33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Quantification of Cardio-Respiratory Interactions in Healthy Children during Night-Time Sleep using Joint Symbolic Dynamics

Muammar M. Kabir, *Student Member, IEEE,* Mark Kohler, Derek Abbott, *Member, IEEE,* and Mathias Baumert, *Member, IEEE*

***Abstract*—The aim of this paper was to study interactions between R-R intervals and respiratory phases in healthy children during night-time sleep using a novel technique based on joint symbolic dynamics. We investigated overnight polysomnography data of 40 healthy children. The R-R time series were extracted from electrocardiograms (ECG) and respiratory phases were obtained from abdominal sensors using the Hilbert transform. Both the series were transformed into ternary symbol vectors based on the changes between two successive R-R intervals or respiratory phases, respectively. Subsequently, words of length '2' were formed and the correspondence between words of the two series for each sleep stage was determined to quantify cardio-respiratory interaction. We found a significantly higher percentage of similarity in the joint symbolic dynamics of R-R intervals and respiratory phases during slow-wave (SW) sleep compared to any other sleep stage. There was, however, no significant effect of age, gender or BMI on cardio-respiratory interaction. In conclusion, joint symbolic dynamics provides a novel efficient technique for the analysis of cardio-respiratory interaction.**

I. Introduction

The association between cardiac and respiratory rhythms has long been recognized [1, 2]. Some of the 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, as these biological signals are inherently non-linear, non-stationary and contain superimposed noise, the techniques mentioned above often prove to be inadequate for characterizing their complex dynamics [5, 6]. Cardio-respiratory coordination is a concept derived from nonlinear systems theory that aims to quantify the interaction [7] between respiratory rate and heart rhythm, assuming they are generated by two independent systems. 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]. Respiratory sinus arrhythmia (RSA), which is a strong modulatory effect of respiration on heart rate [8], is another well-known phenomenon of cardio-respiratory interaction [9]. Although physiological significance of RSA and cardio-respiratory coordination are not completely understood, their quantification 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 the opportunity for an easy interpretation of physiological data by allowing a simplified description of the dynamics of a system by means of a few symbols and has successfully been applied in several studies [14-16]. In this paper we introduce a novel approach that is based on the joint symbolic dynamics of respiratory phase and heart rate to quantify cardio-respiratory interaction in healthy children during night-time sleep. By employing a coarse-graining procedure to both time series some of the detailed information is lost while the robust properties of the dynamics are preserved [14, 15]. We hypothesized that the cardio-respiratory interaction, changes with sleep stages.

II. Methods

A. Subjects

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the Human Ethics Committee of the Women's and Children's Hospital Adelaide. Parental consent and child assent were obtained for all participants. The study comprised of 40 normal (20 males / 20 females), healthy Caucasian children with no underlying medical conditions, respiratory disorders or craniofacial abnormalities. The age and BMI z-score of the subjects ranged 3.1-12.2 years (mean ± SD: 7.7 ± 2.6 yrs) and -1.7-2.3 (mean ± SD: 0.3 ± 0.8) respectively.

B. Data Analysis

1) Overnight polysomnography: Overnight PSG was conducted without sedation or sleep deprivation, and began at each child's usual bedtime. 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,

Manuscript received April 15, 2011.

M. M. Kabir is with the School of Electrical and Electronic Engineering, University of Adelaide, SA 5005, Australia (phone: 61-8-8313-4115; fax: 61-8-8303-4360; e-mail: muammar.kabir@adelaide.edu.au).

M. Kohler is with the School of Psychology, Social Work and Social Policy, University of South Australia, SA 5072, Australia (e-mail: mark.kohler@unisa.edu.au).

D. Abbott is with the School of Electrical and Electronic Engineering, University of Adelaide, SA 5005, Australia (e-mail: dabbott@eleceng.adelaide.edu.au).

M. Baumert is with the School of Electrical and Electronic Engineering, University of Adelaide, SA 5005, Australia (e-mail: mathias.baumert@adelaide.edu.au).

TABLE I

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 2. THE WORDS CAN BE PLACED IN A 9×9 TABLE MATRIX.

RR	0.73	0.69	0.71	0.75	0.76	0.75	0.70	0.67
s^{HR}	1	0	0	0	1	1	1	
w^{HR}:	-	10	00	00	01	11	11	

|PH|	1.89	1.21	0.43	1.71	2.92	2.35	1.18	0.15
s^{PH}	1	1	0	0	1	1	1	
w^{PH}:	-	11	10	00	01	11	11	

w^{PH}	w^{HR} 00	01	02	10	11	12	20	21	22
00	*								
01		*							
02									
10	+								
11				+	**				
12									
20									
21									
22									

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.

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 [17]. For the purpose of this study, sleep stage 3 and 4 were combined and termed slow-wave sleep (SW). Epochs were scored as movement if the EEG and EOG signals were obscured for ≥50% of the epoch by muscle tension or artefact associated with movement of the subject [17]. Movement time was scored as a separate category, and was not included in either sleep or wake time. The scoring of different artifacts during sleep has been discussed in our previous studies [18, 19].

2) ECG analysis: The ECG signal (lead II) was sampled at 500 Hz and saved for off-line analysis. ECG R-wave peaks were detected using algorithms of the libRASCH library (www.librasch.org). The R-R time series obtained from the time-points of the R-peaks were visually scanned for artifacts and, if necessary, manually edited.

3) Respiration analysis: Abdominal respiratory signals, digitized at 32 Hz, were used for this study. Respiratory signals consist of linear, nonlinear and non-stationary components, usually contaminated to some degree by noise.

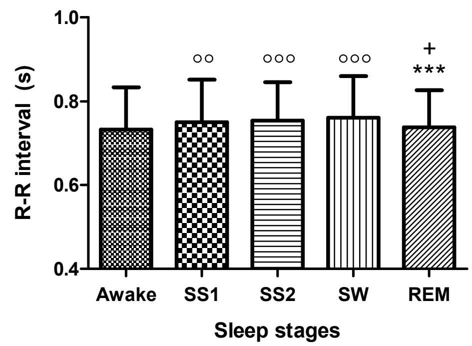

Fig. 1. Sleep stage comparison of average R-R intervals. The circle indicates the significance of differences in R-R interval between the awake and other sleep stages (°° and °°° indicates $p < 0.001$ and $p < 0.0001$, respectively). The star indicates the significance of differences in R-R interval between SW and REM ($p < 0.0001$). The plus indicates the significance of differences in R-R interval between stage 2 and REM sleep ($p < 0.05$).

For our analysis, the respiratory signal 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.

4) Joint symbolic dynamics: From the vectors of the R-R time series and the series of respiratory phases at the instants of R-peaks, PH, we established two symbolic sequences, s^{HR} (HR denoting the heart rate — 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, as described previously [20]

$$S_i^{HR} = \begin{cases} 0 \text{ if } RR_{i+1} - RR_i > 0 \\ 1 \text{ if } RR_{i+1} - RR_i < 0 \\ 2 \text{ if } RR_{i+1} - RR_i = 0 \end{cases}$$

$$S_i^{PH} = \begin{cases} 0 \text{ if } |PH_{i+1}| - |PH_i| > 0 \\ 1 \text{ if } |PH_{i+1}| - |PH_i| < 0 \\ 2 \text{ if } |PH_{i+1}| - |PH_i| = 0 \end{cases}$$

Using the symbol vectors s^{HR} and s^{PH} , we constructed series of words (bins), w^{HR} and w^{PH} of length 2 – containing 2 successive symbols. Consequently, 9 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,…,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} is identical to that of w_i^{PH} (i.e. $w_i^{HR} = w_i^{PH}$), the cardiac and respiratory epochs are considered to be coordinated. The word types

TABLE II
MEAN VALUES (± STANDARD DEVIATION) OF THE PERCENTAGE OF CARDIO-RESPIRATORY INTERACTION DURING DIFFERENT SLEEP STAGES IN 40 CHILDREN DICHOTOMIZED BASED ON GENDER OR THE MEDIAN VALUES OF AGE OR BMI Z-SCORE

Sleep Stages	Age (yrs)		BMI z-score		Gender	
	<7.3	>7.3	<0.37	>0.37	Male	Female
Awake	5.4±2	6.9±3	7.3±3	5.1±2	6.6±3	5.8±3
SS1	5.5±3	6.2±4	6.9±4	4.8±2	6.0±4	5.7±3
SS2	7.9±2	8.8±4	9.3±4	7.5±2	8.2±3	8.6±3
SW	11.7±3	11.5±3	11.9±3	11.2±3	11.7±3	11.4±3
REM	7.2±3	8.4±4	8.6±4	6.9±3	8.0±3	7.6±4

span over a 9×9 vector matrix from $[00,00]^T$ to $[22,22]^T$ (Table I). The percentage of interaction was calculated by dividing the total count of coordinated words by the total number of words.

Artefact such as movements can potentially confound the results and should be removed for data analysis. For the purpose of this study, all 30 s epochs containing artifacts together with an artifact-free epoch immediately before and after each artifact-epoch were excluded.

5) Statistical Analysis: GraphPad Prism version 5.01 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com) was used for statistical analysis. Considering normally distributed data, we investigated the relationship 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). Further, the study cohort was dichotomized based on median values to study of effects of gender, age and BMI.

III. RESULTS

Subject demographics and polysomnographic (PSG) results for the overnight PSG have been reported previously [18, 19].

A. Sleep Stage Effects on R-R and Respiratory Interval

There was a small, but significant shortening in average R-R interval during REM sleep as compared to SW sleep (0.74±0.1 vs. 0.76±0.1 s, $p<0.0001$) (Figure 1). Awake state was associated with a significantly shorter R-R interval as compared to stage 1, stage 2 and SW sleep (Figure 1). However, mean respiratory intervals were not significantly different between sleep stages (Figure 2).

B. Sleep Stage Effects on Cardio-respiratory Interaction

Cardio-respiratory interaction was strongly associated with sleep stages. A significant increase in cardio-respiratory interaction was observed during SW sleep as compared to other sleep stages (SW vs. REM sleep: 11.6±2.9 vs. 7.8±3.3 %, $p<0.0001$, Figure 3).

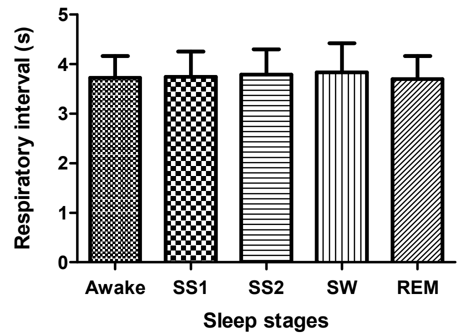

Fig. 2. Average respiratory interval and sleep stage.

C. Age, Gender and BMI Effects on Cardio-respiratory Interaction

The subjects were divided into 2 groups based on the median values of age (median: 7.3 yrs) and BMI z-score (median: 0.37). No significant differences were observed in cardio-respiratory interaction between the corresponding sleep stages of the two groups (Table II).

IV. DISCUSSION

In this paper we introduced a novel method for the investigation of cardio-respiratory interaction in healthy children during night-time sleep. Using a joint symbolic dynamics approach, 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. It is also evident that changes in R-R intervals are associated with sleep stage.

Analysis of respiratory data using symbolic dynamics has been suggested to provide better results than time-domain analyses [21]. In the study by Caminal *et al.* [21] the transformation of the respiratory time series into symbols and their analyses involved different parameters whose values required to be suitably selected. The novel 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.

In this study we found a significant change in heart rate between the sleep stages, which is consistent with an earlier study [22]. Also, there were no effects of age, gender or BMI on cardio-respiratory interaction, which is in line with the findings by Bartsch *et al.* [12]. Likewise, 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, which accounts for up to 12% of the entire sleep duration, employing a joint symbolic dynamics approach with a word length of 2. In a recent study by Kenwright *et al.* [23] it was shown that cardio-respiratory coordination during exercise was significantly decreased due

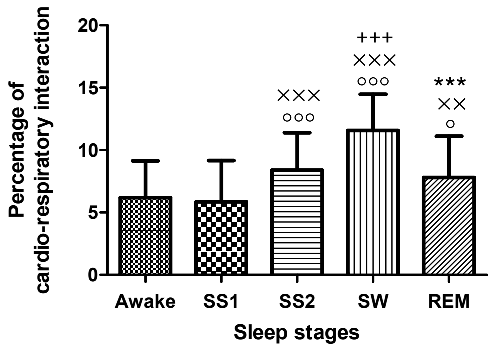

Fig. 3. Sleep related comparison of cardiorespiratory interaction. The circle and cross indicates the significance of differences in cardiorespiratory interaction during awake and stage 2 sleep compared to other sleep stages (º, ×× and ººº/××× indicates $p < 0.05$, $p < 0.001$ and $p < 0.0001$, respectively). The plus and star indicates the significance of differences in cardiorespiratory interaction during SW sleep compared to stage 2 and REM sleep respectively ($p < 0.0001$).

to an increase in cardiac and respiratory frequencies as a result of greater demand for nutrients and oxygen. Since cardio-respiratory interaction was higher during SW sleep compared to REM and other sleep stages, and the average respiratory intervals were not significantly affected by sleep stages, it appears that the heart rate during SW sleep was more regular, and responsible for the cardio-respiratory interaction. However, the physiological mechanisms governing cardio-respiratory interactions are incompletely understood and require further investigation.

From this study it appears that the proposed methodology based on symbolic dynamics provides a simple and efficient approach for the quantification of cardio-respiratory interaction and might provide some additional information which requires being explored in future studies.

V. CONCLUSION

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

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