

Validation of Sympathetic Activity Index From Heart Rate Variability series: A Preliminary Muscle Sympathetic Nerve Activity Study

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Abstract

We recently proposed a Sympathetic Activity Index (SAI) through an orthonormal Laguerre expansion of linear RR-interval autoregressive kernels. The resulting heart rate variability (HRV) instantaneous indices may be used for the effective estimation of cardiac sympathetic outflow because the model is independent from the overlapping dynamics of the sympathetic and vagus nerves in the low frequency (LF) band (0.04-0.15Hz). In this study, we perform a preliminary validation of the SAI performance through concurrent estimates from efferent muscle sympathetic nerve activity (MSNA) recordings. ECG and MSNA were simultaneously recorded in 12 hypertensive patients during a 10min resting state in the supine position and up to 30min sodium nitroprusside (SNP, 0.4 µg/kg per minute) administration. Results show a characteristic increase of the MSNA during SNP intake with respect to the resting state ($p < 0.001$). While SAI was associated with a significant increase during SNP ($p < 0.001$), LF power did not show significant changes between sessions ($p > 0.05$). Spearman analysis highlighted a significant correlation between SAI and MSNA ($r = 0.47$; $p < 0.02$) and a non-significant correlation between LF power and MSNA ($r = -0.09$; $p > 0.05$). This study provides a further validation step of the SAI and supports the use of HRV parameters as a reliable proxy of cardiac sympathetic outflow dynamics.

1. Introduction

The sympathetic and parasympathetic nervous systems are essential to guarantee physiological homeostasis in health and disease states. They play a major role in the effective control for heartbeat dynamics, and their dysfunctional interaction contributes to the evolution of cardiovascular disorders [1]. Consequently, a precise quan-

tification of sympathetic and parasympathetic dynamics is a fundamental requirement for the effective characterization of cardiac states.

While plasma noradrenaline measurement have represented a gold standard measurement for the quantification of sympathetic neural functions, direct recording of efferent postganglionic sympathetic nerve activity (muscle sympathetic nerve activity, MSNA) via microneurography have largely supplanted other approaches [2–4]. MSNA recording has constituted a fundamental tool for the direct assessment of the neuro-adrenergic cardiovascular drive in healthy people and patients with cardiovascular, metabolic, and renal diseases; however MSNA studies have mostly relied on a small number of subjects due to the difficulty in obtaining stable MSNA recordings with optimal signal-to-noise ratios in many patients and experimental conditions.

To generalize the autonomic assessment of cardiovascular control to large populations, heart rate variability (HRV) analysis has been investigated for more than four decades in clinical and laboratory research [5]. If using a frequency-domain analysis, the HRV spectrum comprises a Low Frequency (LF) band, centered at 0.1Hz, whose power is known to be modulated by both cardiac vagal and sympathetic nerve activity, as well as arterial blood pressure [5–7], and a High Frequency (HF) band, including oscillations greater than 0.15 Hz, which has been proposed as a marker of vagal activation. The HF band is driven primarily by the respiratory frequency (so-called Respiratory Sinus Arrhythmia) [5]. Since neither the LF or HF bands are specific for sympathetic activity, it has not been possible to use HRV for a reliable estimation of sympathetic control.

To overcome this limitation, we recently defined the Sympathetic Activity Index (SAI) and the Parasympathetic Activity Index (PAI), which are able to effectively quantify the functioning of the two autonomic branches for time-

varying cardiovascular control without the need for a preliminary calibration at the level of the individual [8–10]. An orthonormal Laguerre expansion is combined through a set of disentangling coefficients estimated from a previous autonomic blockade study [9]. From an estimation viewpoint, there is no need for interpolation of the HRV series, and the SAI and PAI coefficients may be calculated through different optimization methods including least square, instantaneous point-process [9], and beat-to-beat Kalman filtering [8, 10]. The SAI and PAI has been previously evaluated using data gathered from healthy volunteers undergoing different autonomic maneuvers [8, 9], as well as data from patients with congestive heart failure [10].

In this study, we enrich the previous evaluation set by investigating SAI and PAI performance in following MSNA changes. To this end, we use ECG and MSNA data that were simultaneously recorded in 12 hypertensive patients undergoing a resting state in the supine position, and a sympathetic activation session through pharmacological intervention. Details on the signal processing methodology and experimental setup, and results and study conclusions follow below.

2. The Sympathetic and Parasympathetic Activity Indices

Heartbeat events $\{u_k\}$ correspond to R-waves from the ECG, and $RR_k = u_k - u_{k-1} > 0$ denote the k^{th} RR interval, or equivalently, the waiting time until the next R-wave event. The SAI and PAI were estimated from HRV series using a Kalman filtering approach, whose details are reported in [8–10]. Briefly, a model including a theoretical separation between the slow sympathetic and faster parasympathetic dynamics is identified as follows:

$$\mu_{RR}(k, \xi(k)) = g_0(k) + \underbrace{\sum_{j=0}^{P_{\text{Symp}}} g_{1,j}(k) l_j(k)}_{\text{Sympathetic}} + \underbrace{\sum_{j=P_{\text{Symp}}+1}^{P_{\text{ParSymp}}} g_{1,j}(k) l_j(k)}_{\text{Parasympathetic}} \quad (1)$$

where

$$\xi(k) = [g_0(k), g_{1,0}(k), \dots, g_{1,J}(k)]^\top \quad (2)$$

and

$$l_j(k) = \sum_{n=0}^{k-1} \phi_j(n, \alpha) RR(k-n-1) \quad (3)$$

with

$$\phi_j(n) = \alpha^{\frac{n-j}{2}} (1-\alpha)^{\frac{1}{2}} \sum_{i=0}^j (-1)^i \binom{n}{i} \binom{j}{i} \alpha^{j-i} (1-\alpha)^i$$

as the j^{th} -order discrete-time orthonormal Laguerre function, and α the constant of decay parameter of the Laguerre functions. Note that such statistically independent functions at different orders have all the same magnitude and different phase spectra [11], such that a proper combination of Laguerre bases may selectively reflect the actual sympathetic or parasympathetic system response [9]. Note also that the Laguerre functions may effectively be estimated through a recursive form [8, 10].

The SAI and PAI are then defined as a combination of disentangling Laguerre coefficients Ψ_S and Ψ_P , and the coefficients $g_{1,j}$ as follows:

$$SAI(k, \xi(k)) = \left[\Psi_{S_0} + \sum_{j=1}^{N_1} \Psi_{S_j} g_{1,j-1}(k) \right] / RR(k)^2$$

$$PAI(k, \xi(k)) = \left[\Psi_{P_0} + \sum_{j=1}^{N_2} \Psi_{P_j} g_{1,j+1}(k) \right] 2RR(k)$$

In this study, we set $N_1 = 2$ and $N_2 = 7$ and $\alpha = 0.2$ to match the frequency response of the Laguerre filters with the dynamic response of the sympathetic and the parasympathetic systems [5, 6, 9]. The disentangling Ψ_S and Ψ_P kernels were derived from a previous selective autonomic blockade study through multiple regression analysis [6, 9]. Importantly, the use of these coefficients do not need any calibration procedure at a single subject/recording level. Particularly, results reported below were obtained using the following realizations of Ψ_S and Ψ_P coefficients:

$$\Psi_S = \{39.2343, 10.1963, -5.9242\}$$

$$\Psi_P = \{28.4875, -17.3627, 5.8798, 12.0628, 5.6408, -7.0664, -5.6779, -3.9474\}$$

The vector parameter ξ to be estimated may be modeling as the output of a linear dynamic system, which is observed through the series of RR intervals:

$$\xi(k) = \xi(k-1) + \varepsilon_\xi(k) \quad (4)$$

$$RR(k) = \ell(k)^\top \xi(k) + \varepsilon_{RR}(k) \quad (5)$$

where $\varepsilon_\xi(k)$ is the state noise with covariance matrix S_ξ and $\varepsilon_{RR}(k)$ is the observation noise with variance S_{RR} . In this model, (5) replaces (1) while (4) describes how the Laguerre coefficients evolve in time. These coefficients can be readily estimated using a Kalman filter with a time-varying observation matrix [8, 10].

2.1. Experimental Setup, Signal Preprocessing, and Statistical Analysis

Extensive details on the experimental setup and data acquisition are reported in [2]. Briefly, ECG and multiunit recording of efferent postganglionic MSNA series were simultaneously gathered from 12 hypertensive patients in the supine position during a 10min resting state and up to 30min sodium nitroprusside (SNP, 0.4 $\mu\text{g/kg}$ per minute) administration. SNP is a direct vasodilating agent (Malesci) expected to increase MSNA. MSNA was recorded at 1000 Hz (ACQ-16, Gould Electronics) using a microelectrode with diameter 200 μm transcutaneously inserted into the right or left peroneal nerve posterior to the fibular head; the MSNA signal was integrated with a 0.1s time constant, band-pass filtered between 700-2000 Hz. MSNA was identified according to criteria outlined in previous studies [2]. The recording was considered acceptable if the signal-to-noise ratio exceeded the value of 3. The study protocol was approved by the local ethical committee and was in accordance with institutional guidelines. Patients gave their written informed consent to participation in the study after explanation of its nature and purpose.

Regarding ECG, an automatic R-peak detection algorithm based on the Pam-Tompkin procedure was applied to derive HRV series, which were inspected for algorithmic and physiological (e.g., ectopic beats) artifacts through visual inspection and using our previously proposed method based on point-process statistics [12].

Together with the SAI and PAI measures estimated according to the methodology described in the previous paragraph, standard time-varying LF (0.04-0.14Hz) and HF (0.14-0.40Hz) powers were estimated using a similar Kalman approach as well. The features within-session time-varying changes were condensed as median between samples. Consequently, descriptive statistics were expressed as median \pm MAD(X) where $\text{MAD}(X) = \text{median}(|X - \text{median}(X)|)$ and X is the variable of interest (e.g., SAI, PAI, LF, HF). Group-wise, between-session comparison was performed through Wilcoxon non-parametric tests for paired data, with null hypothesis of equal medians between sessions.

Further non-parametric correlation analyses were carried out using the Spearman correlation coefficient, along with a linear regression analysis with least square coefficient estimation, between MSNA-SAI and MSNA-LF pairs.

3. Results

Experimental results are shown in Table 1. As expected, SNP induces a significant increase in MSNA with respect to the rest condition, and similar statistically-significant

changes are with the σ_{RR}^2 , SAI, and SAI/PAI ratio. While SNP also induced a significant decrease in μ_{RR} and PAI, the LF and HF powers did not show statistical changes between sessions.

Table 1. Results from the Rest vs. SNP statistical comparison.

	Rest	SNP	p-value
<i>MSNA</i> [b/100hb]	39 \pm 4.5	54.33 \pm 5	< 0.0005
μ_{RR} [ms]	915.3 \pm 192.22	820.73 \pm 102.17	< 0.002
σ_{RR}^2 [ms]	2384.3 \pm 1407.5	11299 \pm 7133.7	< 0.0005
SAI [a.u.]	39.07 \pm 13.46	52.66 \pm 17.76	< 0.001
LF [ms^2]	61.90 \pm 36.24	63.45 \pm 49.62	> 0.05
PAI [a.u.]	63.90 \pm 12.43	46.99 \pm 8.26	< 0.001
HF [ms^2]	457.97 \pm 315.83	504.53 \pm 418.24	> 0.05
<i>SAI/PAI</i>	0.616 \pm 0.273	1.136 \pm 0.517	< 0.001
<i>LF/HF</i>	0.162 \pm 0.027	0.146 \pm 0.034	> 0.05

p-values are from the Wilcoxon non-parametric test for paired data.

b/100hb indicates bursts per 100 heartbeats;.

Considering aggregated data from all patients in both resting and SNP sessions, i.e., two samples per subject, a Spearman analysis revealed a correlation coefficient as high as 0.475 for the MSNA-SAI samples ($p < 0.02$) and -0.090 for MSNA-LF ($p > 0.05$). Scatter plots and regression lines for these samples are shown in Fig. 1.

4. Discussion and Conclusions

This study demonstrates the reliability of the SAI index for a quantitative, HRV-based, autonomic assessment of MSNA which should be correlated with cardiac sympathetic activity. We have recently proven that the SAI follows sympathetic changes expected in healthy individuals during active and passive postural changes, lower-body negative pressure conditions, and handgrip tests [8, 9], as well as expected increase in sympathetic activity in patients with congestive heart failure [10]. Here, the use of Spearman correlation analysis and between-session statistical tests demonstrated that the SAI is able to follow MSNA changes in hypertensive patients undergoing SNP infusion, which increases sympathetic activity. The MSNA-SAI correlation coefficient was 0.475, presumably due to inter-subject variability (which is not eliminated by the SAI estimation technique). Higher values for MSNA-SAI correlation coefficients would be expected at a single-subject level.

The SAI algorithm relies on the orthonormal Laguerre functions, whose spectral properties and statistical independence between different orders help overcome the lim-

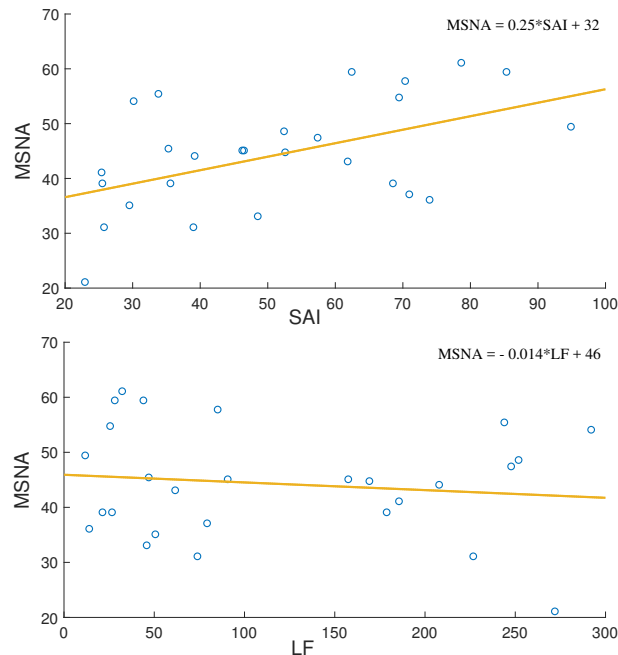


Figure 1. Scatter plots and linear regression analyses (orange line and equations) for the MSNA-SAI (top panel) and MSNA-LF (bottom panel) samples considering data from all patients in both resting and SNP sessions.

its of the HRV spectral paradigm, allowing for an accurate estimate of sympathetic dynamics in the LF band [9]. In fact, as noted, HRV oscillations below 0.15 Hz are mediated by both cardiac vagal and sympathetic nerves [6, 7], resulting in no statistical association between SNP and LF in the resting state or with the changes in MSNA induced by SNP.

From an estimation viewpoint, although a Kalman filtering approach was used to retrieve time-varying (beat-to-beat) SAI estimates, it should be noted that other parameter estimation methods including least square and point-process may also be used depending on the desired resolution in time [9].

Future studies will be directed towards SAI-PAI evaluation, together with MSNA, at a single-subject level, as well as applications in other clinical and applicative settings.

Disclosure

An International patent application (PCT/US2016/044844) was filed on July 29, 2016 for the method described in this paper.

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