

Towards Ambulatory Baroreflex Sensitivity: A Comparison between Indices of Arterial Line and Photoplethysmography in male volunteers.

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Submitted to: JMIR Cardio
on: November 21, 2023

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Towards Ambulatory Baroreflex Sensitivity: A Comparison between Indices of Arterial Line and Photoplethysmography in male volunteers.

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Abstract

Background: The ability of the body to adjust heart rate to control blood pressure is represented as baroreflex sensitivity (BRS). BRS is traditionally quantified by measuring heart rate changes (obtained via an ECG) following a change in arterial pressure (conventionally measured through an arterial line). The invasiveness of arterial line necessitates alternatives, like the volume clamp method and the less invasive pulse photoplethysmography (PPG). The PPG method is also suitable for continuous and free-living conditions.

Objective: This study aims to better understand which PPG-based features for BRS determination perform best in comparison to BRS based on the volume clamp method and gold standard arterial line and in extension, the feasibility of assessing BRS patterns over 24h by means of a single volunteer.

Methods: Twenty eight male volunteers (age 52 ± 7 years, BMI $27 \pm 4 \text{ kg/m}^2$) equipped with four sensing modalities: 1. arterial line, 2. infrared PPG, 3 volume clamp finger pressure and 4. ECG, performed a protocol of three repetitive sessions in supine position. For the extended feasibility on continuous BRS measurement, ECG and PPG data were acquired for 24 hours in free-living conditions from a normotensive male volunteer (33 years).

BRS index was calculated in the low frequency window (0.04-0.15 Hz) taking the average over all trials per intervention per subject. A transfer function was estimated with systolic blood pressure or it's surrogate as input and heart rate (from the ECG) as output.

Results: PPG based BRS features, rise-decay time ratio (RDRatio) and pulse arrival time (PAT), show intra-subject precision of respectively 44% and 23% with inter-subject variation of 91% and 53% respectively. The correlation of BRSPAT,P and BRSRDRatio,P to the gold standard BRSSBP,A is 0.66 and 0.56 respectively. During intervention, the correlations remain high for BRSRDRatio,P (rest: 0.75, Paced-breathing: 0.50, handgrip: 0.46) and BRSPAT,P (rest: 0.69, Paced-breathing: 0.52, Handgrip: 0.62).

On the 24h data the BRSPAT,P and BRSRDRatio,P show changes during the day which are expected considering the activity and correspond to the changes seen in the systolic blood pressure. During the night a cyclic rhythm can be seen for both BRSPAT,P and BRSRDRatio,P.

Conclusions: This study demonstrates PPG-based PAT and RDRatio BRS as suitable surrogates for gold standard BRS derived from arterial line, showing the highest correlation and comparable intra subject coefficient variation, as well as expected changes during controlled activities and a 24-hour feasibility test in free-living conditions. Clinical Trial: Ziekenhuis Oost-Limburg in Genk, Belgium (ethical committee approval number 16/039U)

(JMIR Preprints 21/11/2023:54771)

DOI: <https://doi.org/10.2196/preprints.54771>

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Original Manuscript

Towards Ambulatory Baroreflex Sensitivity: A Comparison between Indices of Arterial Line and Photoplethysmography in male volunteers.

Abstract

Background: The baroreflex sensitivity (BRS) is the body's ability to adjust heart rate to control blood pressure. Traditionally, BRS is quantified by measuring heart rate changes (obtained via an ECG) following alterations in arterial pressure (conventionally measured through an arterial line). However, the invasiveness of arterial line necessitates alternatives, such as the volume clamp method and the less invasive pulse photoplethysmography (PPG). Notably, the PPG method is also suitable for continuous and free-living conditions.

Objective: This study aims to compare PPG-based features for BRS determination based on the volume clamp method and gold standard arterial line. Data from a previous study was used where the primary analysis focused on evaluating the accuracy of PPG-derived heart rate variability, while the current analysis quantifies BRS by measuring heart rate changes following alterations in arterial line pressure or less invasive alternatives. Additionally, we investigate the feasibility of assessing BRS patterns over 24 hours using data from a single volunteer.

Methods: Twenty-eight male volunteers (age 52 ± 7 years, BMI 27 ± 4 kg/m²) equipped with four sensing modalities: 1. arterial line, 2. infrared PPG, 3. volume clamp finger pressure and 4. ECG, performed a protocol of three repetitive sessions in supine position. For the extended feasibility of continuous BRS measurement, ECG and PPG data were acquired for 24-hour in free-living conditions from a normotensive male volunteer (33 years). BRS index was calculated within the low frequency window (0.04-0.15 Hz) averaging over all trials for each intervention and subject. A transfer function was estimated with systolic blood pressure or its surrogate as input and heart rate (from the ECG) as output.

Results: PPG based BRS features, specifically the rise-decay time ratio (RDRatio) and pulse arrival time (PAT), demonstrate intra-subject precision of 44% and 23%, respectively with inter-subject variation of 91% and 53%. The correlation of $BRS_{PAT,P}$ and $BRS_{RDRatio,P}$ with the gold standard $BRS_{SBP,A}$ is 0.66 and 0.56, respectively. During intervention, the correlations remain high for $BRS_{RDRatio,P}$ (rest: 0.75, Paced-breathing: 0.50, handgrip: 0.46) and $BRS_{PAT,P}$ (rest: 0.69, Paced-breathing: 0.52, Handgrip: 0.62). In the 24h data the $BRS_{PAT,P}$ and $BRS_{RDRatio,P}$ exhibit changes during the day corresponding to the activity levels and systolic blood pressure variations. Notably, during the night, a cyclic rhythm is observed for both $BRS_{PAT,P}$ and $BRS_{RDRatio,P}$.

Conclusions: This study demonstrates that in male volunteers PPG-based PAT and RDRatio BRS serve as suitable surrogates for gold standard BRS derived from arterial line, showing the highest correlation and comparable intra-subject coefficient variation. Furthermore, they show expected changes during controlled activities and a 24-hour feasibility test in free-living conditions.

Trial Registration: Ziekenhuis Oost-Limburg in Genk, Belgium (ethical committee approval number 16/039U)

Keywords: Photoplethysmography; pulse arrival time; pulse transit time; blood pressure; pulse wave analysis; heart rate; heart rate variability; baroreceptor sensitivity; baroreflex; arterial line; circadian rhythm

Introduction

The baroreflex is a feedback system controlling arterial blood pressure (ABP). Stretch receptors in the aortic arc wall and carotid sinuses sense the changes in ABP. When arterial transmural pressure increases, the baroreflex responds by lowering heart rate and decreasing cardiac contractility and reducing peripheral vascular resistance, and vice versa [1].

Baroreflex sensitivity (BRS) refers to the body ability to adjust heart rate in response to changes in blood pressure. Maintaining this hemodynamic homeostasis is a continuous process and of vital importance to healthy organ perfusion. A decrease in baroreflex sensitivity is associated with (persistent) hypertension, heart failure, poor outcome after stroke and kidney failure [2–8].

BRS can be modelled in both the time and frequency domain. Traditionally it is quantified by measuring the heart rate changes following variations in arterial pressure. The sequence method is a time-domain method in which three or more consecutive beats with progressively increasing or decreasing arterial pressure are followed by a progressive increase or decrease of heart rate [9]. The frequency domain or spectral analysis is applied on continuous ECG and arterial pressure signals assuming changes in arterial pressure and heart rate, induced by the baroreflex, are oscillations in the same frequency band. In the frequency domain analysis different strategies are used, including non-parametric transfer function, parametric transfer function, and the phase rectified signal averaging method [1,7]. The most used BRS method calculates the spectral relationship between the input signal, commonly the systolic blood pressure (SBP) obtained from the continuous arterial pressure signal, and the output signal, commonly the RR interval obtained from the ECG [7,10]. The BRS is typically quantified as the average spectral gain within the low frequency (LF, 0.04-0.15 Hz) or high frequency (HF, 0.15-0.40 Hz) window [7,8,10,11].

The gold standard for measuring arterial pressure is directly through an arterial line, i.e., a (fluid-filled) catheter inserted into an artery. However, due to its invasiveness of this technique alternative methodologies are necessary. One commonly used alternative is the continuous finger blood pressure measured using the volume clamp method. This method employs a two-sensor system that combines photoplethysmography and a pressure sensor [12,13]. Previous investigations have revealed that, depending on the device, the variability of the systolic pressure has been overestimated by 78% and 103% in the low frequency band [13]. Additionally, the same investigation demonstrated an underestimation of the baroreflex sensitivity by -24% or -31%. Another, more indirect method to estimate arterial blood pressure is through photoplethysmography (PPG), currently predominantly used in research settings [14]. PPG measures the blood volume pulse through light transmission instead of a direct pressure pulse. The PPG signal is composed of a pulsatile ('AC') and baseline ('DC') part. The AC part reflects the changes in blood volume, and is divided into a systolic phase (from foot to primary peak) and a diastolic phase (from secondary peak to foot) [15,16]. The PPG volume pulse contour is related to a pressure pulse [17]. Primary peak amplitude, referred to as systolic amplitude, has been related to stroke volume and changes under influence of vasomotor tone and blood volume [15,16]. Different features have been proposed relating PPG with blood pressure, including pulse arrival time (PAT), pulse width, reflection index and PPG variability [18]. PAT is the time between the electrical activation of the left ventricle, obtained with ECG, and the arrival of the wave in the periphery. PAT is known to be related to the (systolic) blood pressure [14]. As blood pressure increases, the apparent arterial stiffness increases and PAT decreases. Besides this inverse relation, PAT is also determined by the pre-ejection period, i.e., the time between electrical activation and opening of the valve of the left ventricle. PPG has also been related to systemic vascular resistance and vasomotor tone. The DC component of the PPG and pulse width are determined by, among other things, the vasomotor tone [16,19–21]. Pre-ejection period change, related to change in cardiac contractility can also be derived from the PPG signal [22,23]. Hence,

PPG contains more baroreflex related information than just arterial pressure. It has been used to determine BRS and is most often compared to BRS based on volume clamp method [10,24–26]. To the best of our knowledge, BRS obtained from invasive arterial pressure, volume clamp finger pressure and PPG have not been compared directly.

Continuous BRS measurements in a free-living condition could elucidate the variation of the BRS and its potential interaction with the circadian rhythm. BRS over a 24-hour period is useful to monitor autonomic nervous system (dys-)function at night in absence of other influences, to relate it to sleep stages for example in prediabetic patients [27], elderly [28] or hypertensive patients [29,30]. Long term free-living monitoring requires a minimal obtrusive wearable solution, which could be PPG, for instance. To reliably use PPG for BRS determination it is important to understand the benefits and the disputes compared to a direct blood pressure measurement from the arterial line.

This study aims to better understand which PPG-based features for BRS determination perform best in comparison to BRS based on the volume clamp method and gold standard arterial line. In addition, this study, in extension, also aims to assess the feasibility of assessing BRS patterns over 24h by means of a single volunteer.

Methods

This study involves a secondary analysis of an existing dataset [31]. The primary analysis focused on evaluating the accuracy of PPG-derived heart rate variability [31], while in the current analysis the baroreceptor sensitivity is quantified by measuring heart rate changes following alterations in arterial line pressure or less invasive alternatives.

Datasets

Arterial line interventional study

The interventional dataset was used to analyze the differences and similarities between BRS derived from invasive arterial line blood pressure, volume clamp finger pressure and PPG. More details can be found in [31]. In summary, 28 male healthy volunteers (age 52 ± 7 years, BMI 27 ± 4 kg/m², SBP 130 ± 12 mmHg). Participants were equipped with four sensing modalities (see Figure 1): 1. Arterial line inserted into radial artery on the non-dominant arm, 2. Infrared PPG at the index finger of the same arm (Biopac PPG100C, 240 Hz) and 3. Finapres Nova at middle finger of the same arm, 4. ECG in lead II configuration (Biopac ECG100C, 240Hz). Participants performed a protocol of three repetitive sessions in supine position arm resting alongside the body. Each session included several interventions, namely two times paced breathing at 7 breaths for 3 minutes. A handgrip intervention during which the participant was asked to squeeze in a handgrip as much as possible for one and a half minute using their dominant hand. And a dedicated rest period where the participants was asked to close their eyes for 2 minutes. Extra (unlabeled) transition time was allocated in between activities.

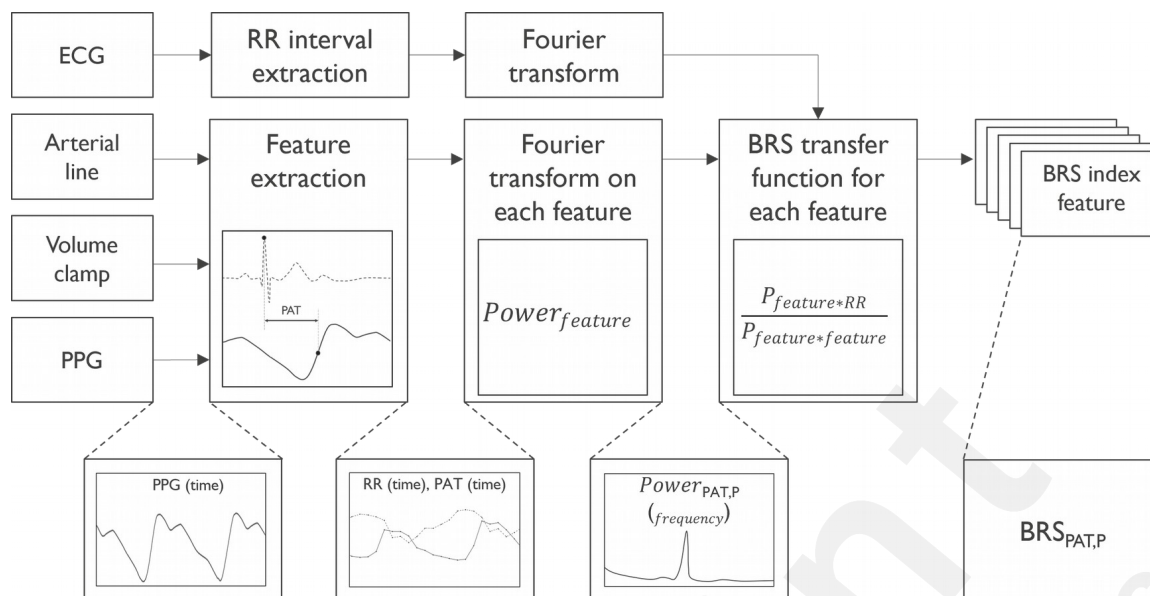


Figure 1.

Overview of the steps to compute BRS indices with example for PAT based on PPG. BRS: baroreflex sensitivity, PAT: pulse arrival time, PPG: photoplethysmography

Ambulatory 24-hour study

In addition, a single 24-hour recording on a healthy volunteer was used to demonstrate BRS trends under free living conditions. In a normotensive male (33 yrs.) a wearable prototype developed by imec was placed that recorded ECG and PPG for 24 hours. The ECG was placed in lead II configuration and the transmissive PPG sensor Nonin 8000J was placed on the left index finger. In addition, an ambulatory blood pressure measurement device (Suntech Medical Oscar2) recorded cuff-based oscillometric blood pressure from the left upper arm in intervals of 15 and 30 minutes during the day and night, respectively. This was a regular office day, including 8 hours of sleep, two walks and office work behind a desk.

Ethical considerations

The interventional study dataset was collected at Ziekenhuis Oost-Limburg in Genk, Belgium and has been approved by the institutional review board (ethical committee approval number 16/039U). All enrolled participants were compensated with a €150,- voucher. The ambulatory 24-hour feasibility data has been approved by the institutional review board of imec The Netherlands in Eindhoven, the Netherlands.

Both studies were conducted under the principles of the Declaration of Helsinki. All eligible participants were given the right to refuse participation and the right to withdraw from the study at any time. Written informed consent was collected from all participants prior to participation. To protect the participants' privacy, all data collected from this study were kept confidential and anonymized and were only accessible to the members of the research team.

Data analysis and statistics

Data preprocessing

Data was processed and analyzed using Matlab R2022a (Mathworks®). The relevant features in the pulse waveforms were computed from fiducial points detected in the first derivative signal, as described in detail by [32], see Figure 2. In brief, all data was band-pass filtered using a Butterworth low-pass filter with cut-off at 10Hz and high-pass filter acting as a differentiator. The differentiated signal is used to first find the upstroke, the local maximum of the differentiated signal. Next the other fiducial points, peak, foot, shoulder, secondary peak and dicrotic notch were extracted using adaptive thresholding. Timestamps of the fiducial points are used to calculate the rise and decay times, amplitudes and their ratio's.

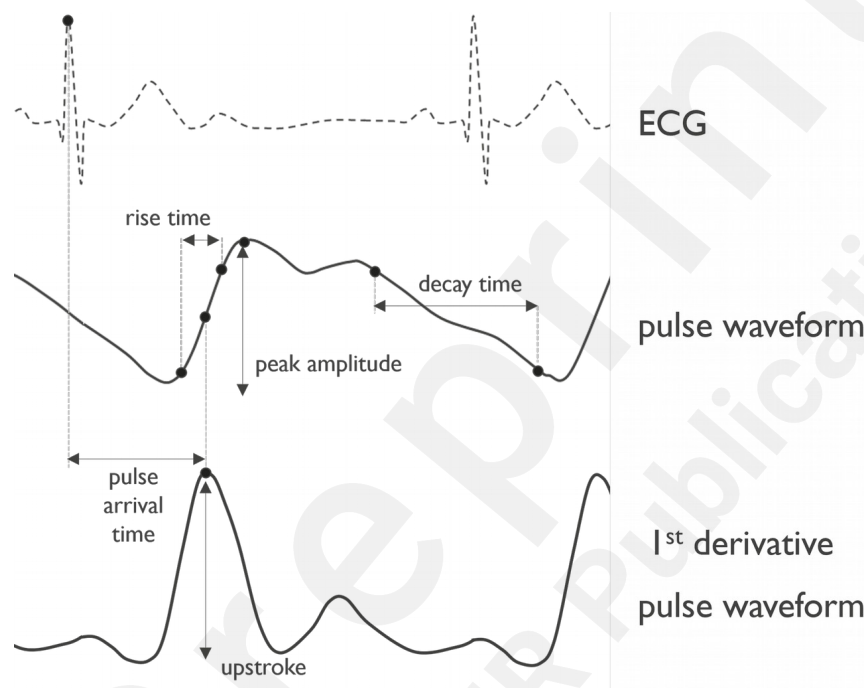


Figure 2.

Visual representation of the features as described. Dashed line is the ECG signal, the solid lines the pulse waveform from either PPG, volume clamp or arterial line and first derivative of the PPG (PPG'). ECG: electrocardiogram, PPG: photoplethysmography

Features

Features were computed per beat for all pulse waveforms, i.e., PPG, volume clamp and arterial line. Error: Reference source not found shows a visual representation of the derived features. Peak amplitude (PA) is the amplitude of the first peak of the PPG. Pulse upstroke (PUS) was defined as the amplitude of the peak in the first derivative of the PPG signal. Pulse arrival time (PAT) was defined as the delay between the R-peak from the ECG and the pulse upstroke in the PPG. Rise-Decay ratio (RDRatio) was defined as the ratio between the rise time (10% to 70% of the peak amplitude in the systolic phase) and decay time (70% to 10% of the peak amplitude in the diastolic phase).

Volume clamp and arterial line features were derived in a similar manner as described for PPG

(subscript P) and are indicated by the respective subscripts V and A. Systolic blood pressure (SBP) is the peak amplitude of either pressure pulse wave.



Transfer function

BRS indices of various modalities were calculated in the low frequency window (0.04-0.15 Hz) taking the average over all trials per intervention per subject. Data was resampled to 4 Hz and a first-order trend was removed. A transfer function was estimated with feature (SBP or surrogate) as input and heart rate (RR interval derived from the ECG) as output. The transfer function was defined as the ratio of the cross power spectral density of the input (x, respectively BP) and output (y, respectively RR interval) and the spectral density of the input (x):

$$H(f) = \frac{P_{xy}}{P_{xx}} = \frac{P_{feature * RR}}{P_{feature * feature}} \quad (1)$$

Coherence levels were determined between SBP (or a surrogate feature) and RR interval for each BRS index. Considering the number of unique data points per segment (120 data point with 50% overlap) the threshold coherence at 95% confidence is set at 0.14 [33,34].

Analysis of arterial line data

A structured analysis was done based on different BRS indices, calculated using the RR intervals from the ECG as input and as output the SBP from the arterial line ($BRS_{SBP,A}$ as gold reference) or other features as potential surrogates. The analysis included the following steps: **step 1** the direct comparison of BRS based on the systolic blood pressure for the arterial line ($BRS_{SBP,A}$) and volume clamp ($BRS_{SBP,V}$) and the corresponding feature peak amplitude of the PPG ($BRS_{PeakAmp,P}$). **Step 2** the comparison of various features (upstroke, PAT and RDRatio) obtained from the arterial line sensor, as this is the signal that is the most direct blood pressure recording with the highest signal to noise ratio. Followed by **step 3**, the comparison of BRS obtained from the same features (SBP /PeakAmp, upstroke, PAT and RDRatio) from arterial line and PPG. Finally, **step 4** a comparison of BRS based on different features (SBP /PeakAmp, pulse upstroke, PAT and RDRatio) obtained from volume clamp and PPG with the gold reference namely BRS obtained from arterial line systolic blood pressure.

Statistical analysis

For each subject and intervention BRS measures were computed across all modalities and features. To mitigate the impact of outliers, we calculated the BRS index as the median value derived from three repeated measurements. The precision of each BRS index within each subject (intra-subject precision) was determined by calculating the standard deviation of the error. This error is the difference between the median of the subject and the individual values. The result was then expressed as a percentage of the mean BRS indices across all subjects. Variation between subjects (inter-subject variation) was calculated by determining the standard deviation of the BRS indices. This was also expressed as a percentage of the mean BRS indices across all subjects. In the final analysis, the correlation among the various BRS indices was determined using both Pearson's and Spearman's correlation methods as not all BRS indices were normally distributed. It's important to note that the results from both the parametric (Pearson's) and non-parametric (Spearman's) methods were largely similar. Therefore, for simplicity, only the results derived from Pearson's correlation method are reported. The level of statistical significance was set to 0.05.

Analysis 24-hour data

The 24-hour dataset was processed in the same way as the interventional dataset with additional windowing. Based on results from arterial line data PAT and RDRatio were selected as the best option for 24h BRS features (see Results and Discussion). From the filtered continuous ECG and PPG data acquired by the wearable prototype, beat-to-beat RR intervals, PAT and RDRatio were computed. Both raw signals and extracted features were (dis-)qualified based on an integration of 5 objective criteria:

- 1) Any beat-to-beat samples 15s prior and 60s post the cuff inflation due to occlusion.
- 2) Beat segments in the PPG signal were qualified using a proprietary signal-to-noise ratio (SNR) algorithm wherein a reference signal template is defined by 5 consecutive beats, and the noise impacting the signal morphology (e.g. due to motion) is defined as deviation of individual beats from this template and disqualified by empirical thresholds.
- 3) Absolute thresholding of beat-to-beat pulse arrival time (PAT) samples deviating from a physiologically valid range, under assumption of a fixed distance and pulse wave velocities from 2-10 m/s.
- 4) Variability thresholding of drastic beat-to-beat changes in heart rate and PAT deviating from physiologically valid ranges of heart rate variability and PAT variability (respectively sympathetic changes in blood pressure and arterial stiffness).
- 5) Disqualification of 1-minute epochs of persistent low-quality, wherein the more robust ECG signal defines the expected number of cardiac cycles, and at least 50% of the PPG beats ought to be present and not undetected or disqualified by the previous criteria.

From here, $BRS_{PAT,P}$ and $BRS_{RDRatio,P}$ were calculated over a 4-minute sliding window (75% overlap), whereafter the median was taken from all BRS values exceeding the coherence threshold of 0.14 within a 1-hour sliding window (75% overlap). Cuff-based blood pressure was measured every 15 minutes during the day and every 30 minutes during the night, providing at least two reference BP measurements included within the 1-hour sliding window. Blood pressure readings were qualified for validity by proprietary software of the ambulatory blood pressure monitor (Suntech Medical Oscar2). The subject was also asked to stand still during the cuff inflation, which ensures stability ECG and PPG signals from the wearable system. For all clarity, no BRS was computed from the ambulatory cuff blood pressure due to overlong sampling intervals. The BRS coherence was calculated over 4-minute windows per feature and the median coherence for the subsequently computed 1-hour window held only the samples above the coherence threshold. Moreover, given the longitudinal character of the 24-hour dataset, heart rate variability (HRV) as indicator of autonomous nervous system activity was computed for relevant frequency bands: high frequency HRV_{HF} , reflecting the parasympathetic-driven respiratory band around 15 cycles per minute or 0.25 Hz on average, and the low frequency HRV_{LF} , reflecting baroreflex activity (balanced by sympathetic & parasympathetic activity) around 6 cycles per minute or 0.1 Hz on average [35]. Consistent with other features, the HRV indices were also averaged with a 1-hour sliding window. Ultimately, for visual inspection, all 1-hour averaged features are displayed on a time grid of 15-minute intervals.

Results

Arterial line intervention study

The dataset consisted of 28 male volunteers. Per subject three sessions were recorded of several interventions, including the interventions analyzed here: rest, paced breathing and hand grip. A total of 420 segments were analyzed to extract BRS values of different (surrogate) features. By averaging over the repeated measures, we obtained 140 data points for each subject and each intervention.

For all subjects and interventions the mean of the $BRS_{SBP,A}$ and $BRS_{SBP,V}$ were 8.1 ± 3.0 ms/mmHg and 6.6 ± 3.0 ms/mmHg, respectively with intra-subject precision of 15% for $BRS_{SBP,A}$ 21% for $BRS_{SBP,V}$ respectively. The PPG-based features show mean values of 3.2 ± 1.9 a.u for $BRS_{PeakAmp,P}$, 93 ± 60 a.u. for $BRS_{Upstroke,P}$, 1.8 ± 1.7 ms for $BRS_{RDRatio,P}$, and 7.7 ± 4.1 ms/ms for $BRS_{PAT,P}$.

The intra-subject precision for the PPG-based features is on average higher: 54% for $BRS_{PeakAmp,P}$, 56% for $BRS_{Upstroke,P}$, 44% for $BRS_{RDRatio,P}$. The intra-subject precision of the $BRS_{PAT,P}$ approaches that of the traditional BRS index (23% for $BRS_{PAT,P}$ compared to 20% and 26% for $BRS_{SBP,A}$ and $BRS_{SBP,V}$ respectively). In all cases the inter-subject variation (37% for $BRS_{SBP,A}$, 46% for $BRS_{SBP,V}$, 59% for $BRS_{PeakAmp,P}$, 64% for $BRS_{Upstroke,P}$, 91% for $BRS_{RDRatio,P}$ and 53% for $BRS_{PAT,P}$) exceeded the intra-subject precision.

As described in the methods section, analysis was done in a step-by-step approach.

Step 1

Direct comparison between the peak amplitude feature between sensor modalities showed that the correlation between $BRS_{SBP,A}$ and $BRS_{SBP,V}$ was 0.78. A lower correlation was found between the $BRS_{SBP,A}$ and $BRS_{PeakAmp,P}$ ($r = 0.59$) and $BRS_{SBP,V}$ and $BRS_{PeakAmp,P}$ ($r = 0.56$). These correlations were all highly significant. Note that the absolute values of the $BRS_{PeakAmp,P}$ cannot be compared to that of the SBP based BRS values as the unit is different.

Table 1. Correlation of baroreceptor sensitivity between alternative features derived from arterial line and systolic blood pressure from arterial line.

arterial features	line	correlation
$BRS_{PAT,A}$		0.46*
$BRS_{Upstroke,A}$		0.54*
$BRS_{RDRatio,A}$		0.66*

Pearson's correlation between baroreceptor sensitivity index (BRS) of features extracted from arterial line (_A) with respect to the gold reference feature systolic blood pressure from arterial line ($BRS_{SBP,A}$). * Indicates significant correlation ($p < 0.05$). $BRS_{PAT,A}$, $BRS_{Upstroke,A}$, and $BRS_{RDRatio,A}$ are BRS surrogate indices obtained from arterial derive features pulse arrival time, upstroke gradient and rise time-decay time ratio, respectively. For details about the features see Error: Reference source not found and Methods.

Step 2

In Table 1, the correlation of BRS obtained from different features from the arterial line sensor showed that $BRS_{SBP,A}$ vary from strong to moderate for the different surrogate features $BRS_{RDRatio,A}$ ($r = 0.66$), $BRS_{Upstroke,A}$ ($r = 0.54$) and $BRS_{PAT,A}$ ($r = 0.46$), all $p < 0.05$

Step 3

Comparing the same feature between arterial line and PPG sensor modalities, revealed that for peak-amplitude and upstroke derived BRS indices the correlation was moderate and weak, respectively. In contrast, the correlation between PAT and RDRatio derived BRS indices across the sensor modalities was strong, see Error: Reference source not found.

Table 2. Correlation between BRS extracted from arterial line (A) and PPG (P)

arterial line		PPG	correlation
$BRS_{SBP,A}$	VS	$BRS_{PeakAmp,P}$	0.59*
$BRS_{PAT,A}$	VS	$BRS_{PAT,P}$	0.75*
$BRS_{Upstroke,A}$	VS	$BRS_{Upstroke,P}$	0.29*
$BRS_{RDRatio,A}$	VS	$BRS_{RDRatio,P}$	0.49*

Baroreflex sensitivity (BRS) from arterial line (subscript _A) and photoplethysmography (PPG or subscript _P) using different features namely, systolic blood pressure (SBP), peak amplitude (PeakAmp), pulse arrival time (PAT), pulse upstroke (Upstroke) and rise time-decay time ratio (RDRatio). For details about the features see Error: Reference source not found and Methods. Note that primary peak (PeakAmp) of arterial line data is the systolic blood pressure (SBP).

* Indicates significant correlation ($p < 0.05$)

Step 4

The comparison of features derived from the PPG, as target sensor, and arterial line SBP, as gold standard or volume clamp are shown in Error: Reference source not found. All correlations in step 4 were significant. As expected, the best correlation was observed between $BRS_{SBP,A}$ and $BRS_{SBP,V}$ ($r=0.78$). The PPG based BRS surrogates had a strong to moderate correlation with $BRS_{SBP,A}$ where $BRS_{PAT,P}$ (0.66) had slightly higher values compared to $BRS_{PeakAmp,P}$, $BRS_{RDRatio,P}$ and $BRS_{Upstroke,P}$ (0.59, 0.56 and 0.54 respectively). However, when $BRS_{SBP,V}$ was used as alternative reference to $BRS_{SBP,A}$ in the PPG based surrogates that are based on PPG timing, a lower correlation was found with $BRS_{SBP,V}$ with respect to $BRS_{SBP,A}$ (0.52 vs 0.66 and 0.46 vs 0.56 for PAT and RDRatio, respectively). In contrast, the PPG amplitude derived parameters, i.e., PeakAmp and upstroke had similar or even higher correlation with $BRS_{SBP,V}$ compared to $BRS_{SBP,A}$ (0.56 vs 0.59 and 0.64 vs 0.54, respectively see Error: Reference source not found).

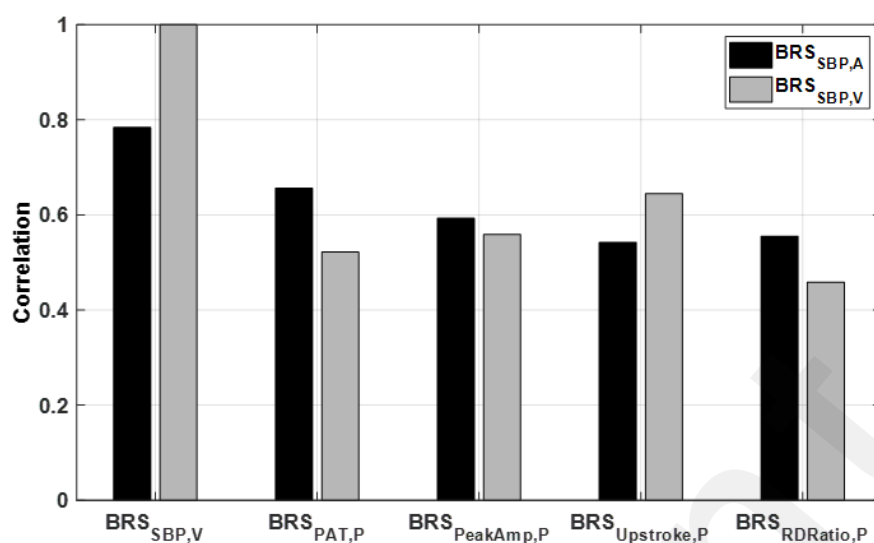


Figure 3.

Correlation of a baroreflex sensitivity (BRS) indices based on a selection of PPG features with BRS from systolic blood pressure measured by arterial line ($BRS_{SBP,A}$, black) and the volume clamp method and ($BRS_{SBP,V}$, grey). The BRS indices from PPG features $BRS_{PAT,P}$, $BRS_{PeakAmp,P}$, $BRS_{Upstroke,P}$, $BRS_{RDRatio,P}$ are based PPG and use pulse arrival time, peak amplitude, upstroke gradient and rise time-decay time ratio, respectively. PPG: photoplethysmography. All correlations were significant ($p < 0.05$).

Table 3. Correlation between BRS extracted from volume clamp (V) and PPG (P) and gold reference BRS based on arterial line derived systolic blood pressure ($BRS_{SBP,A}$)

Correlation to $BRS_{SBP,A}$			
	rest	pacedB	handgrip
$BRS_{SBP,V}$	0.66*	0.88*	0.78*
$BRS_{PAT,P}$	0.69*	0.52*	0.62*
$BRS_{PeakAmp,P}$	0.56*	0.51*	0.53*
$BRS_{Upstroke,P}$	0.33	0.65*	0.16
$BRS_{RDRatio,P}$	0.75*	0.50*	0.46*

Baroreflex sensitivity (BRS) obtained from systolic blood pressure measured by arterial line ($BRS_{SBP,A}$) is correlated to BRS obtained from SBP measured using volume clamp ($BRS_{SBP,V}$). In addition, BRS from photoplethysmography (PPG) is obtained with pulse arrival time (PAT), peak amplitude (PeakAmp), pulse upstroke (Upstroke) and rise time-decay time ratio (RDRatio). Note that primary peak (PeakAmp) of arterial line and volume clamp data is the systolic blood pressure. Interventions are rest, paced breathing (pacedB) and handgrip. For further details see Methods. *Indicates significant correlation ($p < 0.05$)

Interventions

The gold standard BRS, derived from arterial line SBP ($BRS_{SBP,A}$) exhibited an 11% increase during paced breathing and a 22% decrease during handgrip, compared to rest, see Error: Reference source not found. A similar pattern was observed for $BRS_{SBP,V}$ and $BRS_{PAT,P}$. However, the increase in BRS during paced breathing was more pronounced for these indices (58% and 42% respectively). The $BRS_{RDRatio,P}$ showed a comparable increase (54%) during paced breathing as $BRS_{SBP,V}$ and $BRS_{PAT,P}$ but its reduction during handgrip was more significant (60%). The changes in BRS calculated from the other features $BRS_{PeakAmp,P}$ and $BRS_{Upstroke,P}$ were considerably larger during paced breathing with increases of 133% and 155% respectively. At rest, the correlation between $BRS_{SBP,A}$ and both $BRS_{SBP,V}$ and $BRS_{PAT,P}$ was similar. However, during paced breathing, the correlation with $BRS_{SBP,A}$ decreased for $BRS_{PAT,P}$ but increased for $BRS_{SBP,V}$ (see Error: Reference source not found). The correlation between the other surrogate indices and the arterial line was generally lower across interventions, with the exception of $BRS_{RDRatio,P}$, which showed a high correlation with $BRS_{SBP,A}$ under rest conditions.

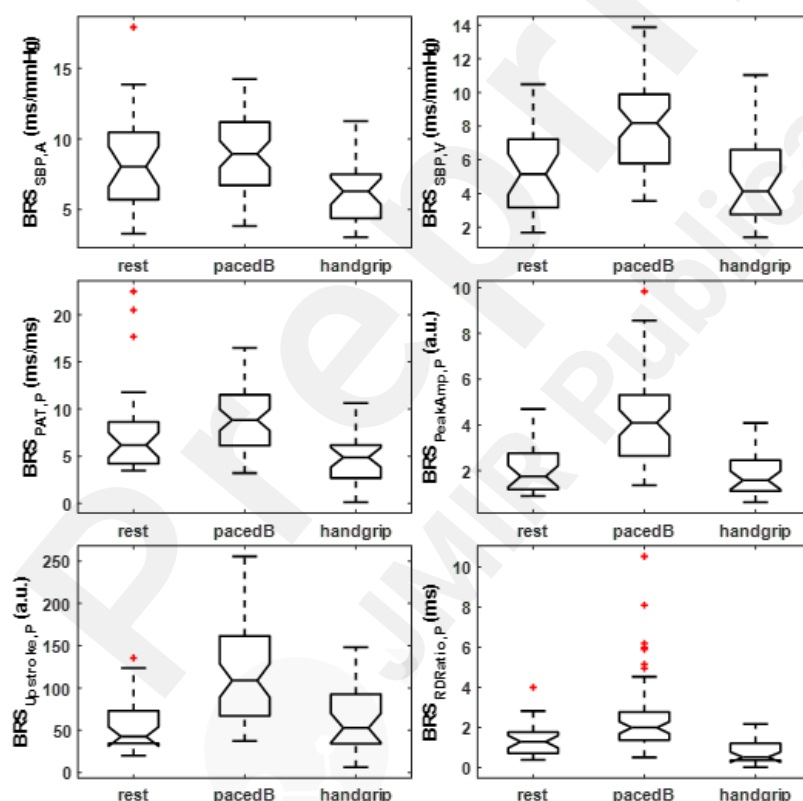


Figure 4.

Baroreflex sensitivity (BRS) indices of different features for each intervention namely: rest, paced breathing (pacedB), handgrip. $BRS_{SBP,A}$, $BRS_{SBP,V}$ are BRS indices based on systolic blood pressure measured by arterial line and volume clamp method, respectively. $BRS_{PAT,P}$, $BRS_{PeakAmp,P}$, $BRS_{Upstroke,P}$, $BRS_{RDRatio,P}$ are BRS indices measured using photoplethysmography using pulse arrival time, peak amplitude upstroke and rise time-decay time ratio, respectively.

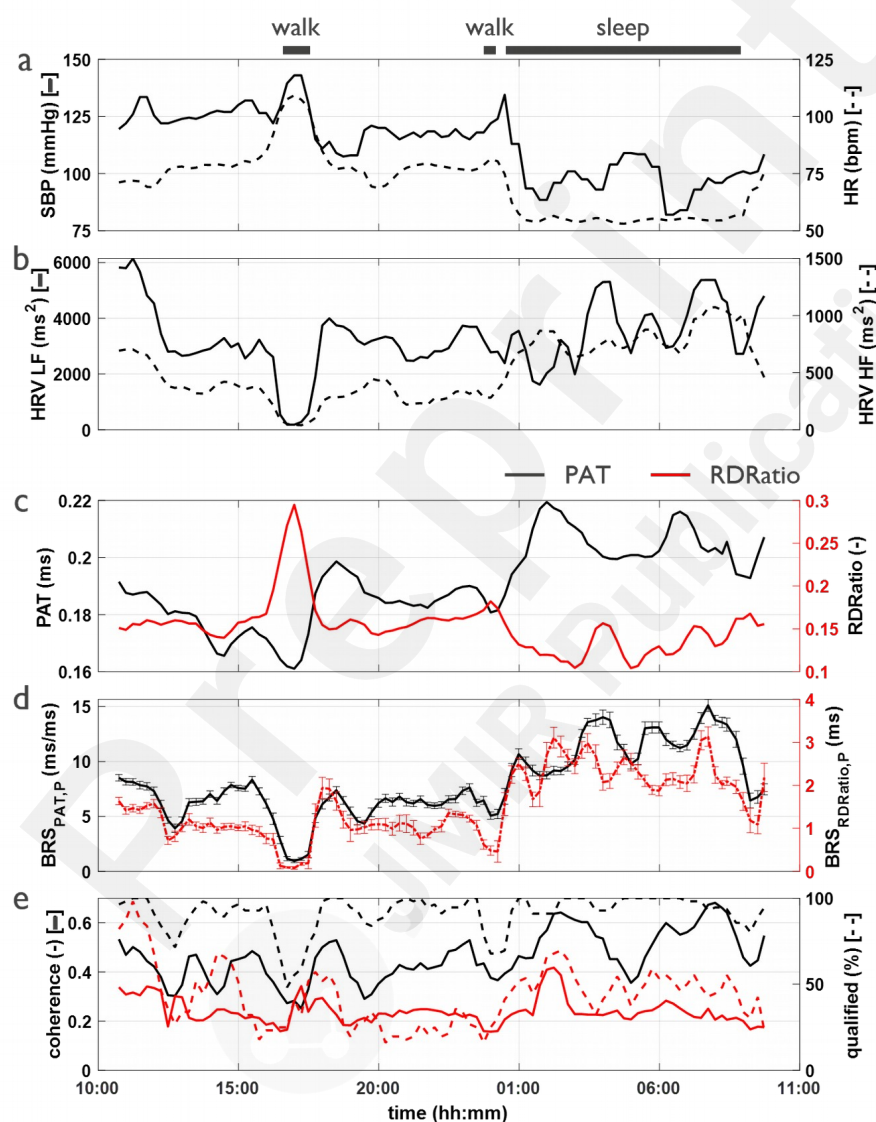


Figure 5.

Analysis of the 24-hour trends for an individual subject. a) trends of reference systolic blood pressure (based on upper arm cuff) and heart rate (HR) over time, b) trends of low frequency (HRV LF) and high frequency heart rate variability (HRV HF). c) trends in the features pulse arrival time (PAT, in black) and rise time-decay time ration (RDRatio, in red). d) Trends in baroreflex sensitivity calculated from pulse arrival time ($BRS_{PAT,P}$) and rise time - decay time ration ($BRS_{RDRatio,P}$) the error bars indicate the standard error of the BRS values within 15-minute segment and e) trends in coherence and qualified percentage of, $BRS_{PAT,P}$ and $BRS_{RDRatio,P}$ values. The horizontal bars on top describe show the activities (walking and sleeping) of the individual.

Ambulatory 24-hour study

The exploratory 24-hour BRS recording from a healthy subject in free-living conditions is shown Error: Reference source not found. Except for a 1-hour walk around 17:00 hours and a short walk before 24:00 hours, the subject spent most of the day doing sedentary work. The subject was in bed between 24:00 hours and 8:00 hours in the morning. The lowest BRS was observed in the afternoon around 17:00 hours when the subject went for a walk, as also indicated by relatively high HR and low HRV. The activities were self-reported.

The BRS indices show a clear pattern over the 24 hours, with both $BRS_{PAT,P}$ and $BRS_{RDRatio,P}$ being at a lower level during the day and increasing at night, effectively during sleep. Given the inverse relation between PAT and SBP, the mirrored pattern of increasing SBP and decreasing PAT (and vice versa) is clearly evident, also during walking activities with contributing HR.. The correlation coefficient between PAT and RDRatio with SBP were high at -0.90 and -0.63 (both $p \leq 0.05$), respectively throughout the 24-hour trajectory. This confirms the essential validity of the observed trends based on the processed and qualified data. Interestingly, the correlation between SBP with the derived BRS indices ($BRS_{PAT,P}$ and $BRS_{RDRatio,P}$) was equally high and significant ($r = -0.74$ vs $r = -0.75$ both $p \leq 0.05$, respectively), while their mutual correlation was better ($r = 0.84$, $p \leq 0.05$). At a close look, the rhythmic oscillations during the night cannot only be seen in $BRS_{PAT,P}$ and $BRS_{RDRatio,P}$ but also in HRV_{LF} . Unlike HRV_{LF} , HRV_{HF} does not show any significant oscillations during the night, but instead displays a clear difference in absolute BRS level between day and night, which could not be observed in HRV_{LF} . Coherence of $BRS_{PAT,P}$ also show a slight increase during the night. Except for a few datapoints during the walking activities, where the measurements were affected by motion artifacts, the percentage of $BRS_{PAT,P}$ above the coherence quality threshold of 0.14 never dropped below 80%, while the qualified coherence % of $BRS_{RDRatio,P}$ was significantly lower, as directly reflected in the coherence profile of $BRS_{RDRatio,P}$. At all times, even during the walking events where motion artifacts are to be expected, sufficient data is above coherence threshold ensuring valid median values throughout the day.

Discussion

This study illustrates that both the baroreflex sensitivity (BRS) based on pulse arrival time (PAT) and the rise time-decay time ratio (RDRatio) derived from photoplethysmography (PPG), serve as appropriate substitutes for the gold standard BRS obtained from arterial lines. This is substantiated by the highest correlation observed during rest, a comparable coefficient of variation within subjects,

as well as anticipated alterations during activities. Furthermore, the feasibility of these measures was successfully tested over a 24-hour period under free-living conditions. This underscores their potential applicability in real-world scenarios.

Evaluation of BRS index surrogates

Baroreflex sensitivity based on arterial line systolic blood pressure (SBP,A) is best correlated with BRS determined from pulse arrival time derived from photoplethysmography (PAT,P) signal: 66% of the variation in $BRS_{SBP,A}$ is explained by $BRS_{PAT,P}$. The correlation of other surrogates to $BRS_{SBP,A}$ is slightly lower. In almost all cases the inter-subject variation is higher than the intra-subject precision which suggests that these BRS features can be used to identify differences between individuals.

The baroreflex plays a crucial role in maintaining blood pressure, acting through various pathways to modulate heart rate, vascular resistance, and cardiac contractility. The challenge in determining the BRS non-invasively is measuring (systolic) arterial pressure as the gold standard method, arterial line, is invasive or obtrusive. The volume clamp method is an often-used non-invasive substitute to determine arterial pressure. It is known to overestimate the central arterial blood pressure [36] and shown to overestimate BRS in the low frequencies [37]. Nevertheless, it has been used as reference to validate other BRS methods, like those derived from PPG [10,24–26]. Comparing BRS using arterial pressure derived from the invasive arterial line with volume clamp method and PPG reveals the disputes and benefits of the methods. The BRS based on systolic blood pressure derived from the volume clamp method shows the best correlation of 0.78 with BRS based on systolic blood pressure from the invasive arterial line and a correlation of 0.59 with the BRS based on the systolic peak in the PPG signal. The latter is lower compared to results from others, reporting a correlation of 0.77 [10]. Nevertheless, our study population is considerably older (compared to 28.5 years), including relatively high blood pressure, lowering the BRS which increases the influence of noise, reducing the correlation. An underestimation of the BRS based on SBP from volume clamp method compared to the arterial line based SBP of 24% was reported [13], similar to the 19% reported here.

The three modalities, arterial line, volume clamp and PPG have differences and similarities important to consider. The volume clamp method uses a PPG signal as well. Although the PPG signal is not used to measure the arterial pressure directly, it is used to maintain a constant volume by adjusting the cuff pressure, such that it equals the finger arterial pressure. Therefore, in contrast to arterial line, both PPG and volume clamp methods are influenced by peripheral perfusion and, hence, temperature, motion and contact pressure. This could potentially cause errors when relating peripheral to systemic hemodynamic changes [15]. These errors would be visible between arterial line and volume clamp or PPG derived features but be similarly present between PPG and volume clamp derived features.

The range of BRS features derived from the PPG used here are also reported previously, like pulse upstroke, peak amplitude, pulse arrival time and rise-time [10,38]. Additionally, models estimating systolic blood pressure using PPG use pulse arrival time (PAT) as the most important feature [14]. Pulse arrival time and rise/decay ratio from PPG correlate equally well with $BRS_{SBP,A}$ and $BRS_{SBP,V}$. Primary peak and pulse upstroke from PPG correlate well with $BRS_{SBP,V}$, but notably less with $BRS_{SBP,A}$. Error: Reference source not found suggesting volume clamp underestimates the performance of $BRS_{PAT,P}$ and $BRS_{RdRatio,P}$ and overestimates the performance of others like $BRS_{Upstroke,P}$. These results suggest that $BRS_{SBP,V}$ can be used as method to measure BRS in a non-invasive way, however, care should be taken to check performance of other (PPG-derived) BRS indices using this method.

Coherence was used as a measure of BRS reliability. It assesses the similarity of two signals in the frequency domain; if the heart rate and arterial pressure have similar frequency components as a

result of the baroreflex, the BRS becomes more reliable.

BRS changes from rest to controlled activities show how well a feature tracks the baroreflex effects of the interventions. The correlation between SBP and heart rate increases for paced breathing intervention therefore an increase in BRS during paced breathing is expected. Especially at 6 breaths per minute at which the heart rate and blood pressure oscillation amplitude are increased [39]. Expectedly, during paced breathing, BRS increases for $BRS_{SBP,A}$ and all BRS surrogates as compared to rest. However, the correlation between $BRS_{SBP,A}$ and $BRS_{PAT,P}$ decreases with paced breathing. It has been shown that during slow breathing of around 6 breaths/min the BRS is overestimated since, in this case, other mechanisms in which respiration influences heart rate also concentrate in the LF frequency band [40]. During the hand grip intervention, the coherence is increased, likely because of a thoracic pressure increase damping the oscillatory pressure effect of respiration (data not shown). An overestimation of the BRS changes based on volume clamp and PPG compared to $BRS_{SBP,A}$ is found, which is more prominent during paced breathing compared to hand grip or hand grip recovery.

Ambulatory 24-hour study

The adequate robustness found for the BRS surrogates during controlled activities suggests a wider applicability for BRS monitoring, which was further assessed by means of a 24-hour recording under free-living conditions. Based on the structured analysis, the BRS based on PAT and RDRatio were considered the most promising to test for the 24-hour ambulatory, it had the lowest intra-subject variation and highest correlation with $BRS_{SBP,A}$ during rest.

A wearable prototype for continuous ECG and PPG signal acquisition allowed for computation of beat-to-beat PAT, RDRatio and RR intervals, and thereby enabled the observation of characteristic patterns in $BRS_{PAT,P}$, $BRS_{RDRatio,P}$ and HRV.

The BRS indices were found to be higher during the night as compared to daytime, which is in line with previous experiments where BRS was obtained from an arterial line [28,41,42]. This expected behaviour of increasing nighttime BRS (and a coherence up to 0.6) could be explained by the absence of other inhibitory influences on the baroreflex like emotional behavior and somatic afferent influences stimulated by muscle contraction, as proposed by [41].

In preceding 24-hour BRS studies, oscillatory patterns of BRS during nighttime were less prominent [28,30,43], likely because these studies either average over subjects or longer time windows and typically report one datapoint per hour (unlike the 15-minute interval in this study). Meanwhile, studies focusing on sleep stages do show an increase in baseline BRS during the night and oscillations in BRS and HRV_{LF} between rapid eye movement (REM) and non-REM sleep stages [44]. Supported by the findings from the interventional study and the coherence with HRV_{LF} , the observed patterns in the proposed BRS indices $BRS_{PAT,P}$ and $BRS_{RDRatio,P}$ undoubtedly reflect nocturnal BRS oscillations. Moreover, the frequency of oscillations also appears to be in line with the typical duration and cycle times of adult sleep stages [45]. However, this remains to be further investigated with proper reference technology and in a larger population.

Furthermore, the proposed BRS indices may add value beyond existing HRV metrics. That is, both BRS indices show the baseline increase and nocturnal oscillations, whereas HRV_{LF} does not show a clear baseline increase and HRV_{HF} does not show oscillations, and its baseline increase may also be driven by different nocturnal respiration levels. Meanwhile, oscillations of $BRS_{PAT,P}$ tend to compare higher with HRV_{LF} , yet $BRS_{RDRatio}$ seems to be more indicative of higher frequency contributions.

Regarding reliability of the proposed indices, $BRS_{PAT,P}$ shows constantly high coherence throughout the 24 hours. Even during activity, a sufficient percentage of qualified samples is present, which may be further enhanced with basic signal and feature qualification strategies. Although the coherence of $BRS_{RDRatio}$ is substantially lower, it also remains above the threshold constantly with sufficient

qualified samples. In terms of usability and technology integration, this may become a relevant compromise given that $BRS_{RDRatio,P}$ holds the theoretical advantage to be computed using a (peripheral) PPG, hence without an ECG.

Clinical implications

The nature of the PPG sensor also allows for free-living recordings, enabling to monitor the BRS of the patients on day-to-day activities. The obtained results from the 24-hour study are encouraging future research, considering the wide range of clinical applications for longitudinal BRS monitoring: as prognostic tool for heart attacks and arrhythmias not only as single point measurement but also during sleep [11] and for cardiac mortality in patients with renal failure [46], or as cardiac as predictor of outcome after surgery [47]. Moreover, present knowledge may be enhanced in day-to-day assessment of spontaneous BRS, which previously relied on 8-minute recordings on two consecutive days [48]. Variations in the 24-hour recordings between young and elderly people have also been reported [28]. Establishing a 24-hour recording could therefor show not only the BRS in short blood pressure changes but also on circadian blood pressure patterns. Ultimately, longitudinal BRS monitoring bears large potential for hypertension diagnostics, in particular for primary hypertension whose origin is widely unknown.

Limitations

The study on arterial lines does present certain limitations, primarily due to the relatively limited sample size and the inclusion of only male subjects. Further research is required to examine the impact of factors such as age and arterial stiffness on the Baroreflex Sensitivity (BRS) indices, as well as to explore their interrelationships. Such comprehensive analysis necessitates the involvement of larger and more diverse cohorts. Overall, these preliminary patterns of the $BRS_{PAT,P}$ and $BRS_{RDRatio,P}$ over a 24-hour period under free-living condition support the findings from the controlled interventional study, demonstrating that it is possible to use PAT and RDRatio derived from the PPG signal to estimate the BRS. However, the key limitation of the 24-hour study is the confinement to a single subject but the findings give rise to further expand this study to investigate circadian and nocturnal BRS patterns in both healthy subjects, and, given the clinical relevance, also patient cohorts.

Conclusions

Baroreflex sensitivity determined from pulse arrival time or rise decay time ratio in a photoplethysmography signal, are best correlated with BRS based on arterial line systolic blood pressure. The $BRS_{PAT,P}$ and $BRS_{RDRatio,P}$ also follow the $BRS_{SBP,A}$ during different physical activities. Moreover, it allows for 24-hour BRS recordings, in which the expected circadian rhythm patterns are present.

Funding Statements: This research is part of the Individualised Care from Early Risk of Cardiovascular Disease to Established Heart Failure (iCARE4CVD) project. iCARE4CVD has received funding from the Innovative Health Initiative Joint Undertaking (IHI JU) and BreakthroughT1D under grant agreement No. 101112022. The JU received support from the

European Union's Horizon Europe research and innovation program and COCIR, EFPIA, Vaccines Europe, EuropaBio and MedTech Europe

Data availability: Data Availability Statement: The data is owned by IMEC and the authors do not have permission to share the data publicly as we are bound to the European General Data Protection Regulation (GDPR) as well as the subjects' consent, stating that data may only be used for specific purposes and not be shared with 3rd parties. This is because the dataset comprises personal identifiable data, which not only holds for demographics but also applies to electrocardiogram or arterial pressure waveforms. That being clarified, there may be ways to make anonymized or minimized data available on requests. However, this must be governed by a data sharing and/or processing agreement, which limits the use of the data (e.g. only to consented purpose, with no attempts to re-identify subjects, etc.). Please contact privacy@imec.nl.

Conflict of interest: no conflict of interest to declare.

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Abbreviations

ABP or A (subscript), arterial line blood pressure

AC: alternating current (pulsatile component)

BMI: body mass index

BRS: baroreceptor sensitivity

BP: blood pressure

DC: direct current (baseline)

ECG: electrocardiogram

GDPR: general data protection regulation

HF: high frequency

LF: low frequency

PPG or P (subscript): photoplethysmography

PAT: pulse arrival time

PA (subscript), peak amplitude

PUS (subscript), pulse upstroke

RDRatio: rise-time decay-time ratio

SBP: systolic blood pressure

SNR: signal to noise ratio

RR: time interval and between two R-peaks ECG

TF: transfer function

V (subscript): volume clamp

Generative AI: no generative AI was used in to right this manuscript.

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Figure Legends

Figure 6.

Overview of the steps to compute BRS indices with example for PAT based on PPG. BRS: baroreflex sensitivity, PAT: pulse arrival time, PPG: photoplethysmography

Figure 7.

Visual representation of the features as described. Dashed line is the ECG signal, the solid lines the pulse waveform from either PPG, volume clamp or arterial line and first derivative of the PPG (PPG'). ECG: electrocardiogram, PPG: photoplethysmography

Figure 8.

Correlation of a baroreflex sensitivity (BRS) indices based on a selection of PPG features with BRS from systolic blood pressure measured by arterial line ($BRS_{SBP,A}$, black) and the volume clamp method and ($BRS_{SBP,V}$, grey). The BRS indices from PPG features $BRS_{PAT,P}$, $BRS_{PeakAmp,P}$, $BRS_{Upstroke,P}$, $BRS_{RDRatio,P}$ are based PPG and use pulse arrival time, peak amplitude, upstroke gradient and rise time-decay time ratio, respectively. PPG: photoplethysmography. All correlations were significant ($p < 0.05$).

Figure 9.

Baroreflex sensitivity (BRS) indices of different features for each intervention namely: rest, paced breathing (pacedB), handgrip. $BRS_{SBP,A}$, $BRS_{SBP,V}$ are BRS indices based on systolic blood pressure measured by arterial line and volume clamp method, respectively. $BRS_{PAT,P}$, $BRS_{PeakAmp,P}$, $BRS_{Upstroke,P}$, $BRS_{RDRatio,P}$ are BRS indices measured using photoplethysmography using pulse arrival time, peak amplitude upstroke and rise time-decay time ratio, respectively.

Figure 10.

Analysis of the 24-hour trends for an individual subject. a) trends of reference systolic blood pressure (based on upper arm cuff) and heart rate (HR) over time, b) trends of low frequency (HRV LF) and high frequency heart rate variability (HRV HF). c) trends in the features pulse arrival time (PAT, in black) and rise time-decay time ration (RDRatio, in red). d) Trends in baroreflex sensitivity calculated from pulse arrival time ($BRS_{PAT,P}$) and rise time - decay time ration ($BRS_{RDRatio,P}$) the error bars indicate the standard error of the BRS values within 15-minute segment and e) trends in coherence and qualified percentage of, $BRS_{PAT,P}$ and $BRS_{RDRatio,P}$ values. The horizontal bars on top describe show the activities (walking and sleeping) of the individual.

Supplementary Files

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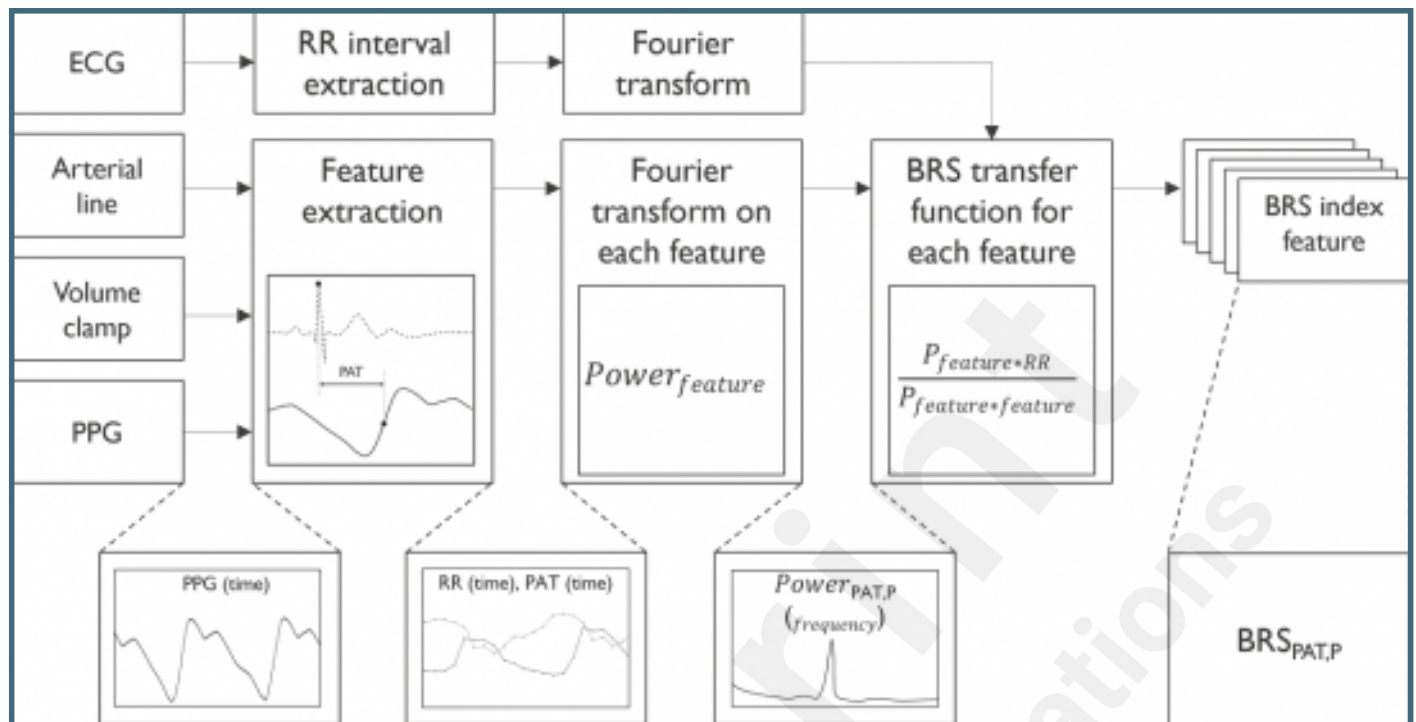
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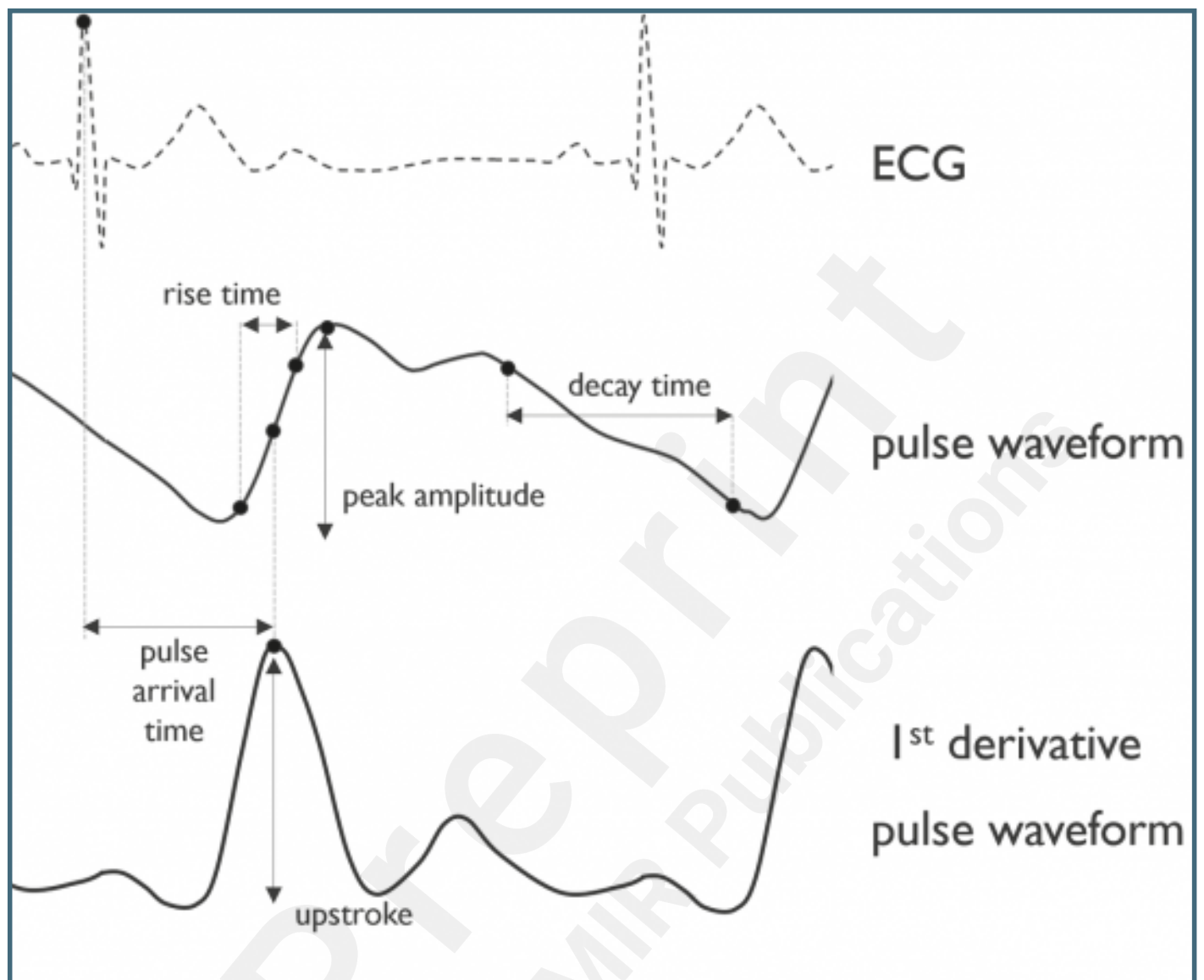
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Figures

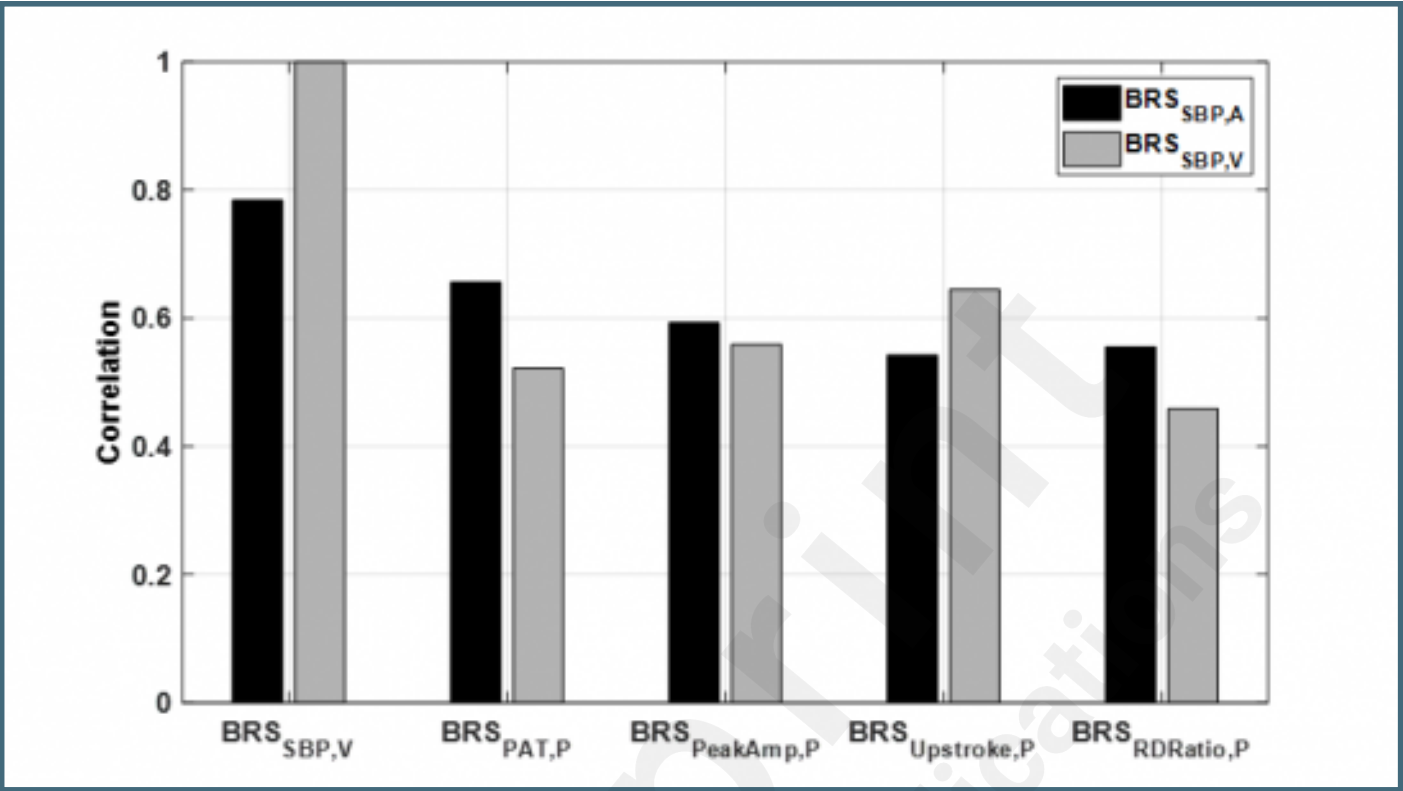
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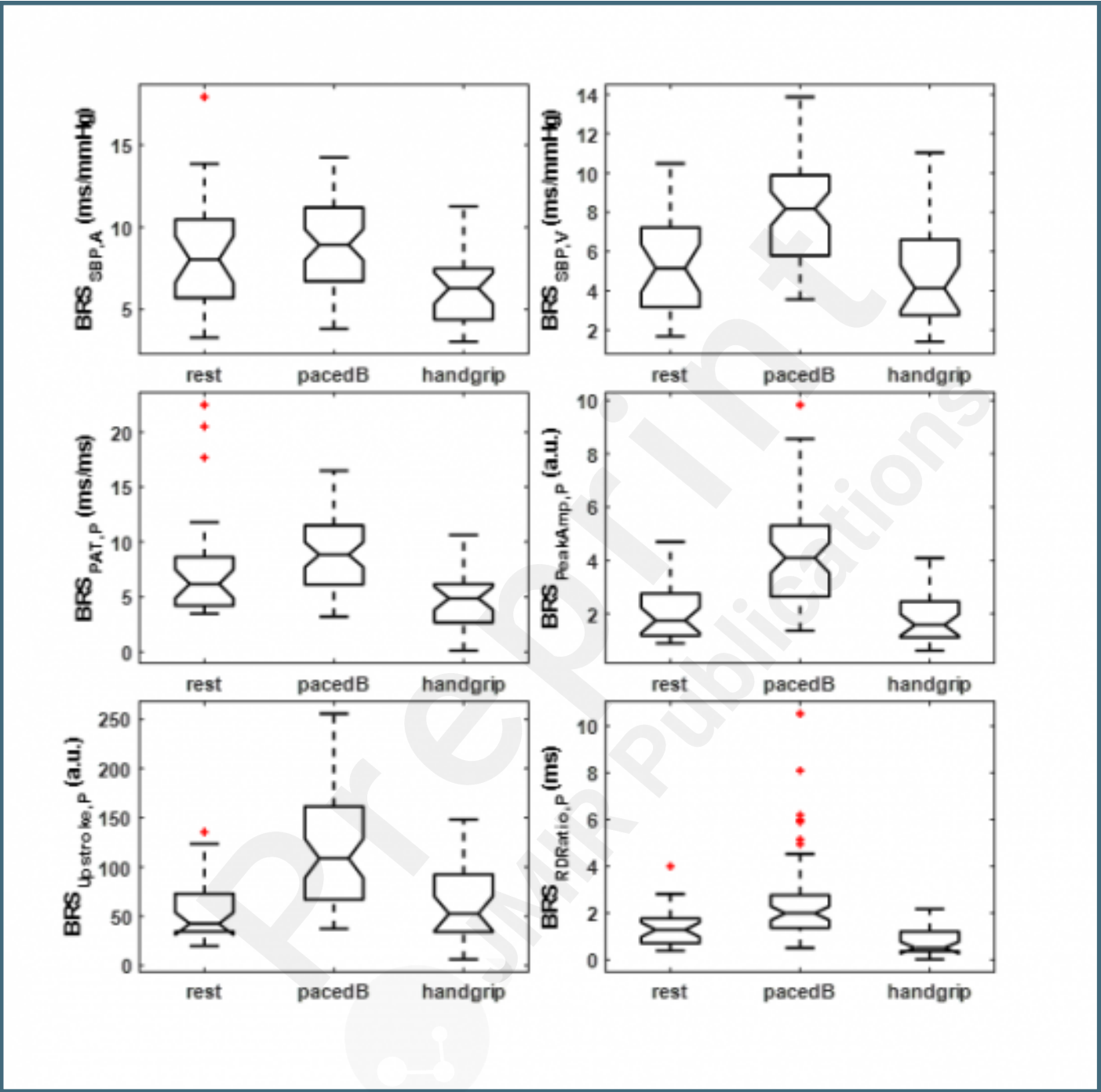
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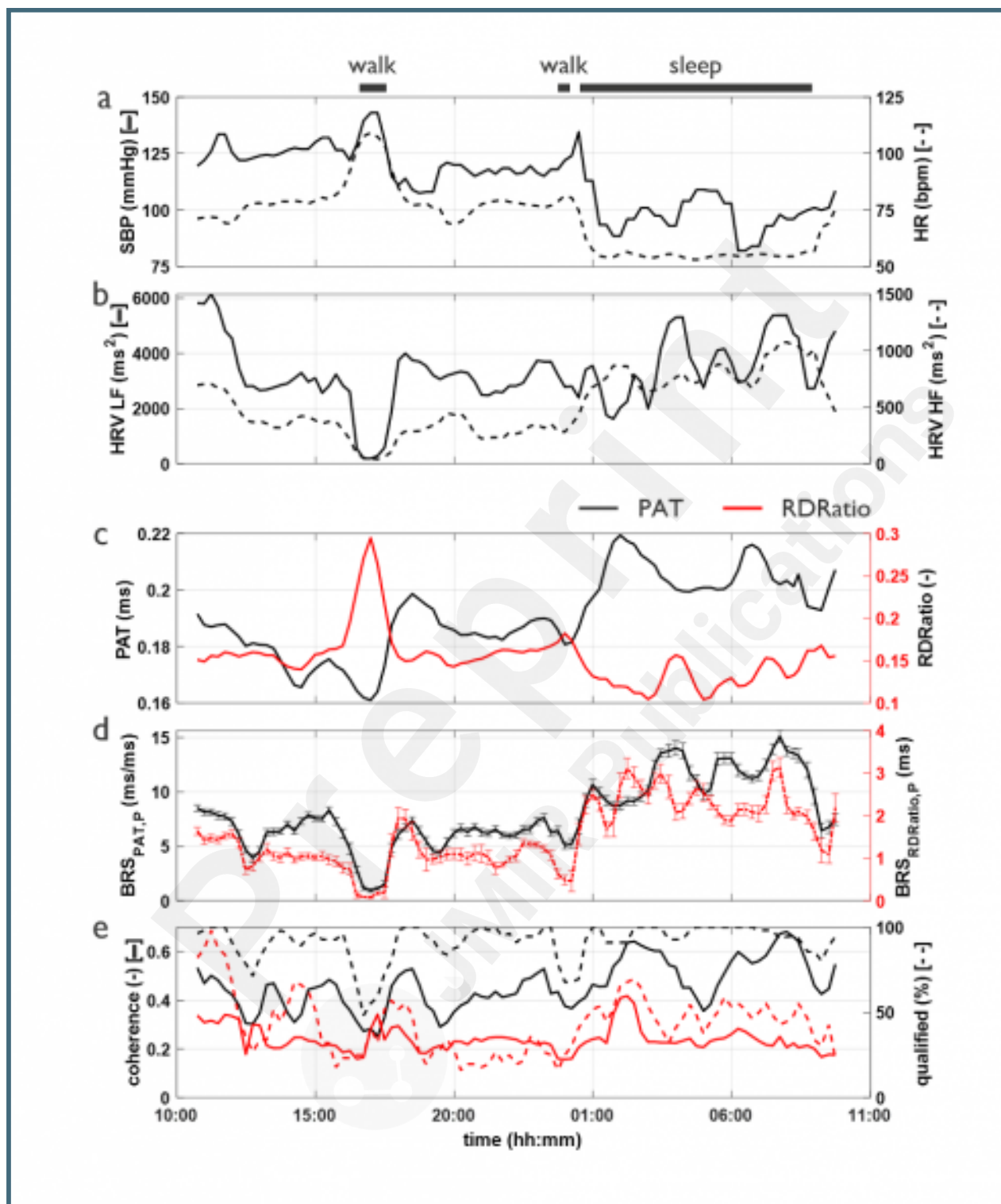
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