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Joint Symbolic Dynamics as an Effective Approach to Study the Influence of Respiratory Phase on Baroreflex Function

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***Abstract*—This study sought to employ a novel approach based on joint symbolic dynamics (JSD) to study the influence of respiratory phase on baroreflex function. We recorded electrocardiograms (ECG), blood pressure and respiration in 10 (5 male/5 female) healthy experienced athletes. For our analysis, time series of R-R intervals and systolic blood pressure were extracted, and respiratory phases were obtained using the Hilbert transform. Based on the changes between successive values, each series was transformed into binary symbol vectors, and words of length '2' were formed. From parallel analysis of the symbolic dynamics in the three time series, the relationship between respiratory phases and baroreflex function was quantified. We analysed baroreflex patterns via different word combinations for specific respiratory phases and observed that baroreflex patterns occurred at similar frequency during expiration, inspiration and phase transitions (25.0±14.4% vs. 33.4±19.5%, expiration-inspiration: 25.0±12.6% and inspiration-expiration: 22.1±17.4%, respectively). From this study, it appears that JSD provides a novel and efficient technique for the combined analysis of interactions between respiration, heart rate and blood pressure.**

I. Introduction

The function of the heart is closely intertwined with that of the lungs. Combined analysis of interactions between heart rate, blood pressure and respiration provides a non-invasive tool for the study of autonomic nervous system activity. One important phenomenon of this interaction, which has not yet been characterized fully, is the inter-relationship between respiratory phase and baroreflex responsiveness. It has been suggested that the study of baroreflex activity and respiration might provide early indicators of autonomic dysfunction [1, 2]. However, the interplay between baroreflex and respiratory sinus arrythmia is thought to result in complex behaviour. Most previous studies were performed using conventional signal-processing techniques such as cross-correlation and coherence analysis, which maybe inadequate for characterizing the complex dynamics of heart rate, blood pressure and respiration, as these signals are non-linear, non-stationary and often contain superimposed noise [3, 4].

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We were interested in employing a recently proposed technique based on joint symbolic dynamics (JSD), which provides easy interpretation of physiological data by means of a few symbols and employs a coarse-graining procedure in which some of the detailed information is lost, but the robust properties of the dynamics are preserved [5-8]. This study was conducted to assess JSD as a new and efficient technique for the quantification of the respiration-baroreflex inter-relationship, thereby allowing further detailed analysis of interactions among these signals. We hypothesized that JSD provides a simple and effective technique for the analysis of interaction between respiration and baroreflex function.

II. Methods

A. Subjects

Ten healthy athletes (5 male and 5 female) participated in this study. Among the athletes, none were taking medication before or during the study. Anthropometric data and peak oxygen uptake are shown in Table 1. The study conformed to the principles outlined in the Declaration of Helsinki. All participants provided written informed consent. More details on the recruitment of subjects are published elsewhere [9].

B. Data and pre-processing

High resolution (1600 Hz) ECG, respiration and noninvasive continuous blood pressure (Portapres M2, TNO Biomedical Instrumentation, The Netherlands [10]), recorded simultaneously for 30 minutes in supine position under standardized resting conditions, were used for this study. Custom-written computer software developed under MATLAB® was used for the detection of ECG R-peaks, systolic blood pressure and inspiratory/expiratory onsets of respiratory signal. Data were visually inspected and all segments containing artefacts were simultaneously excluded from the three recordings during analysis.

Parabolic fitting was used to detect ECG R-peaks, where a parabola of a length based on the sampling frequency of ECG signal is fitted around the R-wave to determine R-wave maximum. The R-R time series, obtained from the time intervals between consecutive R-peaks, were visually scanned for artifacts and, if necessary, manually edited. Systolic blood pressure (SBP) was determined as the peak magnitudes of the continuous blood pressure signal between two consecutive R-peaks.

TABLE I
ANTHROPOMETRIC DATA AND PEAK OXYGEN UPTAKE OF THE ATHLETES PRESENTED AS MEDIANS AND INTERQUARTILE RANGES (IQR).

Gender	Men		Women	
	Median	IQR	Median	IQR
Age (yrs)	26.6	26.5-28.8	24.8	24.7-26.4
Body Mass (kg)	72.0	69.0-86.8	54.8	50.4-61.8
Height (cm)	181	181-182	163	162-168
VO_2 peak (ml/[kg*min])	65.9	61.4-74.6	51.1	48.9-52.2

The respiratory signal was low-pass filtered at 0.5 Hz using a zero-phase forward and reverse digital filter. The inspiratory/expiratory onsets, used to compute the breath-to-breath time series, were determined as the zero-crossings of the first derivative of the respiratory signal. The phases of the respiratory signal were calculated using the Hilbert transform.

C. Joint symbolic dynamics approach

In this study, the respiratory phases, RP, at the instants of R-peaks were considered. In regard to the alignment of the R-R time series to the SBP time series, we started from the R-peak following the first SBP (i.e. the cardiac cycle following the first systolic blood pressure pulse) to ensure that blood pressure mediated baroreflex control of heart rate is reflected in our analysis. From the vectors of R-R time series, SBP and RP we established three symbolic sequences, s^{HR} (HR denoting the heart rate—reciprocal of R-R interval) s^{SBP} and s^{RP}, using the transformation rule below that is based on the differences between successive R-R intervals, SBP and R-instant respiratory phases, respectively, as described previously [8]

$$S_i^{HR} = \begin{cases} 0 \text{ if } RR_{i+1} - RR_i > 0 \\ 1 \text{ if } RR_{i+1} - RR_i \le 0 \end{cases} \quad (1)$$

$$S_i^{SBP} = \begin{cases} 0 \text{ if } SBP_{i+1} - SBP_i \le 0 \\ 1 \text{ if } SBP_{i+1} - SBP_i > 0 \end{cases} \quad (2)$$

$$S_i^{RP} = \begin{cases} 0 \text{ if } |RP_{i+1}| - |RP_i| > 0 \\ 1 \text{ if } |RP_{i+1}| - |RP_i| \le 0 \end{cases} \quad (3)$$

Using the symbol vectors s^{HR}, s^{SBP} and s^{RP}, series of words, w^{HR}, w^{SBP} and w^{RP} of length two (containing two successive symbols) were constructed. Consequently, four different word types were obtained for each vector.

The interactions between the signals were studied by comparing each ith ($i = 1,2,\ldots,n$, where n is total number of words) word from the distributions, w_i^{HR}, w_i^{SBP} and w_i^{RP}. If the sequence of symbols in w_i^{HR} was opposite to that of w_i^{SBP}, it was considered to be a baroreflex pattern. Subsequently, the baroreflex activity was studied for each combination of respiratory phases: inspiratory phase (w_i^{RP}='11'), expiratory phase (w_i^{RP}='00') and transitional phases (w_i^{RP}='01', '10'). The word types span over a 4×4×4 matrix from $[00,00,00]^T$ to $[11,11,11]^T$, as shown in Table II.

TABLE II
TRANSFORMATION OF RR INTERVALS (RR), SYSTOLIC BLOOD PRESSURE (SBP) AND RESPIRATORY PHASES (RP) INTO SYMBOL VECTORS, s^{HR}, s^{SBP} AND s^{RP}, AND WORDS OF LENGTH 2, w^{HR}, w^{SBP} AND w^{RP}, RESPECTIVELY. THE WORDS CAN BE PLACED IN A 4X4X4 TABLE MATRIX.

RR

0.73	0.69	0.71	0.75	0.76	0.75	0.70	0.67

s^{HR}

1	0	1	1	0	1	1

w^{HR}: - 10 01 11 10 01 11

SBP

106	110	108	115	122	118	123	128

s^{SBP}

1	0	1	1	0	1	1

w^{SBP}: - 10 01 11 10 01 11

|RP|

1.89	1.21	0.43	1.71	2.92	2.35	1.18	0.15

s^{RP}

1	1	0	1	0	1	1

w^{RP}: - 11 10 01 10 01 11

w^{HR}	w^{SBP}				w^{RP}
	00	***01***	***10***	***11***	
00				*	***00***
01			*		
10		*			
11	*				
…					***01***
…					***10***
00				+	***11***
01			+		
10		+			
11	+				

The star indicates baroreflex activity during expiratory phase while the plus indicates baroreflex activity during inspiratory phase.

D. Baroreflex analysis

First, the combinations of words between w_i^{HR} and w_i^{SBP} that represent baroreflex activity were considered and their occurrence in each respiratory word type (i.e. phase) was studied. Second, the percentage of baroreflex activity (%baroreflex) for each word type of respiratory phases was determined. For figure 1, %baroreflex was calculated by dividing the total count of a particular word pattern representing baroreflex activity for a specific respiratory phase pattern by the total count of all baroreflex word patterns for that particular respiratory pattern. On the other hand, for figure 2, %baroreflex was calculated by dividing the total count of all words representing baroreflex activity by the total number of words in a specific respiratory phase pattern.

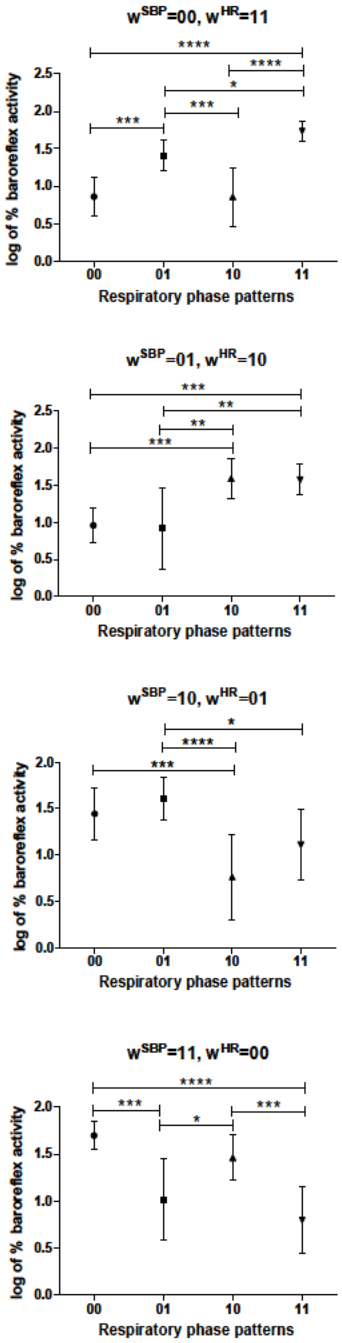

Figure 1. Analysis of the relationship between different patterns of baroreflex response and respiratory phases. A strong association between respiratory phase and baroreflex activity was observed. Here, *,**,*** and **** represents $p < 0.05$, $p < 0.01$, $p < 0.001$ and $p < 0.0001$ respectively, '00','01', '10' and '11' represent different word types.

E. *Statistical analysis*

GraphPad Prism version 5.01 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com) was used for statistical analysis. Percentages of baroreflex activity (%baroreflex) were log-transformed to achieve normal distribution of data across the respiratory phase patterns. We investigated changes in baroreflex activity between different respiratory phases using repeated measures ANOVA. For post-hoc analysis, Tukey's multiple comparison test was used. Values with $p < 0.05$ were considered statistically significant. Data were expressed as mean ± standard deviation (SD).

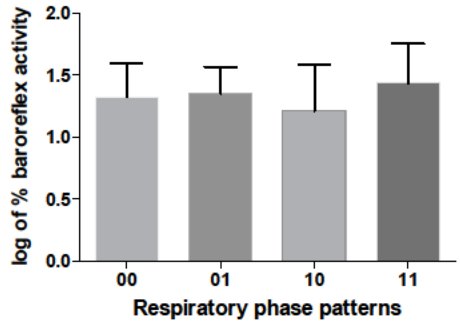

Figure 2. Log-transformed percentage of baroreflex activity for different patterns of respiratory phase. There was no effect of respiratory phase pattern on baroreflex stimulation.

III. Results

The mean R-R interval and respiratory interval of the subjects were 1.1±0.2 s and 4.6±1.0 s, respectively.

A. *Inter-relationship between respiratory phase pattern and baroreflex activity*

A strong association between baroreflex pattern and respiratory phase pattern was observed. The baroreflex pattern w_i^{SBP}=00,w_i^{HR}=11—continuous decrease in SBP and increase in heart rate—was significantly more frequent during inspiration compared to expiration (56.5±16.5% vs. 6.9±6.4%, p<0.0001, see Figure 1 top panel). On the other hand, a significantly higher percentage of baroreflex pattern w_i^{SBP}=11,w_i^{HR}=00 was observed during expiration compared to inspiration (47.3±22.4% vs. 6.8±7.0%, p<0.0001, see Figure 1 bottom panel). Furthermore, there were similar patterns of change in %baroreflex during respiratory phase transitions: high baroreflex activity during inspiratory to expiratory phase transition for a change in SBP from low-high, and vice versa (Figure 1, second and third panel).

B. *Effect of respiratory phase pattern on baroreflex activity*

Baroreflex patterns occurred at similar frequency during expiration, inspiration and phase transitions (25.0±14.4% vs. 33.4±19.5%, expiration-inspiration: 25.0±12.6% and inspiration-expiration: 22.1±17.4%, respectively), see Figure 2.

IV. Discussion

In this paper we investigated inter-relationship between respiratory phase and baroreflex activity using an approach based on joint symbolic dynamics. Our results show that the type of baroreflex pattern is strongly associated with the respiratory phase. The JSD method was able to demonstrate

that baroreflex patterns for which the pattern of systolic blood pressure is reversed compared to that of respiratory phase, i.e. inspiration and expiration are associated to decrease and increase in SBP, respectively occur most frequently. On the other hand, baroreflex patterns occurred at a comparable frequency throughout the respiratory cycle.

In our previous study, analysis of cardio-respiratory interaction using joint symbolic dynamics (JSD) has been suggested to provide improved performance for measuring cardio-respiratory interaction compared to time-domain analyses [8]. For the purpose of this study, in addition to the two parameters (heart rate and respiration), a third parameter, systolic blood pressure, was included to analyse the inter-relationship between respiration and baroreflex activity.

During inspiration, negative intrathoracic pressure causes excessive flow of blood in pulmonary vessels and hence a delay of flow to the left ventricle, causing the SBP to fall and likely generate baroreflex response [11]. Eckberg reported that the gain of baroreflex activation depends on the phase of respiration [12]. According to another study, the cardio-inhibitory response to baroreflex activity is usually smaller during inspiration compared to expiration [2]. This decrease in response during inspiration might be due to a reduction in vagal-cardiac motoneuron responsiveness as a consequence of inhibition originating from inspiratory motoneurons and lung stretch receptors [13]. In this study, baroreflex gain could not be measured since the process of conversion of heart rate and SBP into symbols caused loss of detailed information necessary for gain calculation. From our analysis, however, that considers the pattern of heart rate and SBP, we observed relatively comparable baroreflex activity for all respiratory phases. We observed similar patterns in baroreflex response during inspiratory-expiratory phase transitions, representing the immediate response to SBP changes and causing a delayed heart rate response to respiratory phase changes. This further confirms our previous finding that the response of heart rhythm to respiratory cycle is delayed by one beat [14].

Further investigation is necessary to understand the inter-relation between respiration and baroreflex activity—the methodology proposed in this study may provide the framework for future research.

V. Conclusion

Baroreflex activity is associated with respiratory phases. The approach based on joint symbolic dynamics provides a new representation of the respiratory-baroreflex interaction.

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