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Cardiorespiratory coupling during sleep in difficult-to-control asthmatic patients

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***Abstract*— Heart rate variability (HRV) and respiration recorded during sleep from 8 patients suffering from difficult-to-control asthma were studied to investigate autonomic nervous system control of cardiac and respiratory activities, and of cardio-respiratory coupling during different sleep stages.**

In healthy subjects, HRV monitoring during sleep reveals a predominant parasympathetic drive to the heart during non-rapid eye movement (NREM) sleep and an increased sympathetic activity during rapid eye movement (REM) sleep.

Spectral analysis of HRV and cross-spectral analysis of HRV and respiration signals in the analyzed difficult-to-control asthma patients showed trends in the main spectral indices, which appeared similar to variations observed in non pathologic subjects, but which were possibly affected by a reduction in the sympathetic and cardiorespiratory modulations. The ratio between the tachogram power in the low frequency (LF) band and the tachogram power in the high frequency (HF) band, a marker of the sympatho-vagal balance, increased during deep sleep stage S3 (LF/HF = 0.855 ± 0.876, mean ± s.d.), indicating a predominance of the sympathetic component, and decreased during REM sleep (LF/HF = 0.748 ± 0.716, mean ± s.d.), indicating a drift of the sympatho-vagal balance towards the vagal component. The coherence between the tachogram and the respirogram in the HF band increased during deep sleep stages S2 (coherence = 0.855 ± 0.727, mean ± s.d.) and S4 (coherence = 0.843 ± 0.724, mean ± s.d.) and decreased during REM sleep (coherence = 0.808 ± 0.719, mean ± s.d.), suggesting that a stronger cardiorespiratory coupling was reached with synchronization of sleep.

I. Introduction

Autonomic cardiac control during sleep has been found to be impaired in sleep disorders, such as insomnia and sleep apnea [1]. Autonomic regulation of circulation in healthy subjects fluctuates during sleep [2], with a drift of the sympatho-vagal balance towards the parasympathetic activity during non-rapid eye movement (NREM) sleep and towards the sympathetic activity during rapid eye movement (REM) sleep [3; 4]. Oscillations in cardiac autonomic modulation are reflected in changes in the spectral distribution of the heart rate variability (HRV) signal representing the oscillation in the interval between consecutive heart beats [5]. When studying the HRV in the frequency domain, two main spectral components can be identified on the HRV signal spectrum: the low frequency (LF: 0.04-0.15 Hz) and the high frequency (HF: 0.15-0.4 Hz) components. Given that the HF band reflects vagal control of heart rate (HR) only, their ratio (LF/HF) is considered as a marker of the sympatho-vagal balance mediated control of HR [6].

Changes in heart rhythm during sleep are accompanied by changes in respiration, too. In physiological conditions regularization of respiration goes along with synchronization of sleep, with respiration becoming more irregular during REM sleep [4].

Cardiac and respiratory rhythms have long been known to be coupled [7]. Evidence suggests that a reduced synchronization is a prognostic indicator for cardiac mortality [8].

A higher synchronization between cardiac activity and respiration characterizes deep sleep; a reduction in their synchronization is observed during REM periods [9]. Cardiorespiratory coupling changes in pathological conditions [7]; thus, synchronization analysis could provide information about a subject's patho-physiological status.

Asthma is a chronic disease affecting 10% of worldwide population [10]. In most cases asthma can be successfully managed; however, a small portion of patients are affected by difficult-to-control asthma, a specific phenotype that is insufficiently controlled despite appropriate therapeutic strategies. It accounts for 5% of all asthma cases and is associated with greater morbidity and mortality.

Sleep is a time of vulnerability for asthmatic patients [11], who are likely to experience reduced sleep quality, awakenings, and daytime somnolence [12]. Furthermore, physiological changes and circadian variations in biologic rhythms may negatively affect asthma control during sleep [11] and a better understanding of such mechanisms may lead to an improvement of asthma control and treatment results.

In the present study the HRV signal and the respiration signal recorded during sleep from 8 patients suffering from difficult-to-control asthma were studied to investigate the effects of the autonomic nervous regulation on cardiac and respiratory activities and on cardio-respiratory coupling during different sleep stages.

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II. METHODS

A. Subjects

8 patients suffering from difficult to control asthma, (age = 46.4 ± 13.6 years, mean ± s.d.), participated in the study. The protocol was approved by Committee of Ethics n°316424/2009 of the Universidade Nove de Julho, Sao Paulo-SP, Brazil, and informed and written consent to participate in the study was obtained from all patients.

B. Polysomnographic acquisition

Acquisitions were performed at Nove de Julho University sleep laboratory. Polysomnography was conducted on each subject during a night of sleep and the electrocardiogram (ECG; sampling rate = 200 Hz) and the respiratory activity (sampling rate = 10 Hz) were recorded. Other signals, including the electroencephalogram (EEG), the electrooculogram (EOG) and the electromyogram (EMG) were also simultaneously recorded, and used to derive the hypnogram.

C. Signal processing

For each subject the hypnogram was obtained by visual scoring performed on the EEG, EOG and EMG signals by a physician according to the standardized procedure introduced by Rechtschaffen and Kales and worldwide accepted [13]. Sleep stages S1 to S4, REM and wakefulness states were scored.

The RR-interval signal was extracted from the ECG and the respirogram was extracted from the respiration signal by sampling it in correspondence of each ECG R peak.

D. Analysis

Autoregressive (AR) analysis was performed on stationary, artifact free, signal portions of 250 heart beats, selected within different sleep stages on the tachogram and the respirogram, in order to obtain the power spectral density (PSD) of each segment. The values of the very low frequency (VLF: 0.01-0.04 Hz) power and of the normalized power of the LF and the HF components (LF n. u. and HF n. u.) were obtained by decomposing the PSD into single spectral components, according to the method described in [14]. These parameters, along with the LF/HF ratio, were calculated for each signal portion of the tachogram, while for the respirogram only the HF component (HF % of respirogram, obtained as HF power / respirogram total power) was considered.

For each stationary portion of the tachogram and of the respirogram a bivariate analysis was also performed, in order to obtain the cross-spectrum between the two signals.

According to the method described in [15] a bivariate AR model was estimated and used to calculate the cross spectrum between the signals. The quadratic coherence between the signals in the LF and in the HF bands and the percentages of coherent and not-coherent power between the signals were calculated.

The average values of the tachogram VLF, LF n. u. and HF n. u. power, of the LF/HF ratio, of the respirogram HF %, of the HF band coherence between tachogram and respirogram and of the % of tachogram power coherent and not coherent with respiration were calculated on all subjects, for the whole night.

III. RESULTS

For each patient, PSDs for both the tachogram and the respirogram were calculated and the cross-spectrum between the two signals was computed for different sleep stages. Fig. 1 shows the results obtained for a single patient, during wakefulness and different sleep stages, during the first NREM-REM cycle. The tachogram PSD shows that the HF component increases during deep sleep stages, reaching its highest value during sleep stage S3, and decreases during REM sleep, when the peak is only slightly visible. Also the respirogram PSDs show an increase in the HF component during NREM sleep, with the characteristic peak progressively becoming more pronounced with synchronization of sleep; a decrease of the same component is observed during REM sleep, when a less pronounced and more widely distributed peak is found. The cross-spectra between the tachogram and the respirogram show an increase in the synchronization between the two signals during NREM periods, which reaches its highest value during sleep stage S3, and a decrease during the REM period. Table 1 summarizes the average values, for the whole population, of the tachogram normalized power in the LF and HF bands, of the LF/HF ratio, of the respirogram power in the HF band and of the tachogram-respirogram coherence in the HF band observed for wakefulness, deep sleep stages S2, S3 and S4 and REM sleep, during the whole night.The LF/HF, after an initial small decrease during deep sleep stage S2 (LF/HF = 0.721 ± 0.713, mean ± s.d.) with respect to wakefulness (0.849 ± 0.755, mean ± s.d.), slightly increases during deep sleep stage S3 (0.855 ± 0.876, mean ± s.d.); it slightly decreases during deep sleep stage S4 (0.756 ± 0.733, mean ± s.d.) and during REM sleep (0.748 ± 0.716, mean ± s.d.).With respect to wakefulness (coherence = 0.719 ± 0.737, mean ± s.d.), the coherence between the tachogram and the respirogram in the HF band increases during deep sleep periods (coherence = 0.855 ± 0.727, mean ± s.d., during sleep stage S2; coherence = 0.843 ± 0.724, mean ± s.d., during sleep stage S4), with the exception of deep sleep stage S3, when a decrease is observed (coherence = 0.707 ± 0.721, mean ± s.d.), and decreases during REM sleep (coherence = 0.808 ± 0.719, mean ± s.d.). No appreciable changes can be observed in the tachogram VLF, LF n. u. and HF n. u. power and in the respirogram HF power.

An ANOVA analysis was conducted in order to detect any significant differences between the tachogram LF normalized units (n.u.), HF n.u. and LF/HF values, the HF respiration values and the tachogram-respirogram coherence values observed on all patients during deep sleep stage S4 and REM sleep, but no significant variation was found (p-value > 0.05).

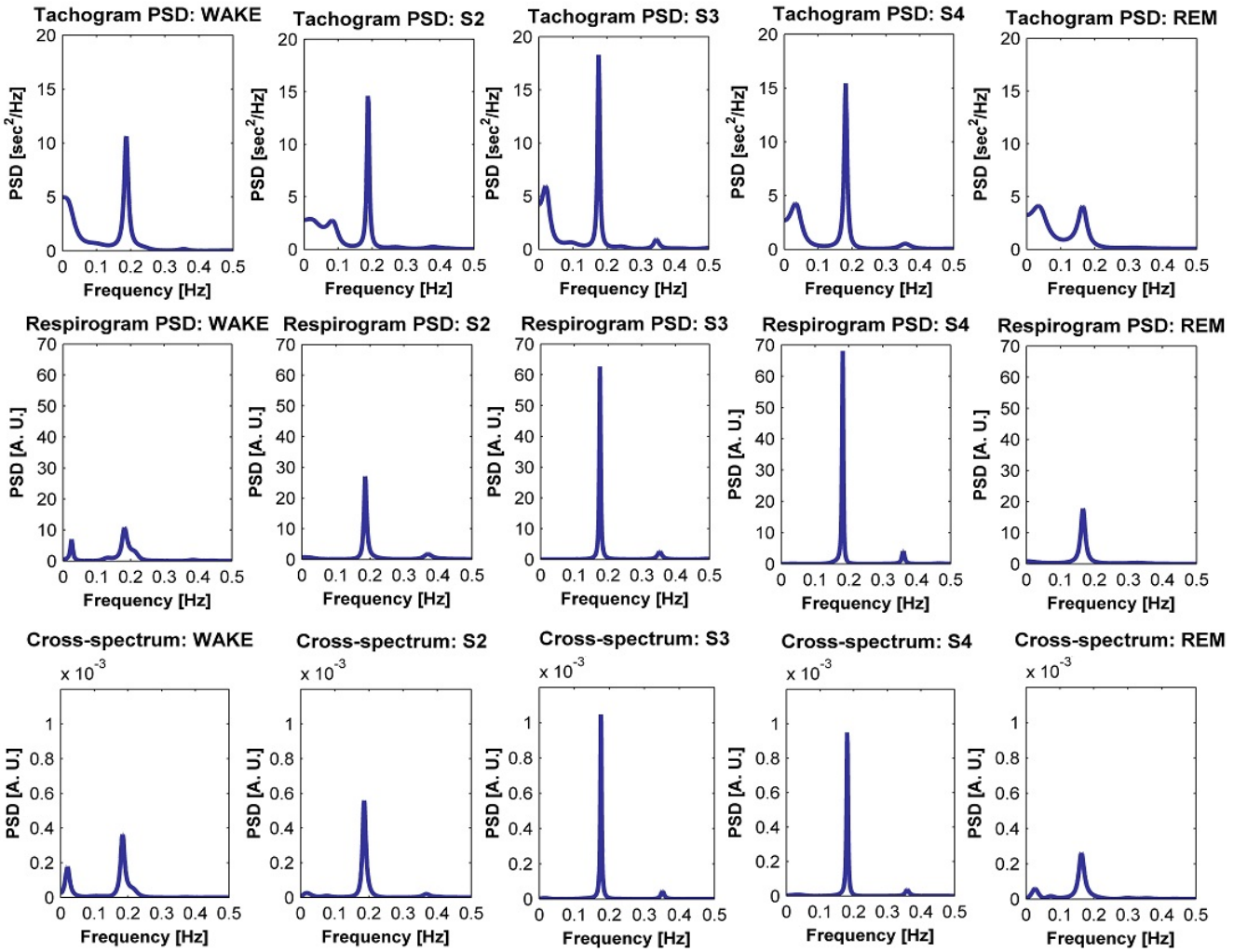

Figure 1. Power Spectral density (PSD) computed from the tachogram of a patient during wakefulness, sleep stages S2, S3 and S4 and REM sleep, during the first sleep cycle (first row); PSD computed from the respirogram of the same patient during wakefulness, sleep stages S2, S3 and S4 and REM sleep, during the first sleep cycle (second row); cross-spectrum between the tachogram and the respirogram of the same patient during wakefulness, sleep stages S2, S3 and S4 and REM sleep, during the first sleep cycle (third row).

TABLE I. AVERAGE VALUES OF THE TACHOGRAM NORMALIZED POWER IN THE LF AND HF BANDS, OF THE LF/HF RATIO, OF THE RESPIROGRAM % POWER IN THE HF BAND AND OF THE TACHOGRAM-RESPIROGRAM COHERENCE IN THE HF BAND OBSERVED ON ALL PATIENTS FOR WAKEFULNESS, DEEP SLEEP STAGES S2, S3 AND S4 AND REM SLEEP STAGE, DURING THE WHOLE NIGHT

Sleep stage	Tachogram LF n. u. (mean ± s.d.)	Tachogram HF n. u. (mean ± s.d.)	Tachogram LF/HF ratio (mean ± s.d.)	Respirogram HF% power (mean ± s.d.)	Coherence in HF band (mean ± s.d.)
W	0.693 ± 0.714	0.807 ± 0.715	0.849 ± 0.755	0.999 ± 0.707	0.719 ± 0.737
S2	0.651 ± 0.708	0.850 ± 0.708	0.721 ± 0.713	0.993 ± 0.707	0.855 ± 0.727
S3	0.668 ± 0.731	0.832 ± 0.731	0.855 ± 0.876	0.976 ± 0.709	0.707 ± 0.721
S4	0.661 ± 0.712	0.839 ± 0.712	0.756 ± 0.733	0.995 ± 0.707	0.843 ± 0.724
R	0.663 ± 0.709	0.837 ± 0.709	0.748 ± 0.716	0.995 ± 0.707	0.808 ± 0.719

IV. DISCUSSION

The HF n. u. power of the tachogram increased during deep sleep and decreased during REM sleep as shown in Table 1. This suggested an augmented vagal drive during deep sleep as compared to the wakefulness state and a reduced vagal tone during REM phases.

The LF/HF ratio behavior observed in all patients and shown in Table 1 hinted that the sympatho-vagal balance drifted towards the sympathetic component during deep sleep stage S3 and towards the parasympathetic component during

REM sleep. This behavior appeared inconsistent with previous studies in healthy subjects [2; 3; 9], which showed a higher vagal drive to the heart during deep sleep and a higher sympathetic activity during REM sleep.

A bivariate analysis was carried out in order to investigate the cardio-respiratory coupling during the different sleep stages. The cross-spectra between the tachogram and the respirogram presented a more pronounced peak centered in the HF band during deep sleep stages as compared to that of the wake state, whereas the peak was smaller during REM sleep. This behavior indicated a more regular respiratory rhythm, synchronized with heart activity, during deep sleep and a less regular respiratory rhythm, and a less marked synchronization between respiration and heart rhythm, during REM sleep, in line with results reported by previous studies [7; 9]. The coherence value between the tachogram and the respirogram in the HF band increased during deep sleep stages S2 and S4 and decreased during REM sleep. This result was consistent with the observation that respiration and heart beat variability display a higher synchronization with progression of sleep, while the opposite occurred during the REM phase, consistent with previous studies [9].

In summary, changes in the HRV spectrum only partially reflected changes observed in healthy subjects: the HF component suggested a higher vagal activity during deep sleep and a higher sympathetic activity during REM sleep, as observed in healthy subjects; nonetheless, the sympatho-vagal balance drift towards the sympathetic component during deep sleep stage S3 and towards the parasympathetic component during REM sleep was not consistent with results obtained from healthy subjects. The respiratory modulation and cardiorespiratory coupling followed a similar pattern to that observed on healthy subjects. Furthermore, no significant differences were found in the tachogram LF n.u. power, HF n.u. power and LF/HF, in the respirogram HF power and in the coherence between cardiac and respiratory signals, between deep sleep stage S4 and REM sleep. This is also inconsistent with a previous study on healthy subjects [9], in which differences observed for the same parameters between deep sleep and REM sleep were always found to be significant. Further investigations are needed to better characterize the autonomic modulation of cardiac and respiratory activities and the cardiorespiratory coupling during sleep in difficult-to-control asthmatic patients.

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