Effect of the Heart Rate Variability Representations on the Quantification of the Cardiorespiratory Interactions During Autonomic Nervous System Blockade

John F Morales[1], Juan Bolea[2], Sabine van Huffel[1], Raquel Bailón[2], Carolina Varon[1]

[1] Department of Electrical Engineering-ESAT, STADIUS Center for Dynamical Systems, Signal Processing and Data Analytics, KU Leuven, and IMEC, Leuven, Belgium
[2] BSICoS Group, Aragón Institute of Engineering Research (I3A), IISAragon, University of Zaragoza and CIBER-BBN, Zaragoza, Spain

Abstract

The Heart Rate Variability (HRV) is a noninvasive tool to evaluate the activity of the autonomic nervous system. To study the HRV, different mathematical representations can be used. The selection of a representation might have an effect on the evaluation of the mechanisms that modulate the Heart Rate (HR). One of these mechanisms is the Respiratory Sinus Arrhythmia (RSA), i.e. an increased HR during inhalation and a decreased HR during exhalation. Different methods exist to quantify the RSA. A common approach is to calculate the power in the High Frequency (HF, 0.15 - 0.4 Hz) band of the spectrum of the HRV representation. More recently proposed methods use the respiratory signals to estimate the strength of the RSA.
This paper studies the effect of the HRV representations on the quantification of the RSA. To this end, an experiment is used in which the sympathetic and parasympathetic branches of the autonomic nervous system are selectively blocked. Three different HRV representations are considered. Afterwards, the strength of the RSA is estimated using three approaches, namely the spectral content in the HF band of the HRV representations, orthogonal subspace projections and a time-frequency representation.
The results suggest that the selection of an HRV representation does not have a significant impact on the RSA estimates in a healthy population.

1. Introduction

The analysis of Heart Rate Variability (HRV) provides insights into the modulation of the Autonomic Nervous System (ANS) in a noninvasive way [1]. To evaluate the HRV, different mathematical tools can be used such as the tachogram [1], the Integral Pulse Frequency Modulation (IPFM) model [2] and the point process model [3] [4]. Each of these tools generates different HRV representations.

Parameters derived from the HRV representations are useful to assess the parasympathetic and sympathetic modulations from the ANS. In the frequency domain, the power spectrum of the HRV can be used, in which the power in the Low Frequency band (LF, 0.04 Hz - 0.15 Hz) is usually linked to both sympathetic and parasympathetic modulations [1]. Besides, the power in the HF band (HF, 0.15 Hz - 0.4 Hz) mainly represents heart rate oscillations synchronous with respiration and is mediated by the parasympathetic branch of the ANS. The synchronization between respiration and heart rate is possible thanks to a physiological process called the Respiratory Sinus Arrhythmia (RSA) [5], which is observed as an increased HR during inhalation and a decreased HR during exhalation. Usually, the RSA is quantified as the power contained in the HF band of the HRV [6]. However, the respiratory rate might be characterized by narrow bands inside the HF or it can fall outside the HF band. For this reason, alternative methods have been proposed for the quantification of the RSA. Two of them are the subspace projections[7] and a Time-Frequency (TF) representation [8], which are evaluated in this study.
The aim of this paper is to evaluate the influence of the HRV representations on the aforementioned RSA quantifications. This evaluation is done using a dataset in which changes in autonomic regulation of the heart are pharmacologically induced with different ANS blockades (atropine or propranolol) in a healthy population.

2. Dataset

The *Pharmacological ANS blockades database (HMS-MIT-FMMS)*, recorded in the Clinical Center at the Massachusetts Institute of Technology 1, was used in this study. Single-lead electrocardiogram (ECG) signals and changes in the instantaneous lung volume with a two-belt chest-abdomen inductance plethysmograph were acquired with a sampling frequency of 360 Hz from 13 healthy male volun-

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teers (Age: 19-38 years) without any history of cardiorespiratory diseases. During the protocol, atropine (0.03 mg/kg) or propranolol (0.2 mg/kg), for parasympathetic blockade and suppression of the sympathetic activity respectively, were administered through a catheter.
The signals were first recorded with the subjects in supine position and without administering any of the drugs. Next, the volunteers were moved to standing position and, after a minimum waiting period of 5 minutes to reach hemodynamic equilibrium, the signals were recorded. Afterwards, the subjects were given one of the two drugs. 7 of them (20.29 ± 1.25 years old) received atropine and 6 (26 ± 6.5 years old) received propranolol. After 10 minutes to reach equilibrium, the signals were acquired in supine and standing positions following the same protocol described above. The recordings on each stage are referred as supine control (SUC), standing control (STC), supine atropine (SUA), standing atropine (STA), supine propranolol (SUP) and standing propranolol (STP). The volunteers were asked to breathe with an irregular respiratory rate following the indications of a recorded tone. The protocol is depicted in Figure 1 and more details can be found in [9].

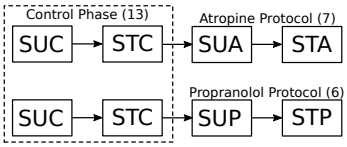

Figure 1. Recording protocol. The numbers in brackets indicate the number of subjects on each phase.

3. Methods

3.1. Preprocessing

Firstly, the ECG signals were upsampled from 360 Hz to 1080 Hz using a cubic spline interpolation. Afterwards, the R-peak locations were found using the method reported in [10]. For this, the software described in [11] with the post-processing and ectopic removal options was used.
Secondly, the respiratory signals were downsampled from 360 Hz to 4 Hz after applying an antialiasing filter and next bandpass filtered between 0.01 and 1 Hz.

3.2. HRV representations

The R-peaks occur at discrete unevenly sampled time points. Therefore, three mathematical descriptions of the HRV were used to generate evenly sampled HRV representations with a sampling frequency of 4 Hz:

- *The uniformly sampled tachogram*: This representation is built by first calculating the RR-intervals, i.e. the time difference between consecutive R-peaks, and then resampling these with a cubic spline interpolation.
- *The Integral Pulse Frequency Modulation Model (IPFM)* [2]: This model assumes that the sympathetic and parasympathetic regulations on the HRV can be represented by a modulating signal that triggers a pulse when its integral reaches a certain threshold. This modulating signal was used as an HRV representation.
- *The Point Process model* [3]: This model characterizes the statistical properties of the pulses in the sinoatrial node as a series of discrete events in continuous time following a time-varying history-dependent inverse Gaussian probability distribution. The model order p was set as 8 and the forgetting factor to 0.98 based on the parameters reported in [3]. Δ was set to 0.25 s to obtain a HRV representation with Fs=4 Hz and the window for the estimation of the initial parameters was empirically set to 50 s. The HRV representation in this case is derived as the first moment of the probability of the RR-intervals.

The three representations were generated for each stage on the experimental protocol. Afterwards, they were bandpass filtered between 0.01 Hz and 1 Hz.

3.3. RSA quantifications

The filtered respirations and the HRV representations were used to quantify the strength of the RSA with three different approaches:

- *Normalized HF band*: The normalized power in the HF band (HFn) of the Power Spectral Density (PSD) estimation of the HRV representations was derived. This band was defined either from 0.15 Hz to 0.4 Hz, or using the extended band from 0.15 Hz to half the mean heart rate [12]. The shortest between these two was chosen. For the calculations, the PSD estimations were computed using the Welch's method and a hamming window of 40 s with 20 s overlap.
- *Orthogonal Subspace Projections (OSP)* [7]: This method was used to decompose each HRV representation into a respiratory component (HRV_{resp}) and a residual component. The relative power of HRV_{resp} (P_{resp}) was used to quantify the dynamics of the HRV linearly related to the respiration and it was calculated as:

$$P_{resp} = (HRV_{resp}^T \cdot HRV_{resp})/(HRV^T \cdot HRV) \quad (1)$$

- *Time Frequency (TF) representation* [8] : The frequency distribution over time of the respiratory signals and HRV representations was characterized based on a Cohen's class TF distribution. This tool analyzes changes in the frequency content of the signals over time while reducing biases in the estimates that occur with other TF representations. The coherence spectrum between the respiratory and HRV signals was also calculated using the same TF representation. The product between the coherence spec-

trum and the spectrogram of the HRV representation was used to extract the spectrum of the respiratory component [8]. This spectrum was normalized by the spectrum of the HRV and then averaged to obtain a quantification of the RSA, denoted as P_{TF}.
The OSP and TF representation were shown in [13] to be better to capture the change on the strength of the RSA with age than other methods

3.4. Comparison of the methods

Two statistical tests were used for the comparisons:
• Significant differences between the estimates of the same parameter, in the same stage of the protocol using the different HRV representations. These differences were evaluated using Kruskall-Wallis and multiple comparisons tests with Bonferroni correction.
• Significant changes on the parameters between the supine and standing positions using the Friedman's tests for repeated measures.
These tests were performed with a 95% confidence interval.

4. Results and Discussion

The results are shown in figure 2 and the tests are discussed in this section.

4.1. HRV representations

The differences for the same parameter, in the same stage of the protocol and with the different HRV representations were not significant between the resampled tachogram and the modulating signal of the IPFM model. Few significant differences (marked with a ⧫ in Figure 2) were found when comparing with the representation based on the point process model ($p < 0.05$). This observation might be explained by the fact that the estimation of the probability distribution of the R-peaks in the point process model requires an initial number of samples. For this reason, the resulting segments are shorter, producing significantly different outcomes in some cases. This effect should be minimized in longer signals.

4.2. Supine vs. Standing position

The tests for the variation of the parameters due to the change from supine to standing position display similar trends. Firstly, the reduction of the parameters during the control stage (SUC to STC) are significant. When a drug is administered, and despite that significant differences were not found in most of the cases, a decreasing trend was also observed. These results are associated with an increased sympathetic activity and/or a decreased vagal modulation

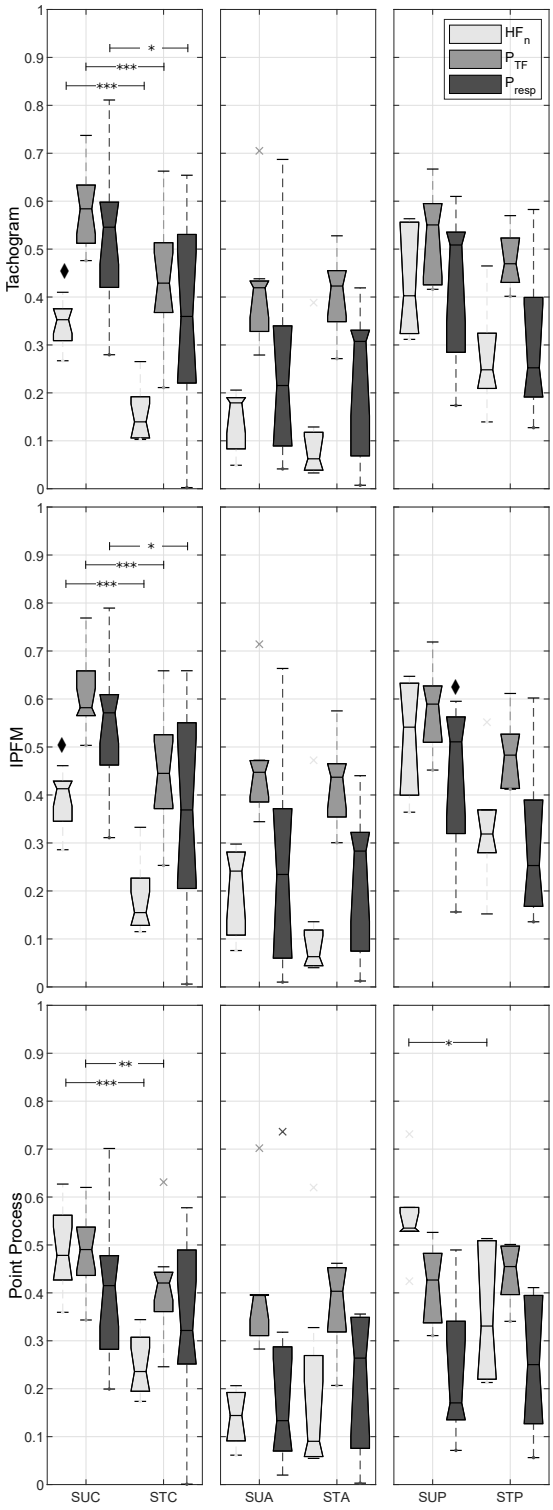

Figure 2. Boxplots for HFn, P_{TF} and P_{resp} calculated with different HRV representations. The ⧫ indicate significant differences in the calculated parameters with respect to the ones calculated with the point process representation. Significant changes due to position changes from supine to standing are indicated with *.

in the standing position, which can be clearly observed using any of the evaluated parameters.

4.3. RSA estimations

As discussed in [7] and as observed in Figure 2, the quantification of the RSA using the HFn parameter tends to underestimate the respiratory modulation on the HRV because the breathing rates tend to fall bellow 0.15 Hz in this dataset. Therefore, the respiratory information is mainly contained in the LF band and this is not captured by the HFn parameter. In contrast, the alternative methods evaluated in this paper do not consider a specific frequency band. On the one hand, the OSP is based on the predictability of the HRV from the respiration, and on the other hand, the TF representation is based on their spectral coherence. Therefore, these quantifications are able to better capture the RSA in conditions in which the spectrum of the respiration falls outside the HF. In general, the trends observed with the two RSA quantifications are consistent.

5. Conclusions

Despite few significant differences, the trends followed by the RSA estimates were very similar with the three HRV representations under investigation. These results suggest that the selection of a HRV representation is irrelevant for the analysis of the RSA in this dataset. However, these signals come from healthy volunteers, while this selection might become more important when a more irregular ECG signal occurs. Further analysis should consider datasets with a significant amount of ectopic beats or with signals recorded during exercise. In addition, the trends on the RSA quantifications when estimated with either the subspace projections or with the TF representation were consistent. This result indicates that these methods measure the respiratory modulation similarly since they are both based on the extraction of the respiratory information from the HRV representation.

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References

[1] Camm, J. et al. "Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology." (1996): 1043-1065.

[2] Bailón, R., et al. "The integral pulse frequency modulation model with time-varying threshold: application to heart rate variability analysis during exercise stress testing." IEEE TBME 58.3 (2011): 642-652.

[3] Barbieri, R. et al. "Analysis of heartbeat dynamics by point process adaptive filtering." IEEE TBME 53.1 (2005): 4-12.

[4] Orini, M. et al. "Introduction to complex cardiovascular physiology." Complexity and Nonlinearity in Cardiovascular Signals. Springer, Cham, (2017). 3-42.

[5] Billman, G. E. "Heart rate variabilitya historical perspective." Frontiers in physiology 2 (2011): 86.

[6] Berntson, G. G. et al. "Respiratory sinus arrhythmia: autonomic origins, physiological mechanisms, and psychophysiological implications." Psychophysiology 30.2 (1993): 183-196.

[7] Varon, C. et al. "Unconstrained Estimation of HRV Indices after Removing Respiratory Influences from Heart Rate." IEEE JBHI (2018).

[8] Orini, M. et al. "A Time-Varying Nonparametric Methodology for Assessing Changes in QT Variability Unrelated to Heart Rate Variability." IEEE TBME 65.7 (2018): 1443-1451.

[9] Saul, J. P. et al. "Transfer function analysis of the circulation: unique insights into cardiovascular regulation." AM J PHYSIOL-HEART C 261.4 (1991): H1231-H1245.

[10] Varon, C. et al. "A novel algorithm for the automatic detection of sleep apnea from single-lead ECG." IEEE TBME 62.9 (2015): 2269-2278.

[11] Moeyersons, J. et al. "R-DECO: An open-source Matlab based graphical user interface for the detection and correction of R-peaks." BioRxiv (2019): 560706.

[12] Bailón, R. et al. "Analysis of heart rate variability using time-varying frequency bands based on respiratory frequency." 2007 29th Annual Proc. IC of the IEEE EMBC. IEEE, 2007.

[13] Morales, J. et al. "Evaluation of Methods to Characterize the Change of the Respiratory Sinus Arrhythmia with Age in Sleep Apnea Patients." Proceedings of EMBC. IEEE, 2019.

[14] Hellman, J. & Stacy, R. W. (1976). "Variation of respiratory sinus arrhythmia with age." J Appl Physiol 41.5 (1976): 734-738.

Address for correspondence:

Name: John Fredy Morales Tellez

Full postal address: Kasteelpark Arenberg 10 - box 2446, 3001 Leuven

E-mail address:jmorales@esat.kuleuven.be