ECG-derived Sympathetic and Parasympathetic Nervous System Dynamics: A Congestive Heart Failure Study

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Abstract

The goal of estimating sympathetic and parasympathetic peripheral outflow from the heartbeat has been a long-lasting challenge in cardiovascular research. Spectral analysis of heart rate variability (HRV) has provided a very successful characterization of the autonomic influence on the heart. However, the definition of simple subdivisions in frequency ranges does not fully reflect separate influences of the two peripheral branches because of their simultaneous action in the LF band (0.04-0.15Hz). To overcome this limitation, we recently proposed a methodological framework defining the Sympathetic Activity Index (SAI) and the Parasympathetic Activity Index (PAI), which have been proven effective in characterizing healthy cardiac dynamics. In this study, we aim to evaluate SAI and PAI performances in Congestive Heart Failure (CHF). To this extent, we here estimate normalized SAI and PAI indices on HRV series from Physionet recordings, i.e., 14 CHF patients and 16 healthy controls (CNT). A set of disentangling coefficients associated with Laguerre functions has been taken from a previous autonomic blockade study. Group comparison is performed through Mann-Whitney non-parametric tests. Results show a characteristic increase of the sympathetic dynamics in CHF with respect to CNT (SAI - CNT: 42.65 $\pm$ 7.47; CHF: 60.25 $\pm$ 11.70; $p < 0.05$) despite the significant reduction of HRV spectral power associated with CHF. Results also highlight a significantly reduced vagal activity in CHF with respect to CNT (PAI - CNT: 58.47 $\pm$ 8.03; CHF: 43.04 $\pm$ 11.94; $p < 0.005$). This study demonstrates the reliability of the proposed measures for a non-invasive autonomic assessment in CHF without the need of model calibration at the individual level.

1. Introduction

Throughout the last decades, Heart rate variability (HRV) analysis has led to a quite successful non-invasive quantification of the Autonomic Nervous System (ANS) influence on heartbeat dynamics, particularly referring to frequency-domain analysis [1, 2].

The HRV spectrum has been divided into three main spectral bands: Very Low Frequency (VLF), Low Frequency (LF) and High Frequency (HF) bands [1, 2]. Historically, LF (centred in 0.1Hz) and HF (greater than 0.15 Hz) oscillations have been associated with sympathetic and parasympathetic (vagal) activity, respectively. Indeed, a vagal activation strongly affects the HF power exclusively, being mainly driven by the respiratory frequency (so-called Respiratory Sinus Arrhythmia [1, 2]). On the other hand, although changes in sympathetic activity often cause significant alterations in the magnitude of LF oscillations, it has been demonstrated how changes within this band are mediated by both cardiac vagal and sympathetic nerves, as well as arterial blood pressure [1–4].

To devise effective, non-invasive measures of sympathetic autonomic outflow, HRV-based methods that need a preliminary calibration phase at a single-subject level [5], as well as multivariate analyses from multiple physiological recordings (e.g., ECG and blood pressure or QT variability) [6, 7], have been proposed. Recently, we devised two novel HRV-based indices, namely the Sympathetic Activity Index (SAI) and the Parasympathetic Activity Index (PAI), which are able to effectively identify the time-varying cardiac sympathetic and parasympathetic activity without the need for a preliminary calibration at the level of the individual [8]. Such indices rely on the orthonormal Laguerre expansion of heartbeat dynamics [9] along with a set of disentangling coefficients estimated from a previous autonomic blockade study [8], and have been tested yet in data from healthy subjects through well-known autonomic manoeuvres [8]. Note that SAI and PAI mathematical definitions are embedded into an autoregressive model of heartbeat dynamics, thus allowing for their estimation from different identification methods, e.g.

least square and maximum likelihood, Kalman prediction, point-process [8, 9].

In this study, we test SAI and PAI performance in discerning sympathetic and parasympathetic autonomic outflow between cardiovascular variability recordings from healthy subjects and congestive heart failure (CHF) patients, during unstructured activity. To this end, original SAI and PAI calculation is here honed to account for intergroup variability. Methodological details, and Experimental Results and Conclusions follow below.

2. Derivation of the Sympathetic and Parasympathetic Activity Indices

The SAI and PAI measures rely on the Laguerre expansion of autoregressive terms predicting heartbeat events. The main rationale is to extend standard HRV analysis in the frequency-domain using information embedded into the HRV phase spectrum. In fact, as orthonormal Laguerre functions at different orders have all the same magnitude and different phase spectra [9], a proper combination of Laguerre bases may selectively reflect the actual sympathetic or parasympathetic system response [8].

Formally, given a set of K heartbeat events $\{u_k\}_{k=1}^{K}$ (in our study, R-waves from the ECG), let $RR_k = u_k - u_{k-1} > 0$ denote the k^{th} RR interval, or equivalently, the waiting time until the next R-wave event.

The j^{th}-order discrete-time orthonormal Laguerre function is defined as follows:

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

with $n \geq 0$ and α the constant of decay. First, the RR interval series is convolved with such functions:

$$\ell_j(k) = \sum_{n=0}^{k-1} \phi_j(n,\alpha)\, RR(k-n-1) \tag{1}$$

Then, the following autoregressive model, including a theoretical separation between sympathetic and parasympathetic dynamics, is identified:

$$\mu_{RR}(k, H_k, \xi(k)) = g_0(k) + \underbrace{\sum_{j=0}^{P_{\text{Symp}}} g_{1,j}(k)\, l_j(k)}_{\textit{Sympathetic}} + \underbrace{\sum_{j=P_{\text{Symp}}+1}^{P_{\text{ParSymp}}} g_{1,j}(k)\, l_j(k)}_{\textit{Parasympathetic}} \tag{2}$$

where

$$\boldsymbol{\xi}(k) = [g_0(k), g_{1,0}(k), \ldots, g_{1,J}(k)]^\top \tag{3}$$

The unknown time-varying Laguerre coefficients can be modelled according to a linear dynamic system, which is observed through the series of RR intervals:

$$\boldsymbol{\xi}(k) = \boldsymbol{\xi}(k-1) + \boldsymbol{\varepsilon}_{\boldsymbol{\xi}}(k) \tag{4}$$

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

where $\boldsymbol{\varepsilon}_{\boldsymbol{\xi}}(k)$ is the state noise with covariance matrix $\mathrm{S}_{\boldsymbol{\xi}}$ and $\varepsilon_{RR}(k)$ is the observation noise with variance S_{RR}. In this model, (5) replaces (2) 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. Note also that the orthonormal Laguerre functions $\boldsymbol{\ell}(k)$ can be rewritten recursively in matrix form as follows:

$$\boldsymbol{\ell}(k) = \mathrm{L}\,\boldsymbol{\ell}(\mathrm{k}-1) + \sqrt{1-\alpha}\,[1, \alpha^{\frac{1}{2}}, \ldots, \alpha^{\frac{J}{2}}]^\top \mathrm{RR}(\mathrm{k}-1) \tag{6}$$

where

$$\boldsymbol{\ell}(k) = [\ell_0(k), \ldots, \ell_J(k)]^\top \tag{7}$$

and L is a lower triangular Toeplitz matrix with $L_{i,i} = \sqrt{\alpha}$ on the main diagonal and $L_{i,i'} = -(1-\alpha)(\sqrt{\alpha})^{i-i'-1}$ below the main diagonal.

Finally, the definition of the SAI and PAI as a combination of disentangling Laguerre coefficients Ψ_S and Ψ_P is as follows:

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

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

In an attempt to match the frequency response of the Laguerre filters with the dynamic response of the sympathetic and the parasympathetic systems [1–3], we have chosen $N_1 = 2$ and $N_2 = 7$ and $\alpha = 0.2$.

The estimation of generalized values of sympathetic Ψ_S and parasympathetic Ψ_P kernels was previously performed through a multiple regression analysis on data involving selective autonomic blockade during postural changes (see [3, 8]). Note that these coefficients represent the first working attempt to estimate ANS activity from heartbeat dynamics exclusively, without the need of any calibration procedure at a single subject level. Particularly, results reported below were obtained using the following realizations of Ψ_S and Ψ_P coefficients:

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

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

3. Experimental Setup and Results

We estimated SAI and PAI indices as described in the previous paragraph from HRV series gathered from the public source Physionet (http://www.physionet.org/) [10], including ECG data from 14 CHF patients (from $BIDMC - CHF$ Database) and 16 healthy controls (CNT, from $MIT - BIH$ Normal Sinus Rhythm Database). Each series was free of algorithmic (e.g., automatic R-peak detection) and physiological (e.g., ectopic beats) artifacts upon visual inspection and after checking with our previously proposed method based on point-process statistics [11]. Each series lasted about 50min (small segments of the original over 20h recordings) and were used in our previous methodological evaluations (e.g., [9]).

Between-group comparison was performed through Mann-Whitney non-parametric tests, with null hypothesis of equal medians between populations.

Box-plot statistics of SAI, PAI, and SAI/PAI ratio are shown in Figure 1. Experimental results are shown in Table 1, which also includes time-, and frequency-domain statistics calculated on the same dataset (see [9] for details), expressed as $\mathrm{Median} \pm \mathrm{MAD(X)}$ where $\mathrm{MAD(X)} = \mathrm{Median}(|\mathrm{X} - \mathrm{Median(X)}|)$ and X is the variable of interest (e.g., SAI, PAI, LF, HF, etc.).

Time domain features showed all statistically significant differences between groups. Particularly, CHF patients were associated with lower mean and standard deviation of the RR intervals, i.e., μ_{RR} and σ_{RR}, as well as lower RMSSD, pNN50, and TINN than CNT. As expected, all traditional frequency-domain parameters resulted significantly lower in CHF patients than in CNT, including the power of LF oscillations. Conversely, the SAI and SAI/PAI ratio were significantly higher in CHF than in CNT, whereas PAI was significantly lower in CHF.

Table 1. Results from the Healthy vs. CHF statistical comparison.

Model	Healthy	CHF	p-value
μ_{RR} [ms]	859.38 $\pm$ 54.69	670.00 $\pm$ 66.00	< 0.03
σ_{RR} [ms]	24.7$\pm$7.0	8.31$\pm$2.2	< 0.001
RMSSD	0.0432$\pm$0.0145	0.0121$\pm$0.0036	< 0.001
pNN50	21.54$\pm$15.49	0.24$\pm$0.22	< 0.001
TINN	0.30$\pm$0.05	0.16$\pm$0.06	< 0.001
LF [ms^2]	316.0$\pm$127.2	7.28$\pm$6.1	< 0.001
SAI [a.u.]	42.65 $\pm$ 7.47	60.25 $\pm$ 11.70	< 0.05
HF [ms^2]	606.1$\pm$344.7	30.59$\pm$21.0	< 0.001
PAI [a.u.]	58.47 $\pm$ 8.03	43.04 $\pm$ 11.94	< 0.005
LF/HF	0.86$\pm$0.7	0.08 $\pm$ 0.1	< 0.05
SAI/PAI	0.72 $\pm$ 0.23	1.43 $\pm$ 0.51	< 0.05

p-values are from the Mann-Whitney non-parametric test.

4. Discussion and conclusions

This study demonstrates the reliability of the proposed SAI and PAI metrics for non-invasive autonomic assessment in healthy controls (CNT) and in congestive heart failure (CHF) patients, without the need of a model calibration at the level of the individual.

Despite their widespread use during the last two decades, approaches based on frequency domain analysis of HRV have been significantly challenged. Several pharmacological studies have in fact confirmed the intrinsic ambiguity of such a spectral approach, as HRV-related changes below 0.15 Hz are mediated by both cardiac vagal and sympathetic nerves [3, 4].

For this reason, instead of base functions defined in limited frequency ranges, a proper weighted sum and/or subtraction of primitives unselectively spanning the frequency domain would be able to decompose the heartbeat variability due to ANS activity by disentangling the unique contribution of each autonomic branch. Such primitives can be defined from discrete-time orthonormal Laguerre bases, which for a given α have equal magnitude and different phase spectra in the frequency domain [9]. Moreover, once a standard autoregressive model has been identified along the Laguerre bases (i.e., after convolving the original RR interval series with the Laguerre bases), the use of SAI and PAI measures does not need calibration at a single subject level. Note that the disentangling coefficients used in this study, which might have limited generality, are the first working attempt to estimate sympathetic and parasympathetic dynamics from ECG.

From a signal processing viewpoint, the SAI-PAI calculation proposed in this study is from a Kalman-based framework, allowing for a beat-to-beat estimation of the autonomic outflow. Note that the SAI-PAI methodology is not dependent on the specific estimation procedure adopted to identify the autoregressive model used to predict heartbeat dynamics.

It is known that CHF is associated with higher sympathetic activity than CNT [12, 13]. This is mainly due to the vicious loop that increases the cardiac sympathetic outflow (through norepinephrine) to compensate the reduced heart pumping capacity [12, 13]. Accordingly, results promisingly confirm that higher sympathetic activity in CHF than in CNT has been revealed by the SAI and SAI/PAI ratio, despite the significant reduction of spectral power (both in the LF and HF bands) associated with HRV series from CHF patients. On the other hand, the PAI shows a reduced vagal activity in CHF patients than in CNT, confirming current pathophysiological knowledge in the field

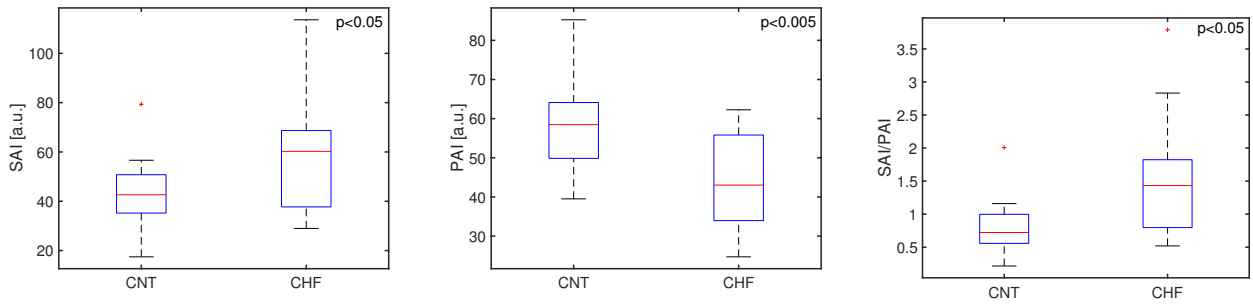

Figure 1. Box-plot statistics for SAI (left panel), PAI (center panel), and SAI/PAI ratio (right panel) between healthy controls (CNT) and patients with CHF.

and standard parasympathetic-related HF index trends.

These results provide reasonable evidence that the proposed methodology, despite the discrepancies of the traditional frequency-based indices (i.e., LF and HF power), is able to effectively identify the separate autonomic functions in CHF patients by using the same framework devised for healthy cardiovascular control.

Future endeavours will be directed towards a SAI-PAI evaluation in other clinical and applicative settings, including sleep, physical activity, and emotional scenarios, as well as to the associated pathophysiology therein.

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