Comparison Between ECG-Derived Respiration and Respiratory Flow for the Assessment of Cardiorespiratory Coupling Before and After Cardiopulmonary Exercise Test Protocol

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Abstract

Evaluation of cardiorespiratory coupling (CRC) usually requires the simultaneous recording of heart period (HP) variability, derived from the electrocardiogram (ECG), and respiration. ECG-derived respiration (ECGDR) exploits the cardiac axis movement due to respiration to estimate respiratory activity directly from the ECG. Since CRC indexes could theoretically be computed using ECGDR, a comparison with results obtained through a more precise monitoring of respiratory activity such as the respiratory flow (RF) is warranted. Therefore, a mixed unpredictability index (MUPI) of HP variability from respiratory dynamics, computed via local k-nearest-neighbor approach, was calculated using ECGDR and RF in patients with preserved functional capacity (PFC) and with reduced functional capacity (RFC) before and after cardiopulmonary exercise test (CPET) protocol. The MUPI computed from RF was found to be significantly increased in PFC patients after CPET protocol, while no effect could be observed when considering the ECGDR. Moreover, the correlation between the two MUPI indexes was limited. We conclude that indexes of CRC might require more direct measures of respiration than ECGDR to detect pathophysiological differences.

1. Introduction

Cardiorespiratory coupling (CRC) refers to the influences of respiration on heart period (HP) changes occurring through a variety of physiological mechanisms [1]. The assessment of CRC usually requires the recording of the electrocardiogram (ECG), necessary for the evaluation of HP, and of a respiratory trace. Cardiac axis movements synchronous with respiration produce amplitude modulations of the ECG that allow one to derive ECG-derived respiration (ECGDR) [2]. ECGDR has been used to estimate respiratory rate, and occasionally some additional respiratory features [3-7]. The ECGDR has the undoubted advantage of monitoring CRC with the minimum number of traces (i.e., without any direct recording of the respiratory activity). However, the accuracy in the estimation of CRC indexes when employing ECGDR is debated [3]. It is therefore of interest to compare results obtained from ECGDR and direct recordings of respiratory activity such as respiratory flow (RF) when modern CRC indexes, explicitly devised to account for the issue of directionality of the interactions and presence of nonlinear features, are computed [8].

It is also known that high intensity physical exercise modifies cardiac control as monitored through HP variability, with significant differences between baseline and recovery in the minutes following exercise cessation [9-12]. The dynamics of vagal reactivation are highly individual but generally dependent on exercise intensity [10], with a greater intensity resulting in a slower recovery of HP and HP variability [9,11,12]. As CRC decreases in situations of sympathetic activation and vagal withdrawal [13], high-intensity physical exercise could potentially influence CRC during the recovery phase.

The aim of this study is to compare ECGDR and respiratory flow (RF) in the evaluation of CRC using a local mixed unpredictability (MUP) approach [8,14,15]. The methodology was tested in patients with preserved functional capacity (PFC) and with reduced functional capacity (RFC) before and after cardiopulmonary exercise test (CPET) protocol on a cycle ergometer.

2. MUP

Given two series $x=\{x_n,\ 1\le n\le N\}$ and $y=\{y_n,\ 1\le n\le N\}$, where n is the progressive sample counter and N the series length, we define the multidimensional mixed pattern $\boldsymbol{x}_n^- \oplus \boldsymbol{y}_n^-$ concatenating m_x past samples of x collected in $\boldsymbol{x}_n^- = [x_{n-\tau_x} \quad \cdots \quad x_{n-\tau_x-m_x+1}]$ and m_y past samples of y collected in $\boldsymbol{y}_n^- = [y_{n-\tau_y} \quad \cdots \quad y_{n-\tau_y-m_y+1}]$, where τ_x and τ_y are assigned latencies [8,14,15]. We refer to y_n as the image of $\boldsymbol{x}_n^- \oplus \boldsymbol{y}_n^-$ through a deterministic function $f(\cdot)$ whose estimate allows the prediction $\hat{y}_n$ of y_n. We exploited a local MUP approach based on k nearest neighbors to calculate $\hat{y}_n$. More precisely $\hat{y}_n$ was computed as the weighted mean of the images of the k nearest neighbors of the reference mixed vector $\boldsymbol{x}_n^- \oplus \boldsymbol{y}_n^-$, whose weights are the inverse of their distance from $\boldsymbol{x}_n^- \oplus \boldsymbol{y}_n^-$ [16]. The complement to 1 of the normalized cross-correlation coefficient ρ^2 between y and the predicted series $\hat{y}$ was utilized to quantify unpredictability. Only $\boldsymbol{x}_n^- \oplus \boldsymbol{y}_n^-$ was excluded from the set of its k nearest neighbors [16]. The portions of $\boldsymbol{x}_n^- \oplus \boldsymbol{y}_n^-$ (i.e., $\boldsymbol{x}_n^-$ and $\boldsymbol{y}_n^-$) were built incrementally according to the strategy of nonuniform embedding [8,17,18]. Each component of the vectors $\boldsymbol{x}_n^-$ and $\boldsymbol{y}_n^-$ at the same time index was added only if the addition was able to decrease unpredictability. The procedure of adding components to $\boldsymbol{x}_n^-$ and $\boldsymbol{y}_n^-$ was stopped when unpredictability did not decrease anymore. The minimum of unpredictability was taken as index of the inability of x to predict y and it will be referred to as the MUP index (MUPI) [8]. MUPI is bound between 0 (i.e., y is perfectly predictable using past values of y and x) and 1 (i.e., y is completely unpredictable using past values of y and x) [8]. According to standard practice [8], k=30, τ_x=0 beats and τ_y=1 beat. In the following, we computed MUPI with x=RF ($MUPI_{RF}$) or x=ECGDR ($MUPI_{ECGDR}$), while y is HP variability.

3. Experimental Protocol and Data Analysis

3.1. Experimental Protocol

Data were acquired from 31 patients who received clinical indication of cardiopulmonary exercise test (CPET) examination at IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy. According to clinical parameters, 20 patients were classified as PFC (age: 58±11 yrs, 9 males) and 11 as RFC (60±11 yrs, 5 males). All patients underwent a standard CPET with incremental ramp protocol on an electronically braked cycle ergometer. ECG and RF were acquired (Quark CPET, Cosmed, Rome, Italy) before CPET protocol (PRE), and during the recovery phase (POST) at a sampling frequency of 500 Hz. The study protocol adhered to the principles of the Declaration of Helsinki for medical research involving human subjects and was approved by the local ethical committee. Written informed consent was obtained from all patients before taking part in the study.

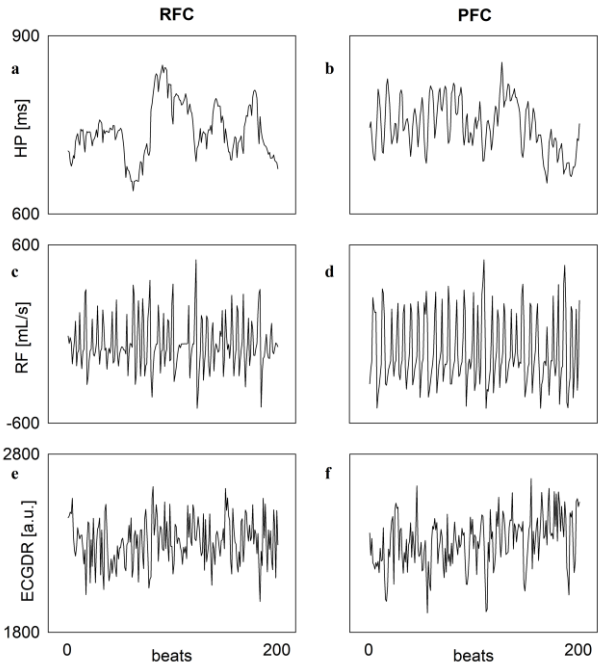

Figure 1. Examples of variability series of HP (a,b), RF (c,d) and ECGDR (e,f) collected in one RFC individual (a,c,e), and one PFC patient (b,d,f) in PRE.

3.2. Series Extraction

R-wave peaks were located according to a threshold-based algorithm working on the first derivative of the ECG [2]. The identified R-wave peaks were then visually checked and manually corrected, if necessary. The time distance between two consecutive R-wave peaks was taken as HP. ECGDR was taken as the amplitude of the first R-wave peak delimiting the nth HP with respect to the isoelectric line [2]. RF signal was sampled at the same time instant. RF values were expressed in mL/s and ECGDR samples in arbitrary units (a.u.). Sequences of 200 consecutive values were selected at random within each experimental session under stationary conditions. Examples of the HP, RF, and ECGDR series acquired from one RFC subjects and one PFC patient in PRE are shown in Fig.1. Mean and variance were computed from the HP variability series, labelled μ_{HP} and σ^2_{HP}, and expressed respectively in ms and ms^2. Respiratory frequency was computed from the two respiratory series, labelled f_{RF} and f_{ECGDR}, and expressed in Hz.

3.3. Statistical Analysis

Normality was tested using the Shapiro-Wilk test. Two-

Table 1. Time domain HP variability and respiratory indexes in PFC and RFC groups.

Index	RFC		PFC	
	PRE	POST	PRE	POST
μ_{HP} [ms]	909±132	797±128*	828±168	646±65*
σ^2_{HP} [ms^2]	2211±1120	2079±1103	1859±1321	1421±881*
f_{RF} [Hz]	0.29±0.04	0.33±0.04	0.27±0.05	0.31±0.04*
f_{ECGDR} [Hz]	0.28±0.04	0.31±0.04	0.26±0.04	0.30±0.05*

RFC: reduced functional capacity; PFC: preserved functional capacity; CPET: cardiopulmonary exercise test; PRE: before CPET protocol; POST: after CPET protocol; HP: heart period; μ_{HP}: HP mean; σ^2_{HP}: HP variance; RF: respiratory flow; f_{RF}: respiratory rate from RF; ECGDR: ECG-derived respiration; f_{ECGDR}: respiratory rate from ECGDR. The symbol * indicates $p<0.05$ vs PRE.

way repeated measures analysis of variance (one factor repetition, Holm-Sidak test for multiple comparisons) was performed to evaluate the between-group differences within the same experimental condition (i.e., PRE or POST) and the effects of CPET protocol within the same experimental group (i.e., PFC or RFC). Pearson's correlation coefficient *r* and type I error probability p were computed between the pooled results of $MUPI_{RF}$ and $MUPI_{ECGDR}$ and of f_{RF} and f_{ECGDR}. Results are presented as mean±standard deviation. Statistical analysis was carried out using a commercial statistical program (Sigmaplot, v.14.0, Systat Software, Inc., Chicago, IL, USA). A $p<0.05$ was always considered as significant.

4. Results

Table 1 summarizes results regarding time domain HP variability and respiratory indexes. While μ_{HP} decreased significantly in POST in both groups, σ^2_{HP} only significantly declined in the PFC cohort. Both f_{RF} and f_{ECGDR} showed similar increases in POST compared to PRE in both groups (i.e., RFC and PFC), although it was only statistically significant in PFC patients.

Table 2 summarizes MUPI in PFC and RFC groups during PRE and POST as computed from RF and ECGDR. $MUPI_{RF}$ tended to increase in POST for both groups, with the difference being significant in PFC patients. This tendency and statistical significance were lost when $MUPI_{ECGDR}$ was considered. $MUPI_{RF}$ and $MUPI_{ECGDR}$ were also found to be only moderately correlated (r=0.457, p=3.99×10^{-4}), while correlation between f_{RF} and f_{ECGDR} was much stronger (r=0.827, p=7.11×10^{-15}).

5. Discussion

The main findings of this study can be summarized as follows: i) ECGDR series is valid to estimate respiratory rate, but it is less useful to detect changes of CRC in response to CPET protocol; ii) RF series indicates that the CPET protocol affects CRC; iii) the modification of CRC after CPET protocol is visible only in PFC patients, thus indicating a more reactive and flexible neural cardiac control.

ECGDR has traditionally been used as a surrogate for respiration to estimate the respiratory rate [3-7]. The present study confirms the validity of ECGDR for the estimation of respiratory rate. Indeed, f_{ECGDR} was strongly correlated with f_{RF} and both estimates suggest similar trend across groups and experimental conditions. Conversely, the conclusion about the similarity of indexes derived from RF and ECGDR does not hold for MUPI. Indeed, in addition to a limited agreement between $MUPI_{RF}$ and $MUPI_{ECGDR}$, the increase of MUPI after CPET protocol was evident only using $MUPI_{RF}$. An increase of MUPI after CPET protocol is expected given that sympathetic activation commonly reduces CRC [13,19,20] as a likely result of a concomitant restraint of the vagal control [21]. A decrease in CRC after CPET protocol could be taken as

Table 2. MUPI in PFC and RFC groups in PRE and POST.

Index	RFC		PFC	
	PRE	POST	PRE	POST
$MUPI_{RF}$	0.38±0.24	0.48±0.25	0.37±0.24	0.55±0.25*
$MUPI_{ECGDR}$	0.55±0.25	0.45±0.23	0.36±0.24	0.46±0.26

RFC: reduced functional capacity; PFC: preserved functional capacity; CPET: cardiopulmonary exercise test; PRE: before CPET protocol; POST: after CPET protocol; RF: respiratory flow; ECGDR: ECG-derived respiration; MUPI: mixed unpredictability index. The symbol * indicates $p<0.05$ vs PRE.

an index of a greater reactivity and flexibility of the neural cardiac control that allows for a more efficient response to stressors [19].

Previous studies suggested that ECGDR and signals more directly linked to respiratory activity could lead to a different characterization of CRC, especially when CRC indexes accounting for causality of the interactions are exploited [3]. Indeed, in [3] it was suggested that direct respiration recordings should be preferred in the assessment of transfer entropy from respiration to HP variability since the noisy nature of ECGDR could degrade causal relationships.

6. Conclusions

We conclude that, while ECGDR is a useful tool for the estimation of respiratory rate, the computation of modern indexes of CRC explicitly accounting for causality and nonlinearities, such as MUPI, might require more direct measures of respiration to detect differences across groups and experimental conditions. Furthermore, MUPI, as derived from RF, was shown to be a useful tool to assess the effect of CPET protocol on CRC and, more remarkably, this effect is different in PFC and RFC groups. This aspect that should be further investigated in conditions of impaired respiratory function such as in COVID-19 syndrome.

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