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Effect of Spontaneous Arousals on Cardio-Respiratory Interaction in Healthy Children

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Abstract—**The aim of this paper was to study the effect of spontaneous arousals during night-time sleep on the interactions between R-R intervals and respiratory phases in healthy children. We collected overnight polysomnography data of 40 healthy children and investigated cardio-respiratory interaction before and after spontaneous arousals during stage 2 sleep using joint symbolic dynamics. 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 was determined to quantify cardio-respiratory interaction for pre- and post-spontaneous arousal episodes. We observed a brief but significant shortening in R-R and respiratory intervals after arousal. There was also a significant short-term increase in cardio-respiratory interaction during the first 30-second post-arousal episode as compared to 30-second pre-arousal episode (7.5±3.4 vs. 5.2±3.7%, p<0.0001, respectively). In conclusion, spontaneous arousals in healthy children during night-time sleep are associated with a temporal but significant increase in cardio-respiratory interaction.**

I. Introduction

It has been reported that about one third of the human population suffers from various sleep disorders possibly due to increase in obesity, increased stress or decreased physical activity [1]. With increasing evidence for the association between repetitive arousals in sleep disorders and cardiovascular dysfunction, investigation of the physiological variables during arousals from sleep has gained interest [2]. Arousal from sleep is associated with an increase in heart rate and blood pressure [3]. Cardio-respiratory interaction is a concept derived from nonlinear systems theory that aims to quantify the interaction between respiratory rate and heart rhythm, assuming they are generated by two independent systems [4]. Quantification of cardio-respiratory interaction is known to have clinical merit, for example, stratifying the risk of cardiac death in patients after myocardial infarction [5] and diagnosing obstructive sleep apnea [6]. While the cardio-respiratory response to arousal has been investigated substantially in adults, comparatively little work has been done in children. An understanding of cardio-respiratory response to spontaneous arousals in healthy children may elucidate pathways underlying the development of cardiovascular disorders in children with sleep disorders.

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The analysis of cardio-respiratory interaction is difficult since cardiac and respiratory signals are inherently non-linear, non-stationary and contain superimposed noise. Conventional signal-processing techniques such as power spectral density and cross-correlation analysis appear to be inadequate for characterizing the complex dynamics of these signals. Recently, a technique based on joint symbolic dynamics of respiratory phase and heart rate has recently been introduced for the quantification of cardio-respiratory interaction [7].The concept of symbolic dynamics employs a coarse-graining procedure in which some of the detailed information is lost but the robust properties of the dynamics are preserved, and therefore provides an easy interpretation of physiological data through a simplified description by means of a few symbols [8-10].

In this paper we used an approach based on joint symbolic dynamics to quantify and analyse cardio-respiratory interaction before and after spontaneous arousals during stage 2 sleep in healthy children. We hypothesized that cardio-respiratory interaction is perturbed by spontaneous arousal.

II. Methods

A. Subjects

The study comprised of 20 male and 20 female healthy Caucasian children with no underlying medical conditions, respiratory disorders or craniofacial abnormalities. Parental consent and child assent were obtained for all participants. 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. 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.

B. Overnight polysomnography

Overnight polysomnography (PSG) was performed using an S series® system (Compumedics, Australia) and was conducted without sedation or sleep deprivation, and began at each child's usual bedtime. For sleep staging and arousal

TABLE I

ILLUSTRATION OF THE TRANSFORMATION OF R-R INTERVALS (RR) AND RESPIRATORY PHASES (RP) INTO SYMBOL VECTORS, s^{HR} AND s^{RP}, AND WORDS, w^{HR} AND w^{RP}, OF LENGTH TWO. AS SHOWN BELOW, 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	1	1	0	1	1
w^{HR}:		-	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^{RP}	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^{RP} and hence is considered coordinated. The minus sign indicates the pair of words with a difference in sequence of symbols.

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 [11]. 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 [11]. 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 described in detail in our previous studies [2, 12].

C. ECG analysis

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

D. Respiratory signal analysis

Abdominal respiratory signals, digitized at 25 Hz, were used for this study. The 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 the Hilbert transform.

E. Joint symbolic dynamics approach

For the purpose of our analysis, the respiratory phases, RP, were determined at the instants of R-peaks. From the vectors of the R-R time series and RP we established two symbolic sequences, s^{HR} (HR denoting the heart rate—reciprocal of R-R interval) and s^{RP}, using the transformation rule below, based on the differences between successive R-R intervals and R-instant respiratory phases, respectively, as described previously [7]

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

$$S_i^{RP} = \begin{cases} 0 \text{ if } |RP_{i+1}| - |RP_i| > 0 \\ 1 \text{ if } |RP_{i+1}| - |RP_i| < 0 \\ 2 \text{ if } |RP_{i+1}| - |RP_i| = 0 \end{cases} \quad (2)$$

Using the symbol vectors s^{HR} and s^{RP}, series of words, w^{HR} and w^{RP} of length two (containing two successive symbols) were constructed—a threshold value of zero ms for s_i^{HR} and words of length two were chosen in this study, since they provided more consistent and significant results as determined by the procedure described previously [7]. Consequently, nine different word types were obtained for each vector.

The interaction between cardiac and respiratory cycles was studied by comparing each i^{th} ($i = 1,2,\ldots,n$, where n is total number of words) word from the distributions, w_i^{HR} and w_i^{RP}. If the sequence of symbols in w_i^{HR} was identical to that of w_i^{RP} (i.e. $w_i^{HR} = w_i^{RP}$), the cardiac and respiratory epochs were considered to be coordinated. The word types span over a 9×9 vector matrix from $[00,00]^T$ to $[22,22]^T$, as shown in Table I. The percentage of interaction was calculated by dividing the total count of coordinated words by the total number of words.

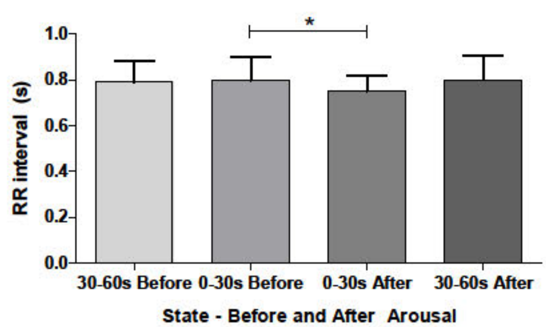

Figure 1. Response of R-R intervals to spontaneous arousals in healthy children. A significant shortening in R-R interval was observed during post-arousal episode as compared to pre-arousal episode. Here, * represents $p < 0.05$.

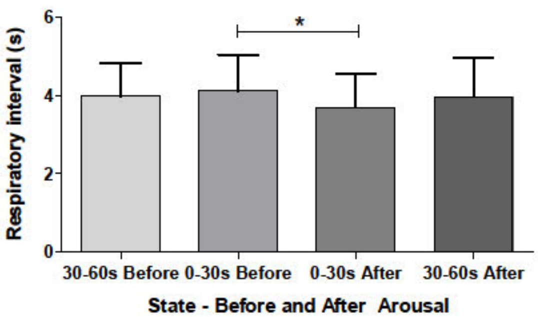

Figure 2. Response of respiratory intervals to spontaneous arousals in healthy children. Similar to R-R intervals, a significant shortening in respiratory interval was observed during post-arousal episode as compared to pre-arousal episode. Here, * represents $p < 0.05$.

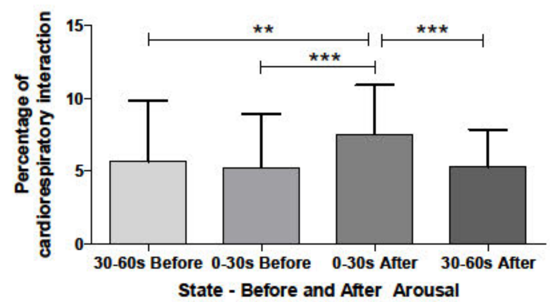

Figure 3. Cardio-respiratory response to spontaneous arousals in healthy children. A brief but significant increase in cardio-respiratory interaction was observed during post-arousal episode as compared to pre-arousal episode. Here, ** and *** represent $p < 0.01$ and $p < 0.0001$, respectively.

Artifacts such as movements can potentially confound the results and hence should be removed prior to 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.

F. Selection criteria for pre- and post-spontaneous arousal epochs

For the analysis of cardio-respiratory interaction during pre- and post-spontaneous arousal episodes, only stage 2 sleep, during which most arousals were observed, was considered. Furthermore, spontaneous arousal episodes were selected such that the 0-30 and 30-60 second epochs immediately before and after each arousal episode were stage 2 and artifact-free.

G. Statistical analysis

GraphPad Prism version 5.01 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com) was used for statistical analysis. For statistical analysis, the first 10 arousal episodes from stage 2 sleep of each subject were considered. Subjects with less than 10 arousal episodes were excluded from the analysis after applying the selection criteria described above. Since data were short, arousal responses were averaged in each subject to obtain overall cardio-respiratory interactions before and after spontaneous arousal.

We investigated changes in cardio-respiratory interaction before and after spontaneous arousals 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).

III. Results

Subject demographics and polysomnographic (PSG) results for the overnight PSG have been reported previously [2, 12].

A. Effect of spontaneous arousals on R-R and respiratory intervals

There was a significant shortening in R-R interval and respiratory interval during the first 30-second post-arousal episode as compared to 0-30s pre-arousal episode (R-R: 0.75±0.07 vs. 0.80±0.1 s, $p<0.05$ and respiration: 3.7±0.9 vs. 4.1±0.9 s, $p<0.05$, respectively), see Figure 1 and 2.

B. Effect of spontaneous arousals on cardio-respiratory intervals

Ten subjects had less than 10 arousal episodes and hence, according to the selection criteria, were excluded from the analysis. A significant increase in cardio-respiratory interaction was observed during the first 30-second post-arousal episode as compared to 0-30 and 30-60 second pre-arousal episode (7.5±3.4 vs. 5.2±3.7 % ($p<0.0001$) and 5.7±4.1 %, ($p<0.01$), respectively), see Figure 3. The 30-60 second post-arousal episode showed a significant decrease in cardio-respiratory interaction as compared to the 0-30 second post-arousal episode (5.3±2.6 vs. 7.5±3.4 %, $p<0.0001$, respectively), see Figure 3. However, there were no significant differences in cardio-respiratory interaction during 30-60 second post-arousal episode as compared to 0-30 and 30-60 seconds pre-arousal episode.

IV. Discussion

In this paper we investigated cardio-respiratory interaction before and after spontaneous arousals in healthy children during night-time sleep, using an approach based on joint symbolic dynamics. Our results show that R-R and respiratory intervals significantly shorten briefly after spontaneous arousal. Also, the amount of interaction between the cardiac and respiratory oscillators significantly increased during the first 30-second of post-arousal episode compared to pre-arousal episode, followed by a significant reduction to pre-arousal levels.

Analysis of respiratory data and cardio-respiratory interaction using symbolic dynamics has been suggested to provide improved performance than time-domain analyses [7, 13]. However, in contrast to the transformation rule suggested by Caminal *et al.* [13], which involves several parameters for transforming respiratory time series into symbols, the methodology described in our previous study [7] and used 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 shortening in R-R intervals during the first 30-second of post-arousal episode compared to pre-arousal episode, which is consistent with earlier studies [14, 15]. In one of our previous studies of the same data set [2], it has been reported that the respiratory rate following spontaneous arousal significantly increased for a brief period with the maximum response at the first breath and returned to baseline level by the third breath post-arousal. In line with the finding, we observed a brief but significant shortening in respiratory interval after arousal.

From the analysis of the interaction between R-R intervals and respiratory phases during two consecutive 30-second (0-30 and 30-60 s) pre- and post-arousal episodes, a significant increase in cardio-respiratory interaction was observed during the first 30-second post-arousal episode. It appears that the significant shortening in R-R and respiratory intervals after arousal are paralleled by a brief but significant increase in cardio-respiratory interaction. Further, although the decrease in the interaction between R-R intervals and respiratory phases during 0-30s pre-arousal episode was not significant compared to 30-60s pre-arousal period, it appears that this brief change elicited arousal, causing a significant increase in cardio-respiratory interaction in the first 30-second post-arousal and subsequently returning to baseline with smaller standard deviation during 30-60s post-arousal. This can be related to the finding by Kesler *et al.* [16] that induced changes in arterial blood pressure in human adults are capable of eliciting arousal from sleep. Furthermore, measures assessing the activation of the autonomic nervous system have been suggested to be more sensitive to sleep disturbance in children [17]. Our finding suggests that the analysis of cardio-respiratory interaction may be used as a marker of autonomic arousals. However, the physiological mechanisms governing cardio-respiratory interactions are incompletely understood. Further studies are required to understand the cause of spontaneous arousals during sleep and its association with cardio-respiratory interaction.

V. CONCLUSION

Cardio-respiratory interaction in healthy children maintains a temporal relationship with spontaneous arousals during night-time sleep and briefly increases immediately after arousal.

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