

Quantifying Redundant/Synergistic Interactions Between Cardiorespiratory Reflexes and Cardiac Control Mechanisms During Light-to-Moderate Bicycle Exercise

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Abstract

Some information domain metrics have been devised to quantify whether subsystems contribute to information carried by a target variable more or less than the sum of their separate contributions leading to synergistic or redundant behaviors respectively. We evaluated the net balance between synergy and redundancy of cardiac and cardiorespiratory controls from spontaneous variability of heart period (HP) and respiration (R). HP variability and R were recorded from 16 healthy subjects (22–58 yrs, 6 males) at rest (REST), during bicycle ergometer exercise at 10%, 20% and 30% of the maximum load and recovery. The net balance between synergy and redundancy was estimated via a linear regression approach along with HP mean, HP variance, HP power in the high frequency (HF, from 0.15 to 0.45 Hz) band ($HF_{a_{HP}}$) and squared HP-R coherence at HF [$K^2_{HP-R}(HF)$]. HP mean, HP variance and $HF_{a_{HP}}$ power significantly decreased during exercise and $K^2_{HP-R}(HF)$ tended to decline. The net balance between synergy and redundancy remained unvaried and was not correlated to traditional variability markers. Despite vagal withdrawal, complex cardiac and cardiorespiratory control interactions are preserved during exercise and indexes of synergy and redundancy might provide extra information that more traditional variability markers cannot capture.

1. Introduction

The regulation of heart period (HP) is noninvasively quantified by assessing various features of spontaneous HP fluctuations such as the amplitude of HP variability at the respiratory rate [1] or the degree of predictability of the current HP based on previous HP values [2].

Cardiorespiratory reflexes [3], comprising Hering-Breuer reflex [4], Bainbridge reflex [5] and central modulation of cardiac vagal motoneuron activity and responsiveness [6], are a specific subset of the overall HP regulatory mechanisms that act in response to respiration (R). While the assessment of cardiac control is grounded on the analysis of spontaneous HP variations [7], the evaluation of the cardiorespiratory reflexes requires the simultaneous recording of HP variability and R as a minimal setup and the use of a causal approach assessing the dynamical interactions from R to HP [8-11]. Due to the specificity of cardiorespiratory reflexes one might be interested in evaluating the degree of synergy/redundancy of cardiorespiratory reflexes and the overall cardiac control mechanisms [10-12]. These markers might provide indexes complementary to those more usually computed in HP variability analysis.

The aim of the study is to quantify the net balance between synergy and redundancy of cardiorespiratory and cardiac controls during a protocol known to alter cardiorespiratory coupling via a graded sympathetic activation, namely incremental light-to-moderate bicycle exercise [7,13,14]. Synergy/redundancy was quantified via a linear regression method grounded on the predictive information decomposition approach taking HP as the target series and exploiting the past of HP and R to characterize the cardiac control and cardiorespiratory reflexes respectively [9].

2. Experimental protocol and analysis

2.1. Experimental protocol

A full description of the experimental protocol and population is reported elsewhere [7,13,14]. We studied 16

healthy humans (aged from 22 to 58 yrs, 40 ± 12 yrs, 6 males). We acquired electrocardiogram (ECG) from lead II (ECG Bioamplifier, Marazza, Monza, Italy) and R signal via thoracic belt (Marazza, Monza, Italy). Signals were sampled at 300 Hz. After a period of 10 minutes for stabilization with the subjects in a recumbent position on the bicycle ergometer (Lode, Groningen, The Netherlands), we recorded ECG and R for 10 minutes at rest (REST), for 4 minutes during electronically braked exercise at 10% (EXE1), 20% (EXE2) and 30% (EX33) of the maximum load, and for 10 minutes during recovery (REC). The maximum load was identified individually during a session of incremental exercise until volitional exhaustion carried out the day before. The study was in keeping with the Declaration of Helsinki for medical research involving human subjects and was approved by the ethical review board of the “Luigi Sacco” Hospital, Milan, Italy. Written signed informed consent was obtained from all subjects.

2.2. Beat-to-beat time series extraction

The HP was approximated as the temporal distance between two consecutive R-wave peaks detected over the ECG. R signal was downsampled in correspondence of the first R-wave apex of the ECG providing the onset of the n th HP. R-wave apexes were fixed using parabolic interpolation. The detections of the R-wave peaks were visually checked and manually corrected in case of erroneous identifications. In case of ectopic beats, the series were corrected by means of linear interpolation. Corrections never exceeded 5% of the total values analyzed in each session. HP and R series of 256 consecutive values were selected randomly in each experimental session [9,15]. We computed mean and variance of HP series indicated, respectively, as μ_{HP} and σ_{HP}^2 and expressed in ms and ms^2 .

2.3. Power spectral analysis

Power spectral densities of HP and R series were computed via an autoregressive power spectral approach. The coefficients of the autoregressive model were identified from HP and R series via traditional least squares technique solved via the Levinson-Durbin recursion. The number of coefficients was optimized through the Akaike information criterion. Power spectral density was estimated from the identified coefficients of the autoregressive model and the variance of the prediction error. The power spectral density was decomposed into spectral components. They were classified as high frequency (HF) whether their central frequency dropped into the range from 0.15 to 0.45 Hz

[9,15]. The sum of the HF components of HP series, expressed in absolute units (i.e. ms^2), was labeled as $HF_{a,HP}$. The $HF_{a,HP}$ power is taken as a marker of respiratory sinus arrhythmia (RSA) representing the visible effect of the action of R on HP variability [1].

2.4. Squared coherence analysis

Squared coherence function between HP and R series at the HF, termed $K_{HP-R}^2(HF)$, is traditionally exploited to assess the strength of the cardiorespiratory coupling. It represents the degree of linear correlation between the two series at the respiratory rate. $K_{HP-R}^2(HF)$ was calculated by sampling at HF the ratio between the square cross-spectrum modulus between HP and R series to the product of their power spectra. $K_{HP-R}^2(HF)$ ranged from 1 (full correlation) to 0 (null correlation) and was dimensionless. The estimation of the cross-spectrum was grounded over the identification of a bivariate autoregressive process and the model order was set to 10 [9]. Sampling was performed in correspondence of the weighted central frequency of the R components in HF band, where the weights were the powers of the R components [9].

2.5. Quantification of the net balance between synergy and redundancy

Synergy between two stochastic variables in relation to a third one is observed when the contribution of the two variables to the information carried by the third variable is greater than the sum of their separate contributions. When the opposite situation is observed redundancy is detected. Let us consider the series $HP = \{HP_n, n=1, \dots, N\}$ and $R = \{R_n, n=1, \dots, N\}$ as two realizations of length N of the stochastic processes HP and R . The HP and R processes describe the functioning of cardiac and respiratory systems respectively. Let us assume that the triplet of stochastic variables $HP_n, HP_{n-1,p} = [HP_{n-1} \dots HP_{n-p}]$ and $R_{n,p+1} = [R_n R_{n-1} \dots R_{n-p}]$ represents the current state of the cardiac system, the past state of the cardiac system and the past state of the respiratory system. Moreover, let us assume that the action of $HP_{n-1,p}$ on HP_n and that of $R_{n,p+1}$ on HP_n is owing to cardiac and cardiorespiratory control mechanisms respectively. According to the predictive information decomposition method the net balance between synergy and redundancy of the cardiac and cardiorespiratory controls can be computed as a linear combination of mutual information (MI) terms [5,12] as

$$I_{HP,R}^{HP}(HP_n) = MI(HP_n; HP_{n-1,p}, R_{n,p+1}) + \\ - MI(HP_n; HP_{n-1,p}) - MI(HP_n; R_{n,p+1})$$

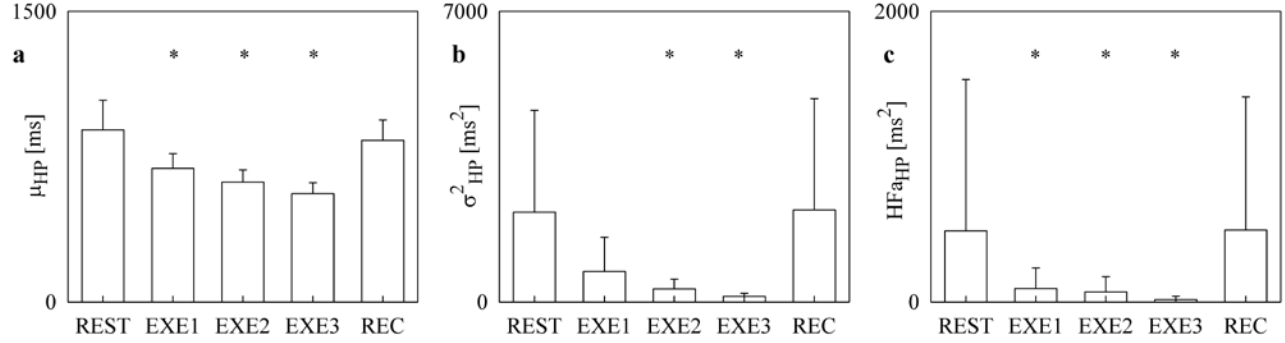


Figure 1. The error bar graphs show μ_{HP} (a), σ^2_{HP} (b), and HFa_{HP} (c) as a function of the experimental condition (i.e. REST, EXE1, EXE2, EXE3 and REC). The symbol * indicates a significant difference compared to REST with $p < 0.05$.

where $MI(HP_n; HP_{n-1,p}, R_{n,p+1})$ is the MI between HP_n and the vector variables $HP_{n-1,p}$ and $R_{n,p+1}$ when they are jointly considered and $MI(HP_n; HP_{n-1,p})$ and $MI(HP_n; R_{n,p+1})$ are the MIs between HP_n and the vector variables $HP_{n-1,p}$ and $R_{n,p+1}$ when they are separately considered. $I^{HP}_{HP,R}(HP_n) > 0$ indicates dominant synergy, while $I^{HP}_{HP,R}(HP_n) < 0$ prevalent redundancy. MI estimates were obtained via a linear regression approach solving an identification problem analogous to that of identifying the coefficients of the autoregressive model in Sect.2.3 but accounting for the exogenous effect of R as well [9].

2.6. Statistical analysis

One-way repeated measures analysis of variance (Dunnett's test for multiple comparisons), or Friedman one-way repeated measures analysis of variance on ranks when appropriate (Dunnett's test for multiple comparisons), was applied to test the significance of the changes of indexes versus REST. Pearson correlation analysis was carried out to assess the degree of the correlation of $I^{HP}_{HP,R}(HP_n)$ on traditional variability markers of HP series (i.e. μ_{HP} and σ^2_{HP}) and on more usual indexes of cardiorespiratory coupling [i.e. HFa_{HP} and $K^2_{HP-R}(HF)$]. Pearson product moment correlation coefficient r and type I error probability p were calculated. Data were reported as mean \pm standard deviation. A $p < 0.05$ was always considered as significant.

3. Results

Figure 1 shows μ_{HP} , σ^2_{HP} and HFa_{HP} as a function of the experimental condition (i.e. REST, EXE1, EXE2, EXE3 and REC). The effect of the exercise protocol was evident: indeed, μ_{HP} (Fig.1a) and HFa_{HP} (fig.1c) decreased compared to REST irrespective of the exercise load, while the decline of σ^2_{HP} (Fig.1b) became visible during EXE2 and EXE3.

Figure 2 and Figure 3 have the same structure as Fig.1 but they show $K^2_{HP-R}(HF)$ and $I^{HP}_{HP,R}(HP_n)$ respectively. A tendency toward a decrease of $K^2_{HP-R}(HF)$ during EXE sessions was manifest but it was not significant due to the

dispersion of the indexes (Fig.2). Conversely, $I^{HP}_{HP,R}(HP_n)$ did not exhibit any apparent trend during EXE sessions (Fig.3).

We computed the degree of the correlation of $I^{HP}_{HP,R}(HP_n)$ on μ_{HP} , σ^2_{HP} , HFa_{HP} and $K^2_{HP-R}(HF)$. Data were pooled together regardless of the experimental condition. None of the markers was found to be significantly associated with $I^{HP}_{HP,R}(HP_n)$ with $p < 0.05$.

4. Discussion

We applied a predictive information decomposition approach [9-12] to assess the net balance between synergy and redundancy of cardiac and cardiorespiratory regulations in governing the HP evolution. Cardiac control mechanisms comprise reflexes adjusting HP in response to R [4-6] as well as regulatory mechanisms targeting again HP but driven by variations of physiological variables different from R (e.g. arterial pressure) [8-10]. The evaluation was carried out during an experimental protocol known to alter the difference between the minimum and maximum HPs during a respiratory cycle, i.e. the RSA, being the apparent consequence of the cardiorespiratory coupling [1]. While

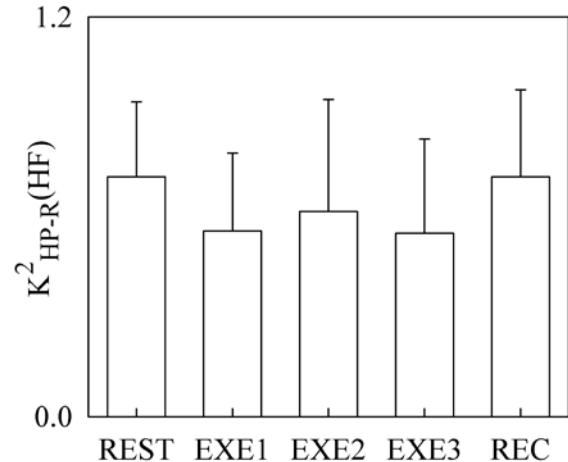


Figure 2. The error bar graph shows $K^2_{HP-R}(HF)$ as a function of the experimental condition (i.e. REST, EXE1, EXE2, EXE3 and REC).

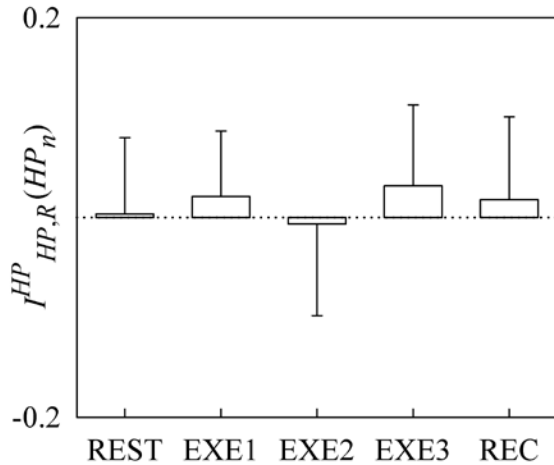


Figure 3. The error bar graph shows $I^{\text{HP}}_{\text{HP,R}}(\text{HP}_n)$ as a function of the experimental condition (i.e. REST, EXE1, EXE2, EXE3 and REC).

bicycle exercise decreased significantly RSA, as estimated via HFa_{HP} , and tended to decline the strength of the HP-R association, as estimated with $K^2_{\text{HP-R}}(\text{HF})$, the net balance between synergy and redundancy of cardiac and cardiorespiratory controls remained unvaried. We conclude that a sympathetic activation induced by bicycle exercise [7,13,14] was not able to affect this peculiar feature. This finding is emphasized by the uncorrelation of $I^{\text{HP}}_{\text{HP,R}}(\text{HP}_n)$ with traditional indexes characterizing HP variability and its link to R. This finding is particularly remarkable whether it is compared to our previous observation that controlled breathing at a frequency slower than the spontaneous one in healthy subjects was able to increase HFa_{HP} and $K^2_{\text{HP-R}}(\text{HF})$, raise redundancy and evoke a certain degree of correlation between synergy/redundancy indexes and more traditional cardiorespiratory variability markers [9]. Indeed, experimental protocols evoking opposite modifications of HFa_{HP} and $K^2_{\text{HP-R}}(\text{HF})$ did not produce trivial courses of $I^{\text{HP}}_{\text{HP,R}}(\text{HP}_n)$.

5. Conclusion

This study stresses that a marker measuring the net balance between synergy and redundancy of cardiac and cardiorespiratory controls provides complementary information to more classical variability indexes derived from HP series and its interactions with R. This complementarity is likely to be linked to the specific experimental protocol evoking sympathetic activation and vagal withdrawal associated to the physical challenge.

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