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Short communication

Non-invasive approach for the assessment of sympathetic baroreflex function: A feasibility study

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ABSTRACT

Background: Evaluation of sympathetic baroreflex (sBR) function in humans requires intra-neural recording of muscle sympathetic nerve activity (MSNA) by microneurography.
Aims: We proposed noninvasive approach for the evaluation of sBR function by applying the threshold-analysis (traditionally, based on MSNA) to systemic vascular resistance (SVR) measurement by photoplethysmography.
Methods & results: In nine healthy subjects (5 M; age: 25 ± 5y), the threshold-analysis was calculated twice: using MSNA and SVR. Both methods yield comparable results in men (T_{50}(burst-vs.-svr): CV = 8.8%, r > 0.9; $Slope_{(burst\text{-}svr)}$: CV = 30.1%; r > 0.9), but not in women.
Conclusions: SVR-based threshold-analysis is feasible in healthy young subjects and provides a promising alternative to the traditional MSNA-based approach.

1. Introduction

Sympathetic vasoconstrictor outflow to muscle (*muscle sympathetic nerve activity*, MSNA) is regulated by the arterial baroreflex in a beat-to-beat fashion. Rises in arterial blood pressure (ABP) lead to immediate sympathoinhibition, while falls in ABP are shortly followed by MSNA bursts (Rudas et al., 1999; Sundlof and Wallin, 1978; Wallin et al., 1974; Hart et al., 2010). The baroreflex-mediated relation between diastolic blood pressure (DBP) and MSNA burst occurrence (recorded under steady-state resting conditions) is used in the threshold-analysis, an established tool for the evaluation of *sympathetic baroreflex* (sBR) *function* (Rudas et al., 1999; Sundlof and Wallin, 1978; Wallin et al., 1974; Hart et al., 2010). More specifically, for each cardiac cycle the value of DBP is determined and assigned to the appropriate DBP bin (the size of the DBP bin is usually fixed to 1 or 2 mmHg) and the percentage of heart beats associated with MSNA burst is plotted as a function of the mean DBP in the assigned bin. The results of the threshold analysis include: (i) a slope of the regression line relating the percentages of the burst-associated cardiac cycles and the DBP bins ($Slope_{burst}$, %/mmHg), and (ii) the DBP value at which 50% of the cardiac cycles were associated with a burst (T_{50}burst, mmHg, see Methods for details). $Slope_{burst}$ was found to be a robust measure of sBR sensitivity (Hart et al., 2010). Lower values of $Slope_{burst}$ indicate greater increase in burst occurrence probability for a given *decrease* in DBP (and thereby higher sBR sensitivity) (Hart et al., 2010). In turn, T_{50}burst represents a midpoint of sBR operating range and therefore lower values of T_{50}burst may indicate that sBR is active at lower DBPs (the threshold for sBR activation is lower) (Hart et al., 2010; Kienbaum et al., 2001). Under certain physiological conditions, sBR operating range may be shifted without any concomitant change in sBR sensitivity (Querido et al., 2011), thus it seems reasonable to use both, $Slope_{burst}$ and T_{50}burst in the studies on sBR physiology.

While the sBR sensitivity and threshold describe the *vascular* response from baroreceptors, heart rate (HR) changes to ABP rise/fall (*cardiac baroreflex sensitivity*, cBRS) provide an insight into the *cardiac* component (Mortara et al., 2000; La Rovere et al., 2008). Although both components contribute importantly to buffering acute changes of ABP in humans, our knowledge on cBRS in health and disease far exceeds the available data on sBR function. One possible reason is that the measurement of MSNA in humans (by microneurography) is time-consuming and technically difficult, and therefore impractical in a clinical setting (Gandevia and Hales, 1997).

We proposed a novel, non-invasive approach for the evaluation of sBR function by modifying the original MSNA-based threshold-analysis (Sundlof and Wallin, 1978; Wallin et al., 1974; Hart et al., 2010; Kienbaum et al., 2001). Briefly, we attempted to perform the threshold-analysis with photoplethysmography-derived systemic vascular resistance (SVR) instead of MSNA. The agreement between *MSNA-based* and *SVR-based* threshold-analysis was studied in a small group of healthy volunteers to assess the feasibility of the proposed method.

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Previous reports demonstrated that the tight relationship between MSNA and SVR at rest observed in young men (Hart et al., 2009a; Hogarth et al., 2007) is absent in young women (Hart et al., 2009b), that may result from greater β-adrenergic vasodilator responsiveness in women (Hart et al., 2011). Therefore, as the agreement between both methods might be expected to be different between males and females (namely, lower in females), we decided a priori to analyse the data from males and females separately.

2. Methods

2.1. Study population

Nine healthy subjects (five men; age: 25 ± 5 yr; BMI: 21.7 ± 2.3 kg/m^2) volunteered for the study. All participants were free from any known diseases and not taking any medication. The study protocol was approved by the local Institutional Ethics Committee. All subjects gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

2.2. Study protocol

Subjects abstained from alcohol/caffeine for >12 h before the examination. The measurements were performed between 8:00–11:00, in a quiet room at ~22 °C, each subject lying supine. After instrumentation, subject rested for ≥5 min before data collection. The next 15-min (*baseline recording*) was used to obtain the *baseline* values of the cardiovascular parameters. Following the *baseline* recording, a microneurographic examination was performed. After a satisfactory MSNA signal was established, all cardiovascular variables and MSNA were recorded for ≥2 min and used to calculate the *baseline* values of the neural parameters and the measures of sBR function.

Data were acquired using an analog-to-digital converter (PowerLab 16/30, ADInstruments, Australia) and laptop with data acquisition software (LabChart 7, ADInstruments) and sampled at 1 kHz.

2.3. Cardiovascular parameters

Instantaneous HR (bpm) was calculated based on ECG (BioAmp, ADInstruments). All other cardiovascular measurements: systolic blood pressure (SBP, mmHg), DBP (mmHg), stroke volume (SV, mL/beat), cardiac output (CO, L/min), and SVR (dyn ∗ s/cm^5) were derived from the Nexfin HD (BMEYE B.V., The Netherlands). Briefly, Nexfin uses the volume-clamp method (Penaz, 1992) to measure finger ABP in a beat-to-beat fashion, and the built-in filters to reconstruct brachial ABP. Beat-to-beat SV is calculated as the area under the SBP curve divided by the aortic input impedance (Z_{in}), a variable related to mechanical characteristics of the aorta. CO is calculated as beat-to-beat SV multiplied by instantaneous HR. SVR is calculated as beat-to-beat MAP divided by beat-to-beat CO.

Clinically acceptable agreement between the measures provided by Nexfin, and the measures obtained using 'gold-standard', invasive techniques have been reported (Chen et al., 2012; Sokolski et al., 2011; Bogert et al., 2010; Broch et al., 2012).

From the *baseline recording*, 10-min of an acceptable quality was selected and the data for each cardiovascular variable were averaged (arithmetic mean) to provide the *baseline* values of the variables.

2.4. Neural parameters

Multi-unit MSNA was assessed by microneurography (Sundlof and Wallin, 1978; Vallbo et al., 2004). Briefly, a tungsten microelectrode (FHC, Inc., USA) was inserted into the right peroneal nerve under the fibular head. The signal was amplified (20,000-fold), bandpass filtered (500–2000 Hz), rectified and integrated (time constant 0.1 s) by a neuro-amplifier (NeuroAmp, ADInstruments). Placement of the microelectrode within a muscle-nerve fascicle was confirmed by: spontaneous pulse-synchronous nerve activity, no response to skin stroking/arousal stimuli, neural activation to end-expiratory apnoea and tapping of the muscle belly. The recordings of the length ≥2 min and the signal-to-noise ratio: ≥3:1 were accepted (Fig. 1).

MSNA bursts were identified automatically using LabChart (ADInstruments). The results were corrected manually by a single investigator (B.P.) who performed all the examinations. MSNA was expressed as burst frequency (bursts/min) and incidence (bursts/100 heart beats). To compensate for the baroreflex-mediated delay between the MSNA burst and the preceding R wave, all cardiovascular recordings were shifted forward by 1.45 s in relation to MSNA recording (Sundlof and Wallin, 1978; Hart et al., 2010).

2.5. An assessment of sBR function by the MSNA-based threshold-analysis

The threshold-analysis (Wallin et al., 1974) is based on the relation between DBP and the occurrence of MSNA bursts in a steady-state resting conditions. Briefly, DBP values are grouped in 2 mmHg intervals (bins). For each cardiac cycle, the DBP value is assigned to appropriate DBP bin, and the presence/absence of MSNA burst within 1.0 s search window is determined. Next, the percentages of MSNA burst-associated cardiac cycles are plotted against DBP bins and the regression line weighted for the number of cardiac cycles for each DBP bin is drawn. The slope of the line ($Slope_{burst}$, %/mmHg) and the DBP value of 50% of the burst-associated cardiac cycles (T_{50}burst, mmHg) are taken (Fig. 2).

2.6. An assessment of sBR function by the SVR-based threshold-analysis

Beat-to-beat SVR data was converted into dichotomous data (SVR increase present/absent) similar to MSNA data after burst identification (MSNA burst present/absent) based on two criteria: the MSNA burst-SVR increase latency, and the magnitude of the SVR increase.

2.6.1. The latency criterion

Fairfax et al. (2013) have demonstrated recently that the MSNA burst–SVR increase latency in healthy human under resting conditions is 7–10 heart beats. To find an optimal latency for each subject, we have used the method similar to the cross-correlation method as applied by Fairfax et al. (2015). The lower DBP, the more MSNA bursts and the greater SVR increase several heart beats later (in fact, Fairfax et al. (2015) have used total vascular conductance (TVC, mL/min/

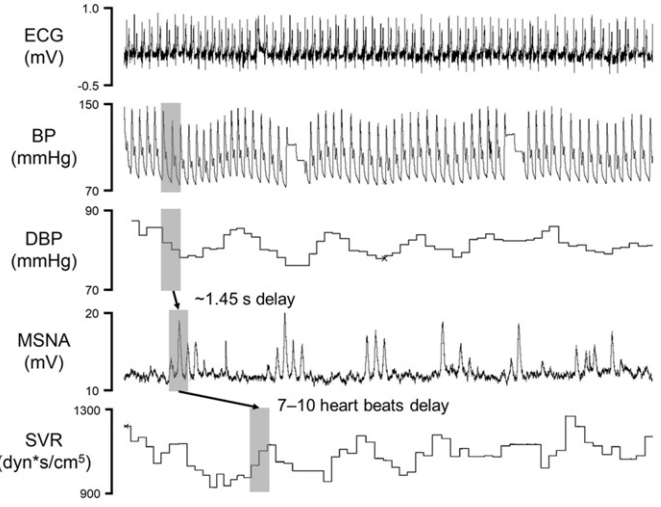

Fig. 1. Original tracings of ECG, arterial blood pressure (BP), diastolic blood pressure (DBP), muscle sympathetic nerve activity (MSNA), and systemic vascular resistance (SVR) from a 28-year-old male subject. The figure shows the temporal relation between: (1) DBP drop, (2) occurrence of MSNA burst (lag of ~1.45 s), and (3) SVR increase (lag of 7–10 heart beats).