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Quantification of Cardio-Respiratory Interactions in Patients with Mild Obstructive Sleep Apnea Syndrome using Joint Symbolic Dynamics

Muammar M Kabir, Hany Dimitri, Prashanthan Sanders, Ral Antic, Derek Abbott, Mathias Baumert

The University of Adelaide, Adelaide, Australia

Abstract

The aim of this paper was to study interactions between R-R intervals and respiratory phases in patients with mild obstructive sleep apnea syndrome (OSAS) during night-time sleep using a technique based on joint symbolic dynamics. We investigated overnight polysomnography data in 123 OSAS patients. The R-R time series were extracted from electrocardiograms (ECG) and respiratory phases were obtained from abdominal displacement sensors using the Hilbert transform. Both series were transformed into ternary symbol vectors based on the changes between two successive R-R intervals and the respective respiratory phases. Subsequently, words of length '3' were formed and the correspondence between words of the two series was determined for each sleep stage to quantify cardio-respiratory interaction. We found a significantly higher percentage of similarity in the symbolic dynamics of R-R intervals and respiratory phases during slow-wave (SW) sleep compared to any other sleep stage (slow-wave vs. stage 1, stage 2 and rapid-eye-movement sleep: 20.9±4.7 vs. 15.5±4.2, 17.0±4.1 and 13.4±2.6, $p<0.0001$, respectively). In conclusion, joint symbolic dynamics provides an efficient technique for the analysis of cardio-respiratory interaction during sleep.

1. Introduction

The association between cardiac and respiratory rhythms has long been recognized [1,2]. Conventional signal processing techniques such as power spectral density and cross-correlation analysis have shown linear dependencies between heart rate and respiratory rate [3,4]. However, these conventional techniques often prove to be inadequate for characterizing the complex characteristics of the biological signals which are inherently non-linear, non-stationary and contain superimposed noise [5,6].

Cardio-respiratory coordination is an aspect of the interaction between heart and respiratory rhythm [7]. It was initially described as short intermittent periods [1] during which the phases of heart rate and respiratory rate coincide with different integer ratios known as phase locking ratios [2]. Another well-known phenomenon of cardio-respiratory interaction is respiratory sinus arrhythmia (RSA) [8], which is a strong modulatory effect of respiration on heart rate [9]. It has been suggested in previous studies that quantification of cardio-respiratory interaction in cardiac patients has clinical merit, for example, utilizing it as a prognostic indicator for cardiac mortality [10], stratifying the risk of cardiac death in patients after myocardial infarction [11], and diagnosing obstructive sleep apnea [12,13].

The concept of symbolic dynamics provides a simplified description of the dynamics of a system with the opportunity for an easy interpretation of physiological data and has successfully been applied in several studies [14-16]. In this paper we introduce an approach that is based on the joint symbolic dynamics of heart rate and respiratory phase to quantify cardio-respiratory interaction in patients with mild OSAS during night-time sleep. Although, by employing a coarse-graining procedure to both time series some of the detailed information is lost, the robust properties of the dynamics are preserved [14,15]. We hypothesized that the cardio-respiratory interaction, changes with sleep stages.

2. Methods

The study conformed to principles outlined in the Declaration of Helsinki and was approved by the local ethics committee, "Human Ethics Committee, Royal Adelaide Hospital". Since de-identified data were collected from participants for this study, the ethics committee waived the need for written informed consents.

2.1. Subjects

Overnight sleep studies were performed in 134 patients (76 males / 58 females) with mild OSAS. We excluded 11 patients (6 males / 5 females) with diabetes mellitus from this study due to suspected diabetic autonomic neuropathy that might potentially confound our results [17]. The age and BMI of the patients ranged 20-77 years (mean ± SD: 49.4 ± 12.3 yrs) and 20.1-73.3 kg/m^2 (mean ± SD: 34.1 ± 8.14 kg/m^2) respectively.

2.2. Overnight polysomnography

Overnight polysomnography was performed using an E series® system (Compumedics, Australia). For sleep staging and arousal scoring standard surface electrodes were applied to the face and scalp, including two-channel electroencephalograms (EEG, C3-A2 and C4-A1), left and right electrooculograms (EOG) and a submental electromyogram. Leg movements were recorded from surface electrodes to tibialis anterior muscle of both legs. Respiratory depth and frequency was monitored using chest and abdominal respiratory inductance plethysmography bands. All PSG were visually scored by the same sleep technician experienced in analyzing paediatric sleep studies. Sleep stages were assigned to consecutive 30 s epochs according to standard rules [18]. For the purpose of this study, sleep stage 3 and 4 were combined and termed slow-wave sleep (SW).

2.3. ECG and respiration analysis

The ECG signal (lead II) was sampled at 128 Hz and saved for off-line analysis. ECG R-wave peaks were detected using the programming library libRASCH (www.librasch.org). The RR intervals time series were visually scanned for artifacts and, if necessary, manually edited.

Abdominal respiratory signals were digitized at 32 Hz. Since respiratory signal consists of linear, nonlinear and non-stationary components usually contaminated to some degree by noise, it was low-pass filtered at 0.5 Hz using a zero-phase forward and reverse digital filter. The inspiratory 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 Hilbert transform.

2.4. Joint symbolic dynamics

From the vectors of the time series' of R-R and respiratory phases at the instants of R-peaks (PH) we established two symbolic sequences, s^{HR} (HR representing the heart rate which is the reciprocal of R-R interval) and s^{PH}, using the transformation rule below, based on the differences between successive R-R intervals and R-instant respiratory phases, respectively,

$$s_i^{\mathrm{HR}} = \begin{cases} 0 \text{ if } \mathrm{RR}_{i+1} - \mathrm{RR}_i > 0 \\ 1 \text{ if } \mathrm{RR}_{i+1} - \mathrm{RR}_i < 0 \\ 2 \text{ if } \mathrm{RR}_{i+1} - \mathrm{RR}_i = 0 \end{cases}$$

$$s_i^{\mathrm{PH}} = \begin{cases} 0 \text{ if } |\mathrm{PH}_{i+1}| - |\mathrm{PH}_i| > 0 \\ 1 \text{ if } |\mathrm{PH}_{i+1}| - |\mathrm{PH}_i| < 0 \\ 2 \text{ if } |\mathrm{PH}_{i+1}| - |\mathrm{PH}_i| = 0 \end{cases}$$

Using the symbol vectors s^{HR} and s^{PH} , we constructed series of words (bins), w^{HR} and w^{PH} of length 3 – containing 3 successive symbols. Consequently, 27 different word types were obtained for each vector.

The interaction between cardiac and respiratory cycles was studied by comparing the i^{th} ($i = 1,2,\ldots,n$, where n is total number of words) words from the distributions, w_i^{HR} and w_i^{PH}. If the sequence of symbols in w_i^{HR} was identical to that of w_i^{PH} (i.e. $w_i^{HR} = w_i^{PH}$), the cardiac and respiratory epochs were considered to be coordinated. The word types span over a 27×27 vector matrix from $[000,000]^T$ to $[222,222]^T$ (Table 1). The percentage of interaction was calculated by dividing the total count of coordinated words by the total number of words.

2.5. Statistical analysis

GraphPad Prism version 5.01 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com) was used for statistical analysis. We investigated the relation between cardio-respiratory interaction and sleep stage using repeated measures ANOVA. Values with $p < 0.05$ were considered statistically significant. Data were expressed as mean ± standard deviation (SD).

3. Results

Subject demographics and polysomnographic (PSG) results for the overnight PSG have been reported previously [13].

3.1. Sleep stage effects on R-R and respiratory intervals

Mean R-R and respiratory intervals we not significantly different between sleep stages (see Figure 1).

3.2. Sleep stage effects on cardio-respiratory interaction

Cardio-respiratory interaction was strongly associated with sleep stage. A significant increase in cardio-respiratory interaction was observed during SW sleep as compared to other sleep stages (SW vs. stage1, stage 2 sleep and REM sleep: 20.9±4.7 vs. 15.5±4.2, 17.0±4.1 and 13.4±2.6 %, p<0.0001, respectively, Figure 2).

Table 1. Transformation of R-R intervals (RR) and respiratory phases (PH) into symbol vectors, s^{HR} and s^{PH}, and words w^{HR} and w^{PH}, of length 3. The words can be placed in a 27×27 table matrix.

RR

0.73	0.69	0.71	0.75	0.76	0.75	0.70

s^{HR}

1	0	0	0	1	1

w^{HR}: - - 100 000 001 011

|PH|

1.89	1.21	0.43	1.71	2.92	2.35	1.18

s^{PH}

1	1	0	0	1	1

w^{PH}: - - 110 100 001 011

w^{PH} \ w^{HR}	000	001	010	011	100	101	110	-	222
000									
001		*							
010									
011				*					
100	+								
101									
110					+				
-									
222									

The star indicates that sequence of symbols in w^{HR} corresponds to w^{PH} and hence is considered coordinated. The plus sign indicates the pair of words with a difference in sequence of symbols.

4. Discussion

In this paper we introduced a method for the investigation of cardio-respiratory interaction in patients with mild obstructive sleep apnea syndrome during night-time sleep. Using an approach based on joint symbolic dynamics, our results show that the amount of interaction between the cardiac and respiratory oscillators is associated with the stage of sleep and is the highest during slow-wave (SW) sleep.

Analysis of respiratory data using symbolic dynamics has been suggested to provide better results than time-domain analyses [19]. In a study by Caminal *et al.* [19], the transformation of respiratory time series into symbolic sequences and their analyses involved different parameters whose values required to be suitably selected. The methodology described in this paper involves only two parameters and is based on the changes in consecutive respiratory phases corresponding to the changes in R-R intervals.

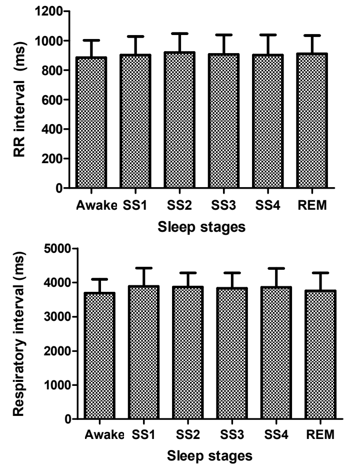

Figure 1. Average R-R and respiratory interval for different sleep stages.

Cardio-respiratory interaction as measured by employing a joint symbolic dynamics approach with a word length of 3 accounted for up to 21% of the entire sleep duration. In accordance with previous studies that were based on the synchrogram technique [12,13],we found a profound sleep stage effect on cardio-respiratory interaction. In line with our current findings, phase-coordination was shown to occur more often and for longer periods in slow-wave sleep compared to REM sleep [13]. The decrease in cardio-respiratory interaction during REM sleep might be the effect of less regular breathing patterns paralleled by sympathetic cardiac activation, making both rhythms more erratic and therefore phase-coordination less likely.

Some of the earlier studies have found changes in heart rate with the change in sleep stages [20,21].However, in this study, the heart rate and respiratory rate showed no significant change with sleep stages. As almost one-third of our study group consisted of patients with heart disease, this co-morbidity as well as its medication might partly explain the different heart rate behaviour.

Comparing the results obtained in this study with the results of one of our previous studies using the synchrogram technique and the same data set [13], it appears that the joint symbolic dynamics approach shows improved performance in detecting changes in cardio-respiratory interaction. In future work, we plan to employ this technique for the screening of OSAS patients.

5. Conclusion

Cardio-respiratory interaction during sleep in patients with mild OSAS is affected by sleep stage. Joint symbolic dynamics provides a simple tool to quantity the relation between cardiac and respiratory rhythms.

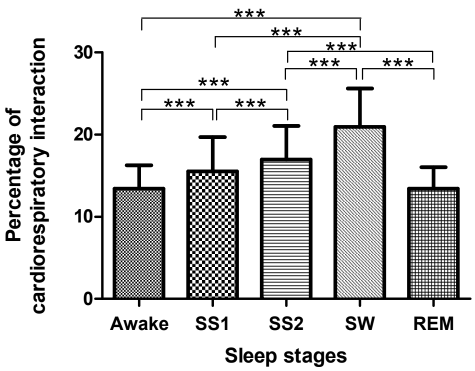

Figure 2. Sleep related comparison of cardiorespiratory interaction. *** indicates $p<0.0001$.

Acknowledgements

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Address for correspondence.

Muammar M Kabir.
School of Electrical and Electronic Engineering,
The University of Adelaide.
SA 5005, AUSTRALIA
E-mail: muammar.kabir@adelaide.edu.au