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Respiratory and Spontaneous Arousals in Patients with Sleep Apnea Hypopnea Syndrome

J. Mesquita, F. Porée, G. Carrault, J.A. Fiz, *Member IEEE*, J. Abad, and R. Jané, *Member IEEE*

***Abstract*—Sleep in patients with Sleep Apnea-Hypopnea Syndrome (SAHS) is frequently interrupted with arousals. Increased amounts of arousals result in shortening total sleep time and repeated sleep-arousal change can result in sleep fragmentation. According to the American Sleep Disorders Association (ASDA) an arousal is a marker of sleep disruption representing a detrimental and harmful feature for sleep. The nature of arousals and its role on the regulation of the sleep process raises controversy and has sparked the debate in the last years. In this work, we analyzed and compared the EEG spectral content of respiratory and spontaneous arousals on a database of 45 SAHS subjects. A total of 3980 arousals (1996 respiratory and 1984 spontaneous) were analyzed. The results showed no differences between the spectral content of the two kinds of arousals. Our findings raise doubt as to whether these two kinds of arousals are truly triggered by different organic mechanisms. Furthermore, they may also challenge the current beliefs regarding the underestimation of the importance of spontaneous arousals and their contribution to sleep fragmentation in patients suffering from SAHS.**

I. Introduction

Increasing evidence shows that arousals are deeply involved in the pathophysiology of sleep disorders [1],[2]. Sleep in patients with Sleep Apnea-Hypopnea Syndrome (SAHS) is frequently punctuated with arousals. Increased amounts of arousals during sleep result in shortening total sleep time and repeated sleep-arousal change can result in sleep fragmentation [3]. Several arousal definitions have been published but the American Sleep Disorders Association (ASDA) 3-second rule of *" an abrupt shift in EEG frequency, which may include theta, alpha, and/or frequencies greater than 16Hz but not spindles"* gathers consensus and is the most widely used [4]. According to the conceptual framework of the ASDA criteria, arousals are a marker of sleep disruption representing a detrimental and harmful feature for sleep. Nevertheless, the nature of arousals in sleep and its role on the regulation of the sleep process raises controversy and has sparked the debate in the last years. Halász et al. [3] offers a contrasting view to the ASDA criteria concluding that arousals are elements weaved into the texture of sleep taking part in the regulation of the sleep process. Younes et al. [5], on the other hand, considered arousals to be incidental events that are not needed to initiate the opening of upper airways or to attain adequate flow. They state that arousals likely increase the severity of SAHS by promoting greater ventilatory instability and the production of further apneas. Fairly recently, Jordan et al. [6] verified that low dilator muscle activity does not occur after the termination of obstructive respiratory events either with or without arousal and the airflow appears to be improved after both events. Their findings suggest that the arousals predispose to further obstruction and this finding may challenge current thinking concerning the role of arousal in the OSA pathogenesis.

In addition to the former raised questions there is also a rising debate on the classification of arousals in two groups: respiratory and spontaneous arousals. Respiratory arousals are all arousals that occur immediately after an apnea/hypopnea event and spontaneous arousals are all arousals that occur spontaneously during sleep and not related with marked apnea/hypopneas. Some studies have focused on studying the indices of these two kinds of arousals by correlating them with AHI [1] and with the sleep stages [7]. However, none of them truly focused on uncovering differences among them. Dingli et al [8], followed later on by Xavier et al [9], both studied the electroencephalographic changes during and at the termination of apneas and hypopneas. In this work we applied similar frequency analysis methods as the ones used in [8] and [9]. The power spectral density curves of the 3 EEG derivations (C3A2, C4A1, O1A2) arousals were generated and the normalised power values for the frequency bands: Theta (4-7.5Hz), Alpha (7.5-12Hz), Sigma (12-16Hz) and Beta (16-25Hz) were calculated. We analyzed and compared the EEG spectral content of all respiratory and spontaneous arousals on a database of 45 SAHS subjects.

II. Database and Methods

A. Database, Polysomnography and Scoring

Forty-five subjects (6 females and 39 males) suspected of having Sleep Apnea Hypopnea Syndrome underwent diagnostic full-night polysomnography (PSG). PSG-EEG data were recorded on the sleep disorders laboratory of the Hospital Germans Trias i Pujol (HGTP) in Badalona, Spain. All subjects were free of any upper airway infection and other diseases throughout this study. The study was approved by the research ethics committee of the HGTP and

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J. Mesquita and R. Jané, are with Dept. ESAII, Universitat Politècnica de Catalunya (UPC), Institut de Bioenginyeria de Catalunya (IBEC) and CIBER de Bioengenieria, Biomateriales y Nanomedicina (CIBER-BBN) Baldiri Reixac, 4, Torre I, 9 floor, 08028, Barcelona, Spain (jmesquita@ibecbarcelona.eu; rjane@ibecbarcelona.eu)

F. Porée and G. Carrault are with INSERM, U1099, Rennes, F-35000, France and also with the Université de Rennes 1, LTSI, Rennes, F-35000, France (fabienne.poree@univ-rennes1.fr; guy.carrault@univ-rennes1.fr)

J. A. Fiz is with Pneumology Service of Hospital Germans Trias i Pujol, Badalona, IBEC and CIBER-BBN, Barcelona, Spain (jafiz@msn.com)

J. Abad is with Pneumology Service of Hospital Germans Trias i Pujol, Badalona, Spain (jabadc.germanstrias@gencat.cat)

informed consent was obtained from all patients. EEG data were recorded with the symmetrical electrode positions C4, C3, A1, A2, O1 and O2 based on the standard international 10-20 system of electrode placement. All subjects' recordings were scored on the C3A2 and C4A1 tracings in accordance with Rechtschaffen and Kales [10] rules for sleep staging and ASDA [4] rules for arousal scoring, respectively. Scoring was performed and double checked by a human expert, blinded to subject. Respiratory events (central, mixed and obstructive apneas and hypopneas) were also scored according to the AASM rules for scoring respiratory sleep disordered breathing events [11].

B. *Pre-Processing*

The 3 EEG derivations: C3A2, C4A1 and O1A2 were filtered with a Butterworth filter of seventh order with cut-off frequencies set at 0.3 and 30Hz. Finally, to minimize the ECG artifacts, a recursive least square (RLS) adaptive filter was applied, where the ECG signal acquired with the PSG was used as reference input.

C. *Respiratory and Spontaneous Arousals*

As previously stated, the arousals were scored as recommended by the ASDA task force criteria. In this work we aimed to assess the characteristics of respiratory and spontaneous arousals. Arousals occurring within three seconds (or less) following or overlapping an apnea/hypopnea were defined as respiratory arousals [1],[7]. Arousals that did not obey the former condition, namely did not overlap with or were adjacent to any apneas/hypopneas, were labeled as spontaneous arousals.

The EEG arousal signal segments were extracted from each of the 3 EEG derivations (fs =256Hz): Der1 – C3A2; Der2 – C4A1 and Der3 – O1A2.

D. *Methodology*

Since we were interested in studying each arousal in the frequency range of 4-25Hz, we applied a high pass Butterworth filter of fifth order with cut-off frequency of 4Hz.

The power spectrum of each of the 3 derivations was calculated using the Welch periodogram with a 128 length Hamming window and 50% overlap. The power spectral density (PSD) curve was generated and the normalized power values as a fraction of the total power (4-25Hz) were calculated for the following frequency bands: Theta (4-7.5Hz), Alpha (7.5-12Hz), Sigma (12-16Hz) and Beta (16-25Hz) bands [12]. Our methods consisted in studying the shapes of the PSD curves for all arousals of each subject (per Derivation) and ascertain the differences between the power band values. The purpose of this work was not only to characterize and scrutinize differences between the two groups of labeled arousals - respiratory and spontaneous arousals- but also to analyze the changes on the spectral content of these two groups of arousals on subjects with different levels of SAHS severity.

III. RESULTS

After PSG, the forty-five subjects were diagnosed with Apnea-Hypopnea Index (AHI) range of 3.7-109.9h^{-1} (Table I). A total of 3980 arousals: 1996 respiratory (m±std =10±2secs duration) and 1984 spontaneous (9±1.2secs) were scored according to the methods described in section II.C and used in this work (Table I).

For each subject, we computed the mean normalized PSD curve of the whole set of PSD curves from respiratory and spontaneous arousals. Inevitably and as expected, less severe SAHS subjects present a smaller number of respiratory arousals since they produce fewer apneas/hypopneas. Yet, the least severe SAHS subject of our database (AHI=3.7h^{-1}) produced a minimum of 6 respiratory arousals which enabled us to compute the mean PSD curve. For our database, a positive correlation between the number of respiratory arousals and the AHI was obtained and is demonstrated in Fig.1 ($r=0.626$, $p=4.18\text{x}10^{-6}$). Conversely, the number of spontaneous arousals and the AHI show negative correlation ($r= -0.47$, $p=6.87\text{x}10^{-4}$).

Results for the mean and mean±sd PSD curves (Der1) for a mild (12.1h^{-1}) and severe (103.8h^{-1}) SAHS subjects are shown in Fig.2 and Fig.3, respectively. A close examination of both respiratory and spontaneous mean PSD curves reveals that their shapes are quite similar and this is confirmed for all 3 EEG derivations.

TABLE I
DATABASE

		NSUB	BMI	Age	AHI	RESP AR	SPONT AR
SAHI<30	**n**	14 (2F;12M)				246	825
	m		26.2	46.8	16.5	17.6	58.9
	sd		2.7	11.4	8.2	12.7	25.9
SAHI≥30	**n**	31 (4F; 27M)				1750	1159
	m		29.5	52.6	57.3	56.5	37.4
	sd		4.7	9.3	24.2	38.2	18.5

NSUB= number of subjects, BMI = Body Mass Index in kg/m^2, AHI = Apnea-Hypoapnea Index in h^{-1}, RESP AR= Respiratory arousals, SPONT AR = spontaneous arousals, F = female, M = male, n = total number, m = mean, sd = standard deviation.

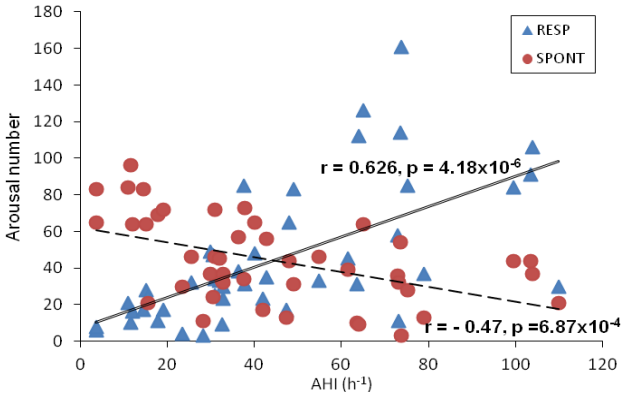

Fig. 1 Correlation between the number of respiratory and spontaneous arousals and the AHI of the 45 SAHS subjects.

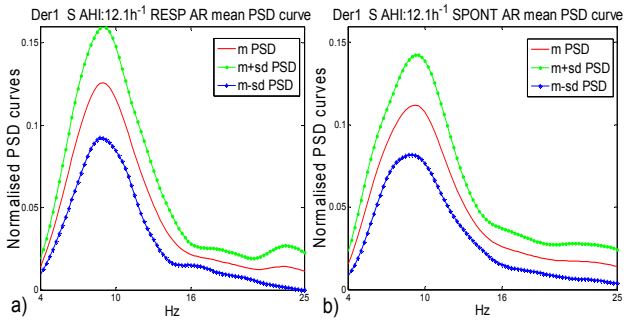

Fig. 2 Respiratory a) and spontaneous b) mean and mean±sd PSD curves for a mild SAHS subject (AHI = 12.1h^{-1}). The mean PSD curves were computed out of a total of a) 16 respiratory arousals and b) 64 spontaneous arousals.

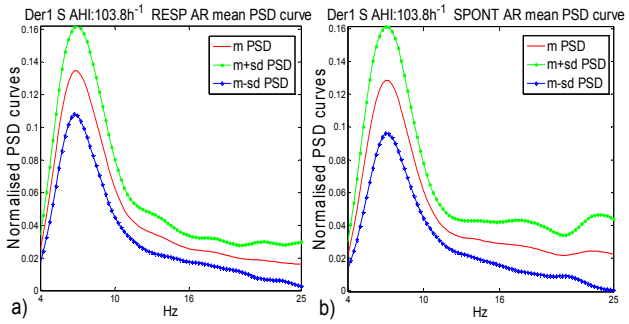

Fig. 3 Respiratory a) and spontaneous b) mean and mean±sd PSD curves for a severe SAHS subject (AHI = 103.8h^{-1}). The mean PSD curves were computed out of a total of a) 106 respiratory arousals and b) 37 spontaneous arousals.

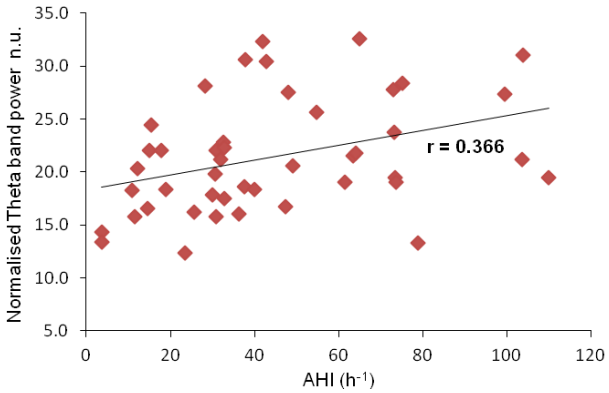

Fig. 4 Correlation between the AHI and the mean normalized Theta band power of spontaneous arousals (Der1).

Furthermore, this similarity is observed not only in less severe SAHS but also in more severe SAHS subjects (Fig.2 and Fig.3, respectively).

Due to space limitations, we cannot include results of the PSD curves for the 3 EEG derivations. For the second part of the analysis, the average band powers were computed for two different groups of subjects.

The whole set of 45 subjects was divided in two groups according to the cut-point of AHI severity of 30h^{-1}. Results obtained (Tables II, III and IV) allowed us to confirm what we had already foreseen when examining the PSD curves: very few differences are seen when comparing spectral content of respiratory and spontaneous arousals.

TABLE II
DER1 – C3A2

		RESP AR				SPONT AR			
		THETA	ALPHA	SIGMA	BETA	THETA	ALPHA	SIGMA	BETA
SAHI<30	m	19.7	41.3	18.3	20	18.6	42.8	18.4	19.5
	sd	6.8	7.5	6.1	7.3	4.4	7.1	6.2	5.4
SAHI≥30	m	22.7	38.6	16.9	21	22.7	38	17.1	21.5
	sd	5.9	7.8	4.5	8.1	5.3	6.8	4.5	7.2
p MW		0.051	0.384	0.470	0.759	0.018	0.057	0.650	0.345

TABLE III
DER2 – C4A1

		RESP AR				SPONT AR			
		THETA	ALPHA	SIGMA	BETA	THETA	ALPHA	SIGMA	BETA
SAHI<30	m	20.1	41.9	18	19.3	19.7	41.4	18.6	19.5
	sd	5.7	9.2	5	7.7	5.4	8.3	5.7	6.2
SAHI≥30	m	23.8	37.6	16.9	20.9	24.2	37	16.8	21
	sd	7.1	7.3	4.2	8	6.6	6.6	4	6.8
p MW		0.057	0.152	0.470	0.598	0.036	0.125	0.384	0.426

TABLE IV
DER3 – O1A2

		RESP AR				SPONT AR			
		THETA	ALPHA	SIGMA	BETA	THETA	ALPHA	SIGMA	BETA
SAHI<30	m	22.5	41.7	16.4	18.5	22.7	41.6	16.5	18.3
	sd	5.9	9.1	4.7	7.4	5.2	7.2	5.1	5.3
SAHI≥30	m	26.3	39.3	14.6	18.9	26.7	38.3	14.9	19.2
	sd	7	9.5	4	7.3	6.6	7.6	3.8	5.8
p MW		0.051	0.532	0.216	0.797	0.064	0.275	0.411	0.598

m(mean) and sd (standard deviation) power values for the Theta, Alpha, Sigma and Beta bands. RESP AR: respiratory arousals. SPONT AR: spontaneous arousals S AHI: Subjects with AHI above and under the cut-point of severity of 30h^{-1}. pMW: significance obtained using Mann-Whitney *U* test.

In what concerns the paired comparison of all 4 frequency band powers with respect to the SAHS severity we can observe the same pattern of differences between the two groups in all 3 derivations. That is, Theta band power is always higher (all 3 derivations) for more severe SAHS subjects ($\geq 30h^{-1}$) than for the least severe ones ($<30h^{-1}$).

This increase is only significant ($p<0.05$) and consistent for the spontaneous arousals of Der1 and Der2. The correlation between the Theta band power of spontaneous arousals (Der1) and the AHI is shown in Fig.4 ($r=0.366$). Alpha and Sigma band powers values decrease for the more severe SAHS subjects, but no significance is observed in any case. Beta band power values also appear to have no correlation with SAHS severity since no significance is seen comparing subjects with opposite levels of SAHS severity.

IV. Discussion and conclusions

In this work, we performed the EEG spectral analysis on a total of 3980 arousals composed of both respiratory and spontaneous arousals. Our goal was to determine if any differences could be found between these two kinds of arousals through the analysis of their spectral content. Since we were interested in studying each arousal in the frequency range of 4-25Hz, we applied a band pass Butterworth filter of fifth order with these frequency limits.

The visual inspection of the shapes of the mean PSD curves for respiratory and spontaneous arousals allows us to attain the similarity on all 3 derivations and for all levels of SAHS severity. Furthermore, the computed band power values showed no difference between respiratory and spontaneous arousals. Regarding the changes in the bands power values with respect to different levels of SAHS severity subjects, we observed the same behaviors for respiratory and spontaneous arousals: Theta and Beta power increased with increasing SAHS severity and Alpha and Sigma powers decreased with increasing SAHS severity. However, the only significant results were obtained for the Theta band power, where fairly good correlation was obtained with the AHI. This outcome is in agreement with the findings made by Dingli et al [8].

Respiratory arousals are generally defined as the ones following, overlapping or adjacent in a small window of time (usually 3 seconds) to apneas/hypopneas [1]. However, there is no widely approved agreement and there are hardly any studies reporting the value of that window of time. The chosen value of that window of time may be crucial on the accurate classification of the arousals and may cause a respiratory arousal to be labeled as spontaneous arousal and vice-versa. Moreover, spontaneous arousals may be caused by undetected respiratory events, severe snoring episodes or even upper-airway intermittent obstruction. Thus, these latter spontaneous arousals would have to be included in an exceptionable group of respiratory-driven arousals since they should be distinguished from the spontaneous arousals that result as an activation of an organic trigger such as intestinal passage, excessive bladder loading or organ dysfunction [3].

Nonetheless, this study has some limitations. First, we are aware that more efforts can be put on the task of uncovering the differences between the two types of arousals. Applying more robust methods and techniques may succeed on that purpose. Finally, our database is composed in its majority of more severe SAHS subjects. However, given that this study is in the scope of arousals, it is likely that No SAHS/mild SAHS subjects will not present sleep fragmentation caused by arousals and therefore could not be object of this study.

Overall, the results obtained allow us to conclude that respiratory and spontaneous arousals have alike spectral contents. Our findings raise doubt as to whether these two kinds of arousals are truly triggered by different organic mechanisms. This may also challenge the current beliefs regarding the underestimation of the importance of spontaneous arousals and their contribution to sleep fragmentation in patients suffering from SAHS.

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