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Oscillatory patterns in heart rate variability and complexity: A *meta*-analysis

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ABSTRACT

The study of instantaneous heart rate changes is a non invasive form to obtain indirect information about heart rate control. This beat-to-beat variation is denominated heart rate variability (HRV) and when estimated through frequency domain methods provides information about the sympathetic (SNS) or parasympathetic (PNS) nervous system. Beat-to-beat variation can also be estimated by nonlinear methods, then termed heart rate complexity (HRC). Even though HRC does not possess a straightforward relationship with the SNS or PNS, these estimators are also utilized to infer changes in the autonomic nervous system (ANS). In many situations, a low value of both indexes (HRV/HRC) is associated with several cardiovascular diseases. On the other hand, there are scenarios (such as, exercise and temperature challenges) in which those indexes appear to be less informative, mainly because the association between HRV/HRC and the ANS ceases to hold tight. Therefore, it is interesting to extract additional information from HRV/HRC analyses that could lead to a broader understanding of cardiac control. Previous experiments in our laboratory suggested the existence of an oscillatory component in HRV/HRC results along the time of experiment. The present study tested the existence of this pattern in HRV/HRC of 13 subjects running at constant speed. For this purpose, sine wave, linear and quadratic models were fitted to the results of these estimators. The sine wave model significantly, and more adequately than the other models, fitted the results obtained. Furthermore, the correlation obtained was significantly higher for the HRC data. This *meta*-analysis is a novel technique not found in the literature survey, moreover, it reveals a new way to approach cardiac control.

1. Introduction

The variation in sequential heart rate beats arises from the dynamical interaction between sympathetic and parasympathetic nervous systems and is considered an estimator of heart rate control [1]. These instantaneous heart rate (HR) changes are studied through variations in R–R intervals (period between two consecutive R waves in an electrocardiogram – ECG) and may be, more commonly, measured by a frequency domain index (heart rate variability, HRV) and nonlinear methods (heart rate complexity, HRC). HRV employs a fast Fourier transform and the different ranges of the spectrum (low frequencies, LF, and high frequencies, HF) are associated with the sympathetic (LF) or parasympathetic nervous system (LF and HF, [2]). Typically, a high value of HRV is associated with an increase in the parasympathetic activation [2]. On the other hand, HRC employs, among other options, methods deriving from the information theory (such as a1ApEn, [3]) to quantify the degree of disorder in time series. Even though the relationship is not as straightforward as in HRV, many studies utilized nonlinear methods to infer alterations in the activity of the autonomic nervous system branches (e.g., [4–8]).

In both HRV and HRC approaches, a low value of such estimators is associated with several cardiovascular diseases [2,9–11]. Nevertheless, the physiology behind these analyses is considered obscure [12]. The main problem is that HRV/HRC data does not match what is expected for the branches of the autonomic nervous system (ANS) in many situations [12–14]. This issue can be illustrated in the context of exercise and in responses to temperature challenges. As we

Abbreviations: HRV, heart rate variability; SNS, sympathetic nervous system; PNS, parasympathetic nervous system; HRC, heart rate complexity; ANS, autonomic nervous system; HR, heart rate; ECG, electrocardiogram; LF, low frequencies components of HRV; HF, high frequencies components of HRV; a1ApEn, area of the ApEn for all tolerances and window size 1; $\dot{V}O_2$**max**, maximal rate of oxygen consumption; FFT, fast fourier transform; nuHF, normalized HF, calculated by nuHF = HF/(LF + HF); Ratio, the ratio between LF and HF; VLF, very low frequencies components of HRV.

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present briefly, our study focuses on the former process, but some discussions shall be extrapolated to the latter.

It is well known that the relationship between beat-to-beat and ANS is particularly problematic when studied during exercise at higher intensities. This is because the increase in HRV/HRC may not be explained by the decrease in parasympathetic activation typically expected in these conditions [15,16]. A plausible rationalization is that at higher magnitudes of exercise, non-neural regulation (e.g., changes in the mechanical cardiac axis due to changes in the ventilatory pattern, and/or atrial transmural pressure associated with intratoraxic pressure and venous return [17,18]) becomes more relevant [19]. This suggestion is corroborated by data that include experiments with ganglion blockage [18] and heart transplanted subjects [17]. However, since beat-to-beat analyses (especially HRV) are limited to inferences regarding the sympathetic and the parasympathetic autonomic nervous systems, there is not a clear way to extract this non-neural information in normal subjects.

The constraints imposed by the HRV/HRC versus sympathovagal modulation paradigm are also reflected in other parameters influencing the heart rate control (e.g., effect of controlled ventilation or drugs on the ANS [12]), leading to the conclusion that the relationship between cardiac control and specific ranges of a spectral power analysis is too simplistic [20]. This is observable, for example, in the few existing studies regarding the effect of high temperatures in HRV/HRC. Brenner et al. [21] obtained, during 50%$\dot{V}O_2$max exercise at high temperatures, a non significant decrease in the parasympathetic activity estimated through the HF component and, moreover, a significant increase in the LF/HF ratio (representing sympathovagal balance). Furthermore, Flouris et al. [8] studied instantaneous heart rate control during exercise along 14 days of high temperature acclimation, and obtained an increase in the parasympathetic activity in 75 of the 102 variables measured (including linear, frequency domain and nonlinear methods). It is possible to identify, therefore, a variety of protocols designed to better understand the relationship between instantaneous heart rate control and temperature. However, this interpretation is, once again, only related to changes in the branches of the autonomic nervous system. This restraint is illustrated by the work of Flouris et al. [8], where 102 heart rate control estimators were utilized to reach a single conclusion, i.e., that there is an increase in parasympathetic activity.

The restriction of this conclusion is highlighted considering that thermoregulation affects very low frequency components of heart rate control [20,22], which are not typically covered by heart rate analysis. Moreover, it is suggested that hot-induced alterations are associated with the necessity to sustain venous return [21] which provoke, in the first instance, cardiac changes unrelated to the ANS (i.e., non-neural) [17].

In this context, even though the analysis of sympathovagal modulation by methods of HRV or HRC contributes in understanding many aspects of cardiovascular physiology, it is important, and a general aim of this study, to extract additional information from HRV or HRC analyses. Such information could lead to a broader understanding of cardiac control and, more specifically, to a better comprehension of the beat-to-beat changes during, as exemplified, exercise or temperature challenges.

Previous pilot experiments in our laboratory measuring HRC and HRV in 7 subjects walking in treadmills suggested that the heart rate control estimators exhibit an oscillatory pattern along the time of experiment. Despite the potential to extract new information from this pattern, it is required, first and foremost, additional analysis with a new set of data to test if this pattern is ubiquitous. For this specific objective of this study, 13 new subjects were studied. We analyzed HRV and HRC, measured through a1ApEn, during 25 min of running; a situation when the autonomic neural components of cardiac control become less detectable [19].

2. Material and methods

The experiments were conducted in 13 healthy male voluntaries (mean age: 29 years, range 20–35; mean body mass index: 24.88, range 19.58–32.95) with different degrees of fitness. All subjects were instructed to be hydrated and to not drink coffee and alcohol in the day of the experiment and to avoid extreme physical activity in the day before. The experiments were conducted at the Biosciences Institute of the University of São Paulo and the experimental protocol was approved by the local ethics committee (Comissão de Ética no Uso de Animais-Instituto de Biociências (CEUA-IB)). All ECG data were collected at ambient temperatures of 21–24 °C and always at the preferential time of the day for physical activity for each individual.

For control purposes, electrocardiogram (ECG) data was recorded for 5 min during resting conditions and, afterwards, each participant had its preferential speed (u) estimated and warmed-up during 5 min at 0.9 u. Subsequently, ECG was recorded during 25 min of running at constant speed u.

ECG data was acquired by means of three superficial electrodes (Unilect Electrodes, Maersk Medical LTD, Copenhagen, Denmark) in the CM5 configuration. ECG was recorded and digitalized using a sampling rate of 1000 Hz by a MP30 interface and the Biopac Student Lab Pro software (Biopac Systems Inc., Goleta, CA, USA). From the filtered raw data, R–R intervals were extracted. The first minute of data was discarded to avoid transient behaviors, hence, 24 min of the original signal were utilized for the analyses. All of the following procedures were performed in sequential (time-ordered) series of 256 points sub-vectors, with 231 points of overlap between each pair of sub-vectors, along the original data set.

For each sub-vector, the heart rate variability and heart rate complexity were analyzed. Heart rate variability, via fast Fourier transform (FFT) was carried out and the spectral components were separated in 0.04–0.15 Hz for low frequencies range (LF, related to both sympathetic and parasympathetic activity) and 0.15–0.4 Hz for high frequencies range (HF, associated with the parasympathetic activity) [2]. Variability was estimated via the normalized HF (nuHF, calculated by nuHF = HF/(LF + HF)) and the ratio between LF and HF (from now on simply referred as to "ratio") [2]. Heart rate complexity was obtained by means of a1ApEn (defined as the area beneath the curve of ApEn, developed by Pincus [23], versus the tolerance r given an $m = 1$ [3]). Notice that, differently from the nuHF and the a1ApEn-HRC, a smaller value of the LF/HF ratio is related to a higher level of heart rate variability.

Both R–R extraction and subsequent analyses were performed through a set of implemented scripts in Matlab (MATLAB version 7.10.0.499 Natick, Massachusetts, USA: The MathWorks Inc.). Since the original dataset is sequentially analyzed, we obtain sequential results, i.e., time-ordered resulting vectors.

The resulting vectors were DC corrected (i.e., shifted along the y axis) in order to have zero mean. These resulting data were fitted through a single sine wave (nonlinear least squares method: Trust-Region algorithm), a linear polynomial and a quadratic polynomial (linear least squares). The linear and quadratic polynomials were chosen to verify if the oscillatory pattern observed (see Introduction) could be explained by simpler linear and nonlinear models.

To verify the correlation between the original variables and the estimated ones (obtained from the three models), a Pearson's correlation test was utilized. To infer the best adequacy of the models, the correlation value obtained and the adjusted R^2 were compared between models utilizing a paired Student's t-test. From the most adequate model, we investigated which one of the three heart rate