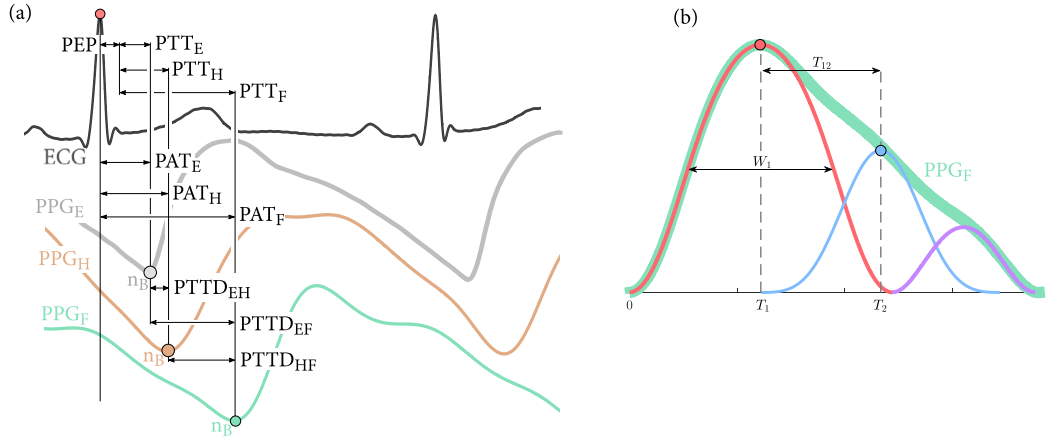

Fig. 1. Illustration of PAT, PTTD, and PDA definitions. (a) The ECG, earlobe (PPG_E), forehead (PPG_H), and finger (PPG_F) PPG signals with the corresponding definitions of PAT_E (earlobe), PAT_H (head), PAT_F (finger), and $PTTD_{EH}$ (earlobe-head), $PTTD_{EF}$ (earlobe-finger), $PTTD_{HF}$ (head-finger). Pulse Transit Time (PTT) refers to the time interval from the end of the Pre-Ejection Period (PEP) following a heartbeat to the arrival of the pulse wave at a peripheral site. The PEP interval shown is merely illustrative. (b) The characteristics of a PPG pulse waveform at the fingertip with PDA are shown. The PPG waveform is depicted in green, while the first, second, and third waves are indicated by red, blue, and magenta colors, respectively. The image emphasizes the morphological features based on the width (W_1) and the time interval (T_{12}) for the first and second inner waves.

$d^u_{PTTD_{HF}}(n)$ and $d^u_{PTTD_{EH}}(n)$, as follows:

$$\begin{aligned} d^u_{PTTD_{EF}}(n) &= \frac{1000}{F_s}\sum_i [n^F_{B_i} - n^E_{B_i}]\cdot\delta(n-n^F_{B_i}) \\ d^u_{PTTD_{HF}}(n) &= \frac{1000}{F_s}\sum_i [n^F_{B_i} - n^H_{B_i}]\cdot\delta(n-n^F_{B_i}) \\ d^u_{PTTD_{EH}}(n) &= \frac{1000}{F_s}\sum_i [n^H_{B_i} - n^E_{B_i}]\cdot\delta(n-n^H_{B_i}), \end{aligned} \tag{3}$$

also expressed in [ms].

Note that, in order to have mostly positive time interval series, the time reference for each PTTD series is defined at finger for $d^u_{PTTD_{EF}}(n)$ and $d^u_{PTTD_{HF}}(n)$, and at forehead for $d^u_{PTTD_{EH}}(n)$.

Third, PDA is a signal processing technique to derive morphology indices from the PPG waveform [22]. Finger PPG pulses are decomposed into three wave components, a main wave and two reflected waves (see Fig. 1(b)). From this analysis, we can derive the pulse waveform characteristics surrogates (S) including main wave pulse width (W_1) and relative time delay between the main wave and the first reflected wave (T_{12}), which is used to derive the stiffness index [16,37].

These are proposed in the present context as PWV surrogates, $S \in \{W_1, T_{12}\}$, measured in [ms]:

$$d^u_S(n) = \sum_i S_i\cdot\delta(n-n^F_{B_i}), \quad S\in\{W_1,T_{12}\}. \tag{4}$$

Finally, PWV estimated values out-of-physiological range are excluded from further analysis. For this, an empirical range is set for valid values of PAT, PTTD and PDA:

- $d^u_{PAT}(n)$ values out of the $[50, 600]$ ms range.
- $d^u_{PTTD}(n)$ values out of the $[-50, 175]$ ms range.
- From PDA, the features of a pulse are rejected if either [22]: (a) the pulse is decomposed in less than 3 waves; (b) the amplitude of the main wave is not the largest of the three waves; (c) the second wave is located at the end of the pulse interval; (d) the third wave occurs before 35% from pulse onset.

The physiological ranges were determined empirically following an exploratory analysis. These ranges correspond to values below the 1st percentile and above the 99th percentile of all PAT and PTTD intervals obtained in the dataset under study. Afterwards, a median-absolute-deviation outlier rejection rule is applied, to complement suppression of spurious values from all the derived PWV surrogate series [38]: the threshold is defined as 5 times the running median-absolute-deviation of the previous 50 pulses.

2.5. Statistical analysis

A two-minute moving window approach with 50% overlap was used to calculate mean and standard deviation series for each stage of the heat stress protocol. To minimize transient effects, the first and last three minutes of each stage were excluded. Linear regression was then applied to the minute-by-minute mean values for each stage to capture the temporal evolution of the parameters, as shown for a representative participant in Fig. 2.

Three key features were extracted for each participant and stage: the initial value, the end-of-stage value, and the slope from the linear regression. These features were then averaged separately for the relaxation and heat stress stages for each participant. The distributions of these three averaged features across all 15 participants for each biomarker (HR, PAT, PTTD, and PDA) are shown as boxplots in Fig. 3.

To compare values between relaxation and heat stress, a Wilcoxon signed-rank test was performed, chosen for its suitability for paired data analysis. Statistically significant differences are marked in Fig. 3 with asterisks ('+', $p < 0.05$; '*', $p < 0.01$; '**', $p < 0.001$).

Finally, we explored the correlation between the various PWV biomarkers and HR across the different stages. To this end, we first calculated the average HR and PWV values for each patient for the relax stages (1, 3, 5, 7, 9) and stress stages (2, 4, 6, 8) separately. This step was crucial to ensure that the subsequent bootstrap analysis would be based on representative mean values rather than individual stage measurements, which could be subject to transitory fluctuations.

We then employed a bootstrap resampling technique, with 1000 iterations for each PWV biomarker, to estimate the 95% confidence intervals for the mean correlation coefficients of PWV with HR. In each bootstrap iteration, participants' correlation values were resampled with replacement, and the correlation between the averaged HR and PWV values was calculated for both relax and stress conditions. The bootstrap process thus generated a distribution of mean correlation coefficients, from which we extracted the 2.5th, 50th (median), and 97.5th percentiles, thereby constructing the 95% confidence intervals for the average correlations in both relax and stress states (see Fig. 4).

3. Results

3.1. PWV analysis

Fig. 2 presents the evolution of HR, PAT, PTTD and PDA, the latter measured using PPG_F, for one representative volunteer during the heat

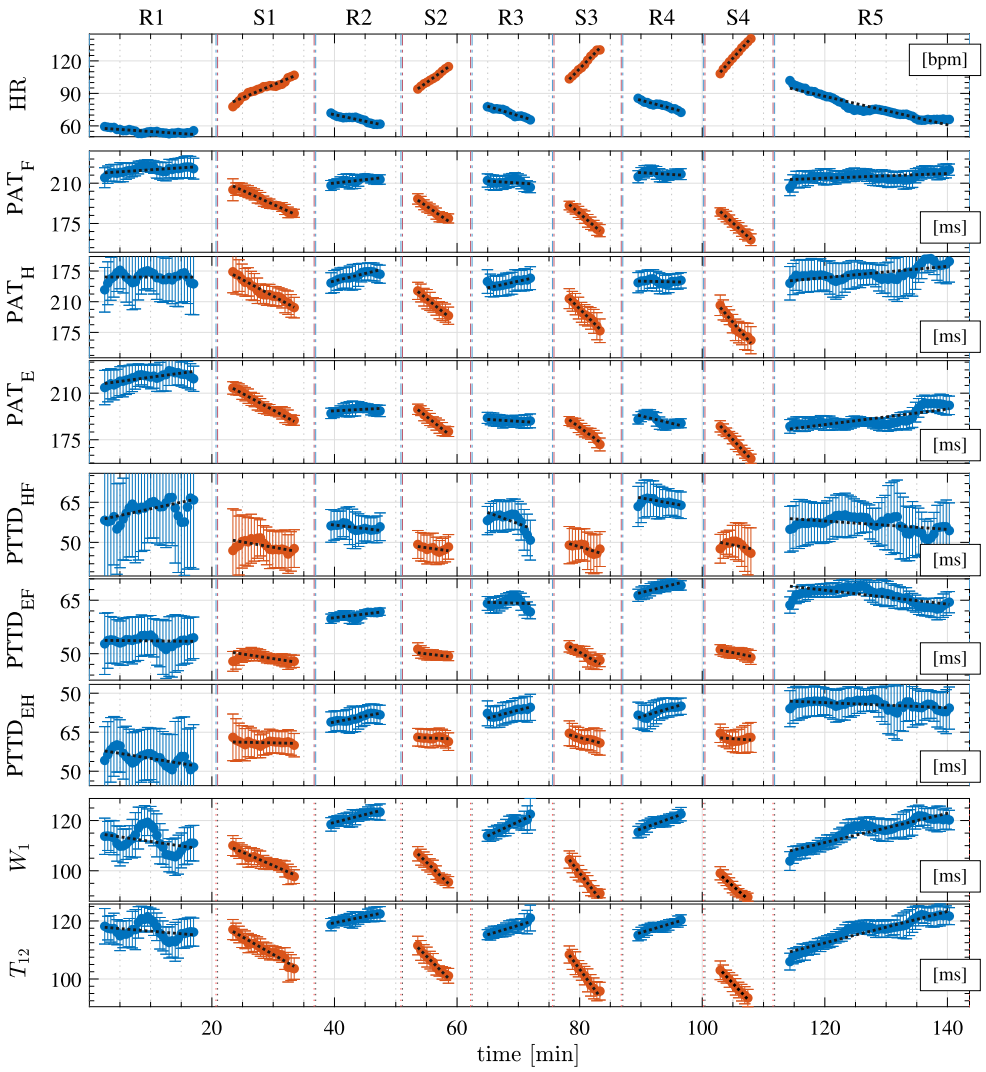

Fig. 2. HR, PAT, PTTD and PDA evolution for one illustrative volunteer. The black dotted lines represent the first order regression obtained for each metric and stage. Data collected during heat stress exposure within the sauna are represented in red, whereas measurements taken during the basal and recovery phases at normal ambient temperature outside the sauna are indicated in blue. Units: HR: [bpm]; others: [ms].

stress protocol. We can observe that during heat stress, PAT exhibits a highly pronounced linear decrease, parallel to the linear increase trend observed in HR. In contrast, during the relax/recovery stages, the PAT values remain relatively stable, with flat slope. The standard deviation of PAT in each 2-minute window does not show a generalized apparent variability.

Regarding PDA evolution, the patterns observed in the first inner wave width (W_1) and the time interval between the first and second inner waves of PPG_F (T_{12}) have trends similar to PAT. During heat stress, vasoconstriction leads to shorter arrival times, hence higher velocities, resulting in reduced W_1 and T_{12}, as expected by physiology.

The distribution of the slope between stages, the initial value, and the end of stage values averaged by stress typology, i.e., in relax vs. stress stages, have been calculated and displayed in boxplots in Fig. 3. The arrival times of the pulse wave differ among the PPG measurement sites, with the fingertip PAT presenting the longest absolute values, followed by the forehead and finally the earlobe; with median values for all volunteers around 205 ms, 155 ms, and 135 ms, respectively, in relax compared to 174 ms, 136 ms, and 123 ms during heat stress (absolute reduction around 15% under stress, see Fig. 3(b)). On average, PTTD values are also longer during the relax stages compared to the stress stages, as expected. The end-of-stage median values for PTTD in relax compared to stress (Fig. 3(b)) are: 47 ms vs. 36 ms, respectively, for $PTTD_{HF}$; 65 ms vs. 48 ms for $PTTD_{EF}$; and 20 ms vs. 13 ms for $PTTD_{EH}$ (an absolute reduction around 30% under stress). As shown in Fig. 3(a), the PTTD values did not change during the corresponding stages, having changes close to 0ms/min, whereas PAT presents a linear decrease $\approx$ 2.5 ms/min, while stress remains. For those interested in a more detailed examination of the data, we have provided the boxplots of PAT, PTTD, and PDA across all stages of the protocol in Supplementary Fig. S1, offering a comprehensive view of the variations and trends observed in these parameters throughout all stages of the study. A notable observation in Fig. S1 is that as the protocol progresses, the end-of-stage PWV values in the stress stages gradually decrease, indicating a memory effect (that can be seen for a representative participant in Fig. 2).

3.2. Heart rate correlation with PWV surrogates

Fig. 4 displays the 95% confidence intervals for the average correlation coefficient (ρ) between the evolution of HR and PWV biomarkers averaged across the two types of stages: relaxation and stress. A notable correlation is observed between HR and the PWV estimates from PAT_F, PAT_H, PAT_E, W_1, and T_{12} during stress stages, with coefficients significantly deviating from zero and approaching -1, indicating a strong inverse relationship under stress. Conversely, PWV estimates

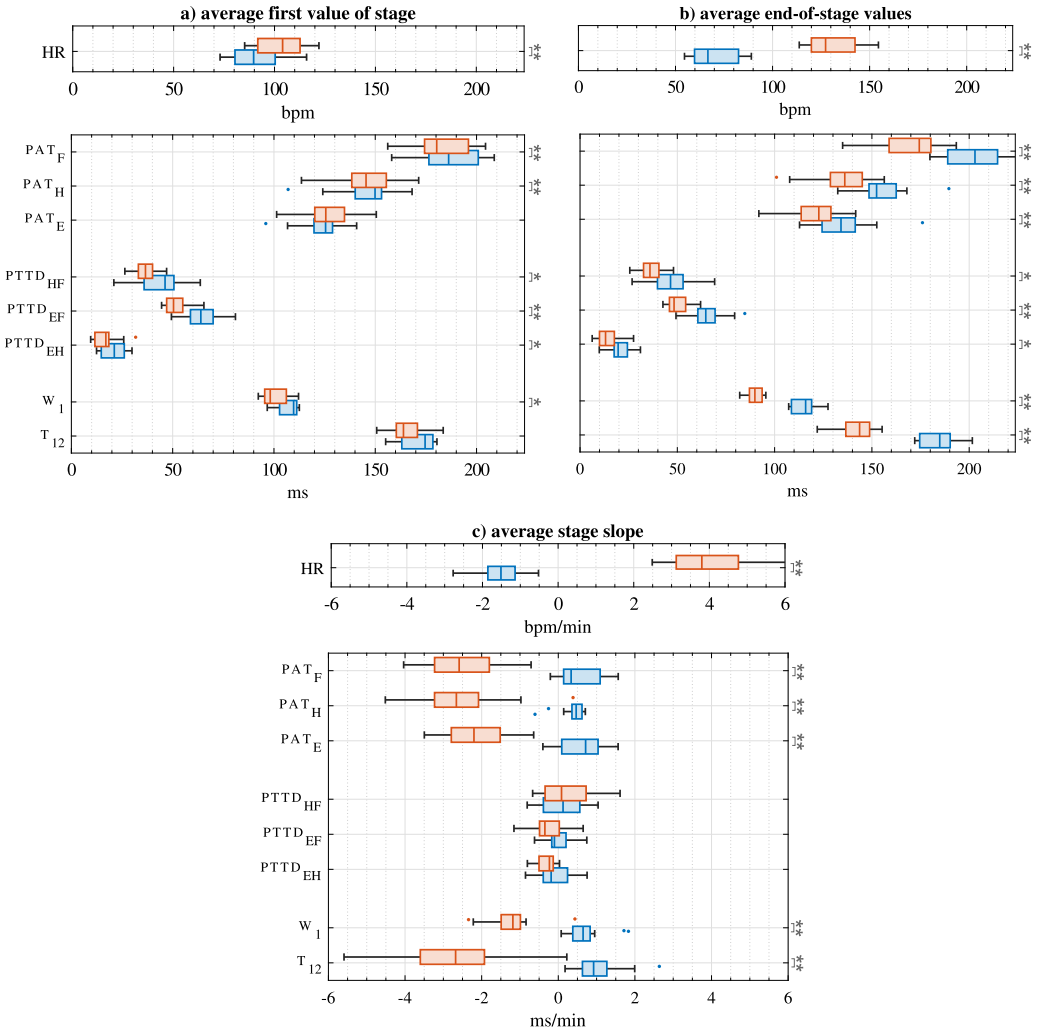

Fig. 3. Distribution of HR and PWV biomarkers for the 15 subjects, averaged by typology of stress: relax [blue] vs heat stress [red]. (a) represents the average of the first value in the stage, (b) the average end-of-stage PWV values, and (c) the intra-stage change (represented as the slope of a first-order fit). Statistically significant differences comparing relax vs stress values are displayed with asterisks ('+', $p < 0.05$; '*', $p < 0.01$; '**', $p < 0.001$). Units: (a) and (b): HR in [bpm], others in [ms]; (c) HR in [bpm/min], others in [ms/min].

from PTTD exhibit no significant correlation with HR during either relaxation or stress stages, suggesting a lack of association in these measures.

4. Discussion

The study involved 15 healthy volunteers, and the analysis focused on assessing PWV from PPG at different anatomical locations using PAT, PTTD, and PDA. These surrogate measures offer valuable insights into the relative changes in vasoconstriction, i.e., vascular reactivity. However, it is important to consider the methodological and physiological differences among these metrics, as they can affect the interpretation and usability in various scenarios.

4.1. PWV for vascular reactivity assessment

PWV is a crucial indicator of arterial stiffness and overall vascular health. Our study findings, as highlighted in the boxplots of Fig. 3, demonstrate that all three PPG-based methods—PAT, PTTD, and PDA—effectively detect changes in PWV and vascular reactivity during heat stress. These methods reveal significant differences in PWV values between relax and stress stages, underscoring their efficacy in capturing vascular dynamics.

Specifically, we observed that the intrastage slope for PAT and PDA, as a measure of vascular reactivity, is highly negative during heat stress, as evidenced in Fig. 3. This pattern suggests a progressive increase in PWV under these conditions. However, PTTD presents a different response: even as HR undergoes abrupt changes during heat stress stages, the slope of PTTD estimates remains much smaller, especially in $PTTD_{EH}$, while the average level of PTTD does change. This finding implies that PTTD is sensitive to vasoconstriction changes but less so to progressively increasing changes, which could be partially attributed to PEP [14,15]. This is likely because PTTD omits the influence of HR and PEP variations by its definition, focusing instead on acute vascular changes.

The distinct behavior of PTTD is further illustrated in Fig. 2, which depicts the evolution of these parameters in one representative volunteer. The three PTTDs show a significant and immediate change at the onset of stress exposure, followed by a period of stable values. This immediate response and subsequent stability contrast markedly with the delayed adaptations seen in other biomarkers like HR, PAT, and PDA, which only become evident after a prolonged duration of stress.

This PTTD's unique response highlights its sensitivity and consistency in reflecting swift physiological changes triggered by stress. The key difference lies in the initial values of PTTD at the beginning of stress exposure, which are significant. However, unlike the changes observed

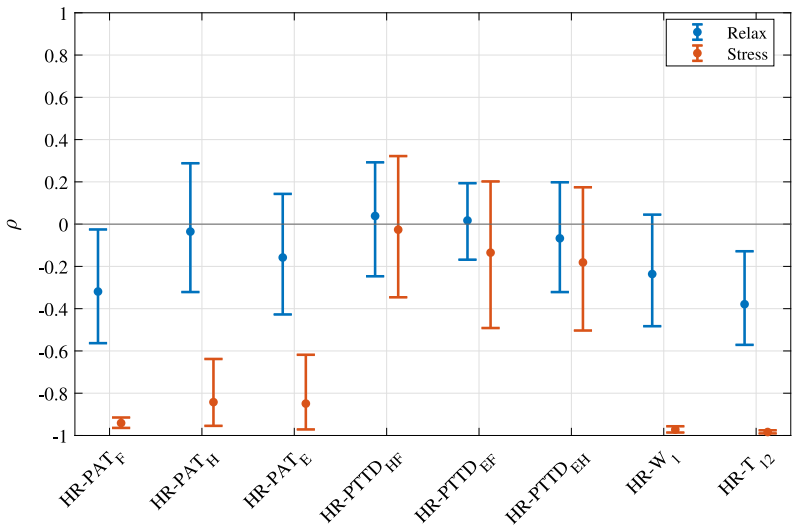

Fig. 4. Median and 95% confidence intervals for the average correlation, ρ, between HR and the PWV biomarkers of all participants, for Relax and Stress Stages.

in PAT and PDA biomarkers, the alteration in PTTD values during the stress stage itself is not statistically significant, indicating its potential as a stable and sensitive marker of rapid vascular changes.

As found by [14], PEP is a cardiovascular parameter linearly correlated with HR, but the relationship is weaker or stronger under differing circumstances (rest: $\rho^2 = 0.06$, physical stress: $\rho^2 = 0.65$). This remarks that during stress, PAT provides information about vasoconstriction, but PAT will also exhibit a high component of PEP, since the definition of PAT includes this period. Regarding the correlation obtained in this study of each PWV metric with HR (Fig. 4), results suggest that the influence of HR is consistently and highly affecting PAT and PDA specially during heat stress. ρ values of all PAT and PDA estimates are very close to (−1), exhibiting the strong inverse proportionality between HR and these PWV estimates under stress. On the contrary, PTTD has no significant correlation with HR, supporting the hypothesis that the progressive increasing changes observed in PAT and PDA are mainly due to HR variations, mediated through PEP, the ejected systolic volume, also known as stroke volume, and the other cardiac output (CO) modulators.

PTTD exhibits a similar behavior to HR and PAT during the relax stages. However, during the heat stress stages, unlike PAT, we did not observe the same pronounced trend following the one for HR, which is a novel and interesting finding. Of note, the standard deviation of PTTD is larger than for PAT, as a result of lower precision and/or lower dynamic range.

Therefore, based on these results, PTTD seems to have a superior performance for the evaluation of vasoconstriction reactivity, since PAT and PDA surrogates include additional SNS modulation variables other than vasoconstriction. However, it is important to mention that the standard deviation of PTTD is greater than the one of PAT or PDA measures, which may be indicating a lower signal-to-noise ratio, likely due to the resolution (dependent on the sampling frequency of PPG), and lower dynamic range of PTTD. Besides, PTTD measurements from the fingertip to head (HF) or earlobe (EF) show greater variability than earlobe to head (EH), indicative of the pulse wave's longer travel time. Shorter PTTD travel distances, such as in EH, result in a narrower dynamic range, suggesting that PTTD measurements over longer distances (HF or EF) are more effective for evaluating vascular dynamics and reactivity.

We also performed a complete analysis encompassing frequency domain indices of PAT, PTTD, and PDA, although the details are beyond the scope of the present study. However, it should be highlighted that the significant number of periods where PTTD could not be determined results in a substantial amount of temporal gaps. This limitation arises from the small dynamic range, and the requirements for high sampling rates and high quality of the original PPG signals, which makes frequency analysis of PTTD not feasible. Consequently, future research into PTTD should prioritize studying the evolution of average PTTD absolute values over specific time intervals, such as 2-minute periods, instead of frequency domain analysis.

Our findings are consistent with previous studies that have used PWV measures to assess changes in vascular reactivity during various stressors. For example, several studies have demonstrated that PWV is a sensitive indicator of changes in cardiovascular function under stress [39,40]. Considering the methodological differences, PAT values obtained in this work are equivalent to values previously reported [37]. Our study extends these findings by characterizing PWV estimates for monitoring changes in vascular reactivity during heat stress, taking into account the effect of PEP.

4.2. Physiological implications and applications

The ability to monitor changes in vascular reactivity, particularly under heat stress, has crucial physiological implications. SNS activity influences BP and HR, essential for thermoregulation during heat exposure [41]. During heat stress, SNS-mediated modulation of the sinus node results in elevated HR and CO.

Arterioles, with their high smooth muscle concentration [42], are central in PWV regulation, differing from larger vessels in their impact on vascular resistance and compliance. While veins primarily support venous return, especially from lower extremities, arterioles are key in modulating vascular dynamics.

SNS activity induces arteriole vasoconstriction leading to increased preload, since constriction of the veins improves venous return, and increased afterload, as the constriction of the arteries and arterioles increases total peripheral resistance. Concurrently, it enhances myocardial contractility, impacting stroke volume and further elevating BP [43]. Sauna bathing showcases these physiological dynamics. It increases skin blood flow, significantly contributing to CO, while internal organ blood flow decreases [44]. Contrary to assumptions, BP and HR increase during sauna sessions, leading to heightened myocardial oxygen consumption [29,41]. PWV is influenced by these mechanisms, altering PAT, PTTD, and PDA estimates in different ways. For example, myocardial contractility and vasoconstriction decrease W_1 and T_{12}, while an increase on HR will exhibit a strong linear correlation to an increase on PWV, as in [14].

Vasoconstriction, in response to SNS activation, is a rapid physiological process. Upon exposure to a stimulus, the SNS triggers the release

of norepinephrine, initiating vasoconstriction. This response can start within 1–2 s, with significant constriction typically occurring within 5–10 s [45,46]. Vasoconstriction responses are immediate, while BP increases require more time due to complex systemic activation to augment CO. PTTD values change more gradually during stress stages, reflecting SNS modulation, while PAT and PDA estimates rise in tandem with HR during heat stress. These novel findings may suggest that the sensitivity of PTTD to vasoconstriction has an immediate and consistent response upon stress exposure, a pattern that is not observed in HR, PAT, and PDA measurements. Based on the physiology, we propose that PTTD may predominantly reflect changes in arterial stiffness and BP linked to vasoconstriction, thus differentiating these specific effects from other physiological influences.

Then, our findings suggest PTTD's unique response to vasoconstriction, with immediate and consistent values during stress stages, unlike HR, PAT, and PDA. PTTD primarily reflects changes in arterial stiffness and BP associated with vasoconstriction, differentiating it from other physiological influences. Unaffected by CO and PEP changes, PTTD correlates well with carotid-femoral PWV, requiring only two PPG sensors [47,48].

4.3. Limitations and future work

This study has two main limitations. The first limitation is the lack of PEP measurements, to compare our PWV estimates with the actual PEP. Although previous studies analyzed the interrelationship between HR and PEP, the absence of this data in these recordings limits the interpretation and capability to draw definitive conclusions. Future studies could benefit from including it to further validate the relationship between PEP and PWV, with respect to variations in HR, too. Furthermore, the incorporation of CO measurements could yield valuable information. One possible approach to address the influence of HR on PEP, PAT, and PDA measures is to compute HR-corrected PWV estimates, as demonstrated in [49]. Therefore, considering the influence of HR on PWV estimation could provide a more accurate reflection of vascular reactivity, unaffected by PEP.

Secondly, it is important to recognize that due to the study design, the available data are limited to male participants. Therefore, there is a need to extend the recordings to include data from the female population. This would provide valuable insights into potential gender differences and enhance the generalization of the findings.

In this study, it is essential to clarify that the term 'PWV' refers to measurements derived from transit times rather than directly measured velocities. Traditional PWV calculations typically require the distance the pulse wave travels, necessitating measurements of vessel length or, by approximation, arm length or participant height. However, for within-subject comparisons where vessel length is constant, transit times can serve as a surrogate for velocity changes, as demonstrated in our results. In contrast, population-based analyses should include normalization against height or arm length to account for inter-individual variability and prevent potential confounding.

5. Conclusions

The study provides valuable information on PWV and its surrogate measures during heat stress. PWV measures offer a reliable and non-invasive approach for assessing cardiovascular function. The distinct patterns observed in PAT, PTTD, and PDA, along with their relationships with HR, contribute to a superior understanding of vascular reactivity.

The study underscores the importance of considering the impact of concurrent physiological conditions on PWV biomarkers. Our findings demonstrate differences in the evolution between relax and stress stages, possibly due to the activation of additional physiological mechanisms through the SNS response to stress, which potentially do not affect PWV measurements during relax conditions.

While PAT is a recognized PWV surrogate measure, and it has been extensively studied for many applications such as assessing arterial stiffness, evaluating endothelial dysfunction, and estimating blood pressure, rather less attention has been given to PTTD and PDA. Our study highlights that PTTD, requiring only two PPG sensors, offers a superior description of vasoconstriction by suppressing, among others, the isovolumetric contraction period, which is significantly variable and HR dependent under stress conditions. The trade-offs of using PTTD involve its lower dynamic range and the need for two PPG sensors at different body locations.

CRediT authorship contribution statement

Pablo Armañac-Julián: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Spyridon Kontaxis:** Writing – review & editing, Supervision, Software, Methodology, Formal analysis, Conceptualization. **Jesús Lázaro:** Writing – review & editing, Supervision, Software, Investigation, Conceptualization. **Andrius Rapalis:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Data curation. **Marius Brazaitis:** Writing – review & editing, Supervision, Resources, Investigation, Funding acquisition. **Vaidotas Marozas:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Data curation. **Pablo Laguna:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Raquel Bailón:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Eduardo Gil:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.bspc.2025.107641.

Data availability

Data will be made available on request.

References

[1] L.M. Van Bortel, S. Laurent, P. Boutouyrie, P. Chowienczyk, J. Cruickshank, T. De Backer, J. Filipovsky, S. Huybrechts, F.U. Mattace-Raso, A.D. Protogerou, et al., Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity, J. Hypertens. 30 (3) (2012).

[2] L. Peter, N. Noury, M. Cerny, A review of methods for non-invasive and continuous blood pressure monitoring: Pulse transit time method is promising? IRBM 35 (5) (2014).

[3] S.J. Vermeersch, E.R. Rietzschel, M.L. De Buyzere, D. De Bacquer, G. De Backer, L.M. Van Bortel, T.C. Gillebert, P.R. Verdonck, P. Segers, A. Investigators, et al., Age and gender related patterns in carotid-femoral PWV and carotid and femoral stiffness in a large healthy, middle-aged population, J. Hypertens. 26 (7) (2008).

[4] G. Mancia, R. Fagard, K. Narkiewicz, J. Redon, A. Zanchetti, M. Böhm, T. Christiaens, R. Cifkova, G. De Backer, A. Dominiczak, et al., 2013 ESC/ESH practice guidelines for the management of arterial hypertension: ESC-ESH the task force for the management of arterial hypertension of the European society of hypertension (ESH) and of the European society of cardiology (ESC), Blood Press. 23 (1) (2014).

[5] B. Hametner, S. Wassertheurer, J. Kropf, C. Mayer, B. Eber, T. Weber, Oscillometric estimation of aortic pulse wave velocity: comparison with intra-aortic catheter measurements, Blood Press. Monitor. 18 (3) (2013).

[6] F. Cuomo, J. Ferruzzi, J.D. Humphrey, C.A. Figueroa, An experimental–computational study of catheter induced alterations in pulse wave velocity in anesthetized mice, Ann. Biomed. Eng. 43 (2015).

[7] B. Jiang, B. Liu, K.L. McNeill, P.J. Chowienczyk, Measurement of pulse wave velocity using pulse wave doppler ultrasound: comparison with arterial tonometry, Ultrasound Med. Biol. 34 (3) (2008).

[8] P. Salvi, G. Lio, C. Labat, E. Ricci, B. Pannier, A. Benetos, Validation of a new non-invasive portable tonometer for determining arterial pressure wave and pulse wave velocity: the PulsePen device, J. Hypertens. 22 (12) (2004).

[9] X. Ding, Y.-T. Zhang, Pulse transit time technique for cuffless unobtrusive blood pressure measurement: from theory to algorithm, Biomed. Eng. Lett. 9 (2019).

[10] P.H. Charlton, P.A. Kyriacou, J. Mant, V. Marozas, P. Chowienczyk, J. Alastruey, Wearable photoplethysmography for cardiovascular monitoring, Proc. IEEE 110 (3) (2022).

[11] P.H. Charlton, J. Allen, R. Bailon, S. Baker, J.A. Behar, F. Chen, G.D. Clifford, D.A. Clifton, H.J. Davies, C. Ding, et al., The 2023 wearable photoplethysmography roadmap, Physiol. Meas. (2023).

[12] I. Cheol Jeong, D. Bychkov, P.C. Searson, Wearable devices for precision medicine and health state monitoring, IEEE Trans. Biomed. Eng. 66 (5) (2018).

[13] D.B. Newlin, Relationships ol pulse transmission times to pre-ejection period and blood pressure, Psychophysiology 18 (3) (1981).

[14] N. Pilz, A. Patzak, T.L. Bothe, The pre-ejection period is a highly stress dependent parameter of paramount importance for pulse-wave-velocity based applications, Front. Cardiovasc. Med. 10 (2023).

[15] J. Krohová, B. Czippelova, Z. Turianiková, Z. Lazarová, I. Tonhajzerová, M. Javorka, Preejection period as a sympathetic activity index: a role of confounding factors, Physiol. Res. 66 (2017).

[16] P.H. Charlton, B. Paliakaite, K. Pilt, M. Bachler, S. Zanelli, D. Kulin, J. Allen, M. Hallab, E. Bianchini, C.C. Mayer, et al., Assessing hemodynamics from the photoplethysmogram to gain insights into vascular age: a review from VascAgeNet, Am. J. Physiol.- Hear. Circ. Physiol. 322 (4) (2022).

[17] T.H. Huynh, R. Jafari, W.-Y. Chung, Noninvasive cuffless blood pressure estimation using pulse transit time and impedance plethysmography, IEEE Trans. Biomed. Eng. 66 (4) (2018).

[18] M. Nitzan, B. Khanokh, Y. Slovik, The difference in pulse transit time to the toe and finger measured by photoplethysmography, Physiol. Meas. 23 (1) (2001).

[19] P. Armanac, J. Lázaro, P. Laguna, R. Bailón, E. Gil, et al., Cardiovascular changes induced by acute emotional stress estimated from the pulse transit time difference, in: Computing in Cardiology, CinC, 2019.

[20] M.C. Baruch, D.E. Warburton, S.S. Bredin, A. Cote, D.W. Gerdt, C.M. Adkins, Pulse decomposition analysis of the digital arterial pulse during hemorrhage simulation, Nonlinear Biomed. Phys. 5 (1) (2011).

[21] M. Huotari, A. Vehkaoja, K. Määttä, J. Kostamovaara, Photoplethysmography and its detailed pulse waveform analysis for arterial stiffness, J. Struct. Mech. 44 (4) (2011).

[22] S. Kontaxis, E. Gil, V. Marozas, J. Lázaro, E. García, M. Posadas-de Miguel, S. Siddi, M.L. Bernal, J. Aguiló, J.M. Haro, et al., Photoplethysmographic waveform analysis for autonomic reactivity assessment in depression, IEEE Trans. Biomed. Eng. 68 (4) (2020).

[23] C. Crandall, J. Gonzalez-Alonso, Cardiovascular function in the heat-stressed human, Acta Physiol. 199 (4) (2010).

[24] S.F. Morrison, Central control of body temperature, F1000Research 5 (2016).

[25] S.S. Bruce-Low, D. Cotterrell, G.E. Jones, Heart rate variability during high ambient heat exposure, Aviat. Space, Environ. Med. 77 (9) (2006).

[26] P. Zalewski, M. Zawadka-Kunikowska, J. Słomko, J. Szrajda, J.J. Klawe, M. Tafil-Klawe, J. Newton, Cardiovascular and thermal response to dry-sauna exposure in healthy subjects, Physiol. J. 2014 (2014).

[27] S. Kontaxis, R. Bailón, A. Rapalis, M. Brazaitis, M. Cernych, J. Lázaro, P. Laguna, E. Gil, V. Marozas, Autonomic nervous system response to heat stress exposure by means of heart rate variability, in: Computing in Cardiology, CinC, 2019.

[28] Z.J. Schlader, Y. Okada, S.A. Best, Q. Fu, C.G. Crandall, Arterial stiffness during whole-body passive heat stress in healthy older adults, Physiol. Rep. 7 (9) (2019).

[29] M. Cernych, A. Satas, A. Rapalis, V. Marozas, L. Malciene, A. Lukosevicius, L. Daniuseviciute, M. Brazaitis, Exposure to total 36-hr sleep deprivation reduces physiological and psychological thermal strain to whole-body uncompensable passive heat stress in young adult men, J. Sleep Res. 30 (2) (2021).

[30] N. Charkoudian, Mechanisms and modifiers of reflex induced cutaneous vasodilation and vasoconstriction in humans, J. Appl. Physiol. 109 (4) (2010).

[31] J.P. Martínez, R. Almeida, S. Olmos, A.P. Rocha, P. Laguna, A wavelet-based ECG delineator: evaluation on standard databases, IEEE Trans. Biomed. Eng. 51 (4) (2004).

[32] J. Mateo, P. Laguna, Analysis of heart rate variability in the presence of ectopic beats using the heart timing signal, IEEE Trans. Biomed. Eng. 50 (3) (2003).

[33] M. Elgendi, Optimal signal quality index for photoplethysmogram signals, Bioengineering 3 (4) (2016).

[34] P. Armañac-Julián, S. Kontaxis, A. Rapalis, V. Marozas, P. Laguna, R. Bailón, E. Gil, J. Lázaro, Reliability of pulse photoplethysmography sensors: coverage using different setups and body locations, Front. Electron. 3 (2022).

[35] J. Lázaro, E. Gil, J.M. Vergara, P. Laguna, Pulse rate variability analysis for discrimination of sleep-apnea-related decreases in the amplitude fluctuations of pulse photoplethysmographic signal in children, IEEE J. Biomed. Heal. Inform. 18 (1) (2013).

[36] R. Mukkamala, J.-O. Hahn, O.T. Inan, L.K. Mestha, C.-S. Kim, H. Töreyin, S. Kyal, Toward ubiquitous blood pressure monitoring via pulse transit time: theory and practice, IEEE Trans. Biomed. Eng. 62 (8) (2015).

[37] P. Salvi, E. Magnani, F. Valbusa, D. Agnoletti, C. Alecu, L. Joly, A. Benetos, Comparative study of methodologies for pulse wave velocity estimation, J. Hum. Hypertens. 22 (10) (2008).

[38] R. Bailón, L. Sornmo, P. Laguna, A robust method for ECG-based estimation of the respiratory frequency during stress testing, IEEE Trans. Biomed. Eng. 53 (7) (2006).

[39] F. Milatz, S. Ketelhut, R.G. Ketelhut, R. Ketelhut, Favorable effect of aerobic exercise on arterial pressure and aortic pulse wave velocity during stress testing, Vasa 44 (4) (2015).

[40] A. Saz-Lara, I. Cavero-Redondo, C. Álvarez-Bueno, B. Notario-Pacheco, M.C. Ruiz-Grao, V. Martínez-Vizcaíno, The acute effect of exercise on arterial stiffness in healthy subjects: a meta-analysis, J. Clin. Med. 10 (2) (2021).

[41] S. Ketelhut, R. Ketelhut, The blood pressure and heart rate during sauna bath correspond to cardiac responses during submaximal dynamic exercise, Complement. Ther. Med. 44 (2019).

[42] L.A. Martinez-Lemus, The dynamic structure of arterioles, Basic Clin. Pharmacol. Toxicol. 110 (1) (2012) 5–11.

[43] J.R. Mitchell, J.-J. Wang, Expanding application of the wiggers diagram to teach cardiovascular physiology, Adv. Physiol. Ed. 38 (2) (2014) 170–175.

[44] M.L. Hannuksela, S. Ellahham, Benefits and risks of sauna bathing, Am. J. Med. 110 (2) (2001).

[45] J.R. Levick, Levick's Introduction to Cardiovascular Physiology, 6th Edition, 2018.

[46] A.J. Pappano, W.G. Wier, Cardiovascular Physiology, 9th Edition, McGraw-Hill Education, 2018.

[47] Q. Zhong, M.-J. Hu, Y.-J. Cui, L. Liang, M.-M. Zhou, Y.-W. Yang, F. Huang, Carotid–femoral pulse wave velocity in the prediction of cardiovascular events and mortality: an updated systematic review and meta-analysis, Angiology 69 (7) (2018).

[48] B. Williams, G. Mancia, W. Spiering, E. Agabiti Rosei, M. Azizi, M. Burnier, D.L. Clement, A. Coca, G. De Simone, A. Dominiczak, et al., 2018 ESC/ESH guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European society of cardiology (ESC) and the European society of hypertension (ESH), Eur. Heart J. 39 (33) (2018).

[49] G. Valenza, B. Nackley, B.H. Friedman, R. Barbieri, Validation of sympathetic activity index from heartbeat series: a preliminary study on pre-ejection periods, in: 12th Conference of the European Study Group on Cardiovascular Oscillations, ESGCO, 2022.