Sleep Science

ORIGINAL ARTICLE

Electroencephalographic and electrocardiographic synchronic activation during sleep apneas detected using coherence wavelet method

Ativação eletroencefalográfica e eletrocardiográfica sincronizada durante apneia do sono detectada por meio do método coherence wavelet

Susana Blanco[1], Marcela Smurra[2], Hernando Sala[3], Cecilia Di Risio[4]

ABSTRACT

Objective: Breath perturbations associated with sleep are accompanied by cortical micro-awakenings. Seventy per cent of them are visible by direct observation on the polysomnographic study. The remaining may be evaluated using techniques such as neural networks or by spectral analysis using Fourier's method. The objective was to establish whether the application of a dynamic mathematical method for polysomnographic tracing enables the identification of an association frequency of the electroencephalogram and the electrocardiogram as a response to breathing events. **Methods:** Polysomnographs of 22 patients (14 males and 8 females) with sleep disordered breathing (SDB) and 3 normal subjects (2 males and 1 female). In order to establish the relationship between cortical activation (micro-awakening) and the electrocardiographic (ECG), both signals were analyzed. The mathematical method used consisted of a wavelet band decomposition of the electroencephalographic (EEG) and the ECG signals together with wavelet coherence. **Results:** The most evident synchronisation pattern occurred between the ECG band corresponding to the high frequencies QRS complex and the EEG alpha band. A correlation was found between the micro-awakening frequency and the frequency of the maximum values of the correlation between the EEG alpha band and the ECG fast band. These frequencies represent synchronization times between 1.5 and 2.8 seconds. **Conclusion:** Above a cut point of 40 micro-awakenings/hour, the population with a significant myocardial activity was grouped showing a significant autonomic activity detectable in the polysomnographic tracing. When sleep fragmentation level is high, a significant myocardial activation appears.

Keywords: Sleep apnea syndromes/diagnosis; Sleep disorders; Polysomnography; Fourier analysis; Electroencephalography; Electrocardiography

RESUMO

Objetivos: Perturbações respiratórias associadas ao sono são acompanhadas de microdespertares corticais. Setenta por cento destes são visíveis em observação direta no estudo polissonográfico. Os restantes devem ser avaliados por meio de técnicas como redes neurais ou análises espectrais que utilizem o método de Fourier. O objetivo deste estudo foi estabelecer se a aplicação de um método matemático dinâmico para análise do traçado polissonográfico possibilita a identificação da frequência de associação do eletroencefalograma e eletrocardiograma como resposta a eventos respiratórios. **Métodos:** Polissonografias de 22 pacientes (14 homens e 8 mulheres) portadores de distúrbios respiratórios de sono e 3 indivíduos hígidos (2 homens e 1 mulher). Para estabelecer a relação entre ativação cortical (microdespertares) e eletrocardiograma, ambos os sinais foram analisados. O método matemático usado consiste de uma decomposição de banda *wavelet* dos sinais eletroencefalográficos e eletrocardiográficos juntos com coerência *wavelet.* **Resultados:** O padrão de sincronização mais evidente foi observado entre a banda eletrocardiográfica correspondente aos complexos QRS de alta frequência e as bandas eletroencefalográficas alfa. A correlação foi encontrada entre a frequência de microdespertares e a frequência dos valores máximos da correlação entre banda eletroencefalográfica alfa e banda eletrocardiográfica rápida. Essas frequências representam tempos de sincronização entre 1,5 e 2,8 segundos. **Conclusão:** Acima do ponto de corte de 40 microdespertares por hora, a população que apresenta significante atividade miocárdica foi agrupada demonstrando significante atividade autonômica, detectada no traçado polissonográfico. Quando o nível de fragmentação do sono é alto, uma ativação miocárdica significante torna-se evidente.

Descritores: Síndromes da apneia do sono/diagnóstico; Transtornos do sono; Polissonografia; Análise de Fourier; Eletroencefalografia; Eletrocardiografia

INTRODUCTION

Breath perturbations associated with sleep are accompanied by cortical micro-awakenings. Seventy per cent of them are visible by direct observation on the polysomnographic

[1]PhD, Consejo Nacional de Investigaciones Científicas y Técnicas – CONICET, Facultad de Ingeniería, Universidad de Belgrano, Buenos Aires, Argentina.
[2]MD, Hospital Tornú, Buenos Aires, Argentina.
[3]MD, Hospital Nacional Profesor Alejandro Posadas, Buenos Aires, Argentina.
[4]PhD, Facultad de Ingeniería, Universidad de Belgrano, Buenos Aires, Argentina.
Corresponding author: Marcela Smurra – (1431) Hospital Tornú - Combatientes de Malvinas 3002 – (5411) 45233200 – Ciudad Autónoma de Buenos Aires – República Argentina – E-mail: marsmurra@yahoo.com
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study[1]. The remaining 30% may be evaluated using techniques such as neural networks[2] or by spectral analysis using Fourier's method[3], which improve the detection of the cortical activity associated with breathing events that are not visible for those who process the study.

Other types of responses, such as the autonomic ones, that appear together with the breathing phenomena are: variations of cardiac frequency, arterial tension or variability of the cardiac response with the sympathetic/parasympathetic balance.

In some cases, other methods of autonomic measurement are required, like pulse transit time (PTT) or peripheral arterial tonometry, that represent an indirect determination of autonomic phenomena such as vasoconstriction or arterial tension variation associated with abnormal breathing events during sleep[4,5].

In a direct way, the presence of oscillations of heart rate variability at the high frequency band (HF) (> 0.10 Hz) is associated with parasympathetic activity related to breath, while oscillations at the low frequency band (LF) (0.01 - 0.05 Hz) are not related to respiration and are thought to correlate sympathetic activity. Intermediate frequencies are still undefined in their cause[6]. In healthy individuals, a decrease in vagal tone was observed, as well as a sympathetic predominance during REM sleep in men[7]. In the sleep disordered breathing (SDB), a decrease of HF components is detected together with a relative increment of the LF components[8]. The cortical activation without visible micro-awakenings (alpha rhythm: 8-12 Hz) in the electroencephalography (EEG), associated with simultaneous variation of the arterial tension in patients with Cheyne Stokes breath[9], suggests a questioning of the presence of other EEG rhythms associated with cardiac autonomic events in patients with sleep apnea and this breathing pattern.

The wavelet transform is a mathematical method[10] that allows a decomposition of the biological signal, separating its components more effectively than the usual Fourier analysis, by adding the time variable to the evaluation of non steady signals such as EEG and electrocardiography (ECG).

As concerns these topics, the objective of the present work was to apply a dynamic mathematical method for the identification of EEG and ECG frequency interaction associated to breathing events, and to evaluate this method as a tool for the association of EEG behaviour with the cardiac variability, in order to know if the frequencies of both biological signals may be related in the SDB. This relationship, as severity clinical feature, could explain some facts in the development of cardiovascular morbidity in patients with SDB.

METHODS

A total of 25 polysomnographic studies were analyzed, belonging to 22 patients with SDB: 10 corresponding to slight-moderate SDB (5-30 apneas-hypoapneas/hour), 12 with severe SDB (> 30 apneas-hypoapneas/hour) and 3 normal subjects (no apneas), that represent a 10% of the sample.

Patients included were those with obstructive sleep apneas with less than 5 central apneas/hour and less than 50% of the apnea-hypoapnea index. Patients who presented neurological disorders, periodic leg movements, narcolepsy or took medication that could interfere with sleep patterns were excluded from the considered population. Moreover, patients with arrhythmia or cardiological history were also excluded.

The polysomnograph was carried out using a computerised system recording:

1) three EEG channels: two central (C3 and C4) and one occipital (O1) referred to right and left mastoids (A2-A1);

2) two electroculography (EOG) channels with palpebral right and left electrodes;

3) three electromyography (EMG) channels, two of them in sub-chin and the other in tibial locations;

4) ECG recorded from two electrode derivations in the second right and left intercostal space in paraesternal location;

5) oronasal flow sensors, one of them of the thermistor type and the other constituted by a nose canula, with pressure transductor to detect flow limitation by nose pressure measurement;

6) thoracic and abdominal piezoelectric band to record breathing efforts;

7) body position sensor;

8) pulse oxymetry (as part of the polysomnograph equipment, Praxis 18 – Line AMP18P, Lermed S.R.L., Argentina).

Visual assessment of the alpha band power behaviour with respect to the marked micro-awakenings was performed with the software associated to the AMP 18P - Lermed S.R.L. equipment. The remaining algorithms required to calculate the correlation between ECG and EEG channels were developed with MatLab 7.0.

Polysomnograph tracings in non-rapid eye movement (NREM) sleep stage were chosen and read sequentially in order to avoid the bias produced by the simultaneous observation of EEG and breathing events. At first, the EEG stratification was performed according to Rechtschaffen-Kales standards[11]; micro-awakenings were then defined as the appearance of sudden changes in alpha frequencies in the EEG (not sleep spindles) of at least 3 seconds and no more than 15 seconds[12], assuming there were sleep records 10 seconds before and after the micro-awakening.

The rapid eye movement (REM) stage was not considered in the signal analysis due to the greater stability in NREM sleep stages, considering that the cortical activity reappearing in REM with alpha type (8-12 Hz) and theta type (5-8 Hz) frequencies is an intrinsic part of such stage.

The second sequence was analyzed on those breathing events classified as follows:

1) obstructive apnea: breath flow ceased or signal drop to 85% during 10 seconds or more, with persistence of breathing effort (activity of thoracic-abdominal bands);

2) central apnea: breath flow ceased or signal drop to 85% during 10 seconds or more, without evidence of breathing effort in thoracic-abdominal bands;

3) hypopnea: significant decrease in breath flow signal during 10 seconds or more, with a decrease in the breathing effort signal amplitude with more than 3% of desaturation or presence of a micro-awakening;

4) flow limitation: flattening pattern in the flow sensor due to nose pressure of at least three breaths followed by the normalisation of the plot morphology.

Mathematical method: wavelet transform and wavelet coherence

The correlation in the spectral analysis indicates the possibility of some relation between two time series through a common frequency.

Fourier Transform can determine linear interactions in stationary time series, but nonlinear interactions in non stationary time series are better analyzed by means of the wavelet coherence method. This mathematical operation gives valuable information about when and how two signals synchronized in time.

The wavelet transform (WT) uses a base of periodic functions, which is built from a located function named "mother function". The wavelet base function changes its scale by "expanding" or "compressing", and each scale is convoluted with the analyzed signal, moving the signal along it.

While in the Fourier approach only the frequency parameter was varied and the base function remained unchanged, in the WT the base function changes its shape according to two parameters, one of them related to the displacement on the signal and thus to time and the other related to translation or to scaling, that analyzes frequency simultaneously.

These operations allow decomposing the original signal in sub-signals called approximations, each corresponding to the original signal filtered in the band of the respective expansion scale. Each approximation is associated with a set of coefficients called details, obtained from the convolution of the wavelet with the signal, that represent the relative values of the band importance as a function of time.

In summary, the scale identifies the frequency band, while the position locates such frequency components in time. Their functional dependence may be expressed as follows:

$$C(scale, position) = \int_{-\infty}^{\infty} f(t).\Psi(scale, position, t).dt$$

where f(t) is the original series and Y are the infinite elements of the wavelet base.

The spectrum decomposition results asymmetric towards low frequencies, which produces a numerical advantage. With this method, details have a high frequency definition and a poor time location. Approximations, instead, have a low frequency location but a high time location. This choice for signal decomposition is not arbitrary. The signals usually found are time-localised bundles, that is to say, they have high frequency components during a short period of time, and low frequency components of long duration.

As the convolution process is iterative, it could be theoretically continued indefinitely. A reasonable number of decomposition steps are usually chosen based on the particular needs of the actual problem. Once the decomposition level required is achieved, it is possible to analyze each band to look for information.

If the mother function used for decomposition is a base in the mathematical sense, the details squared may be considered as the energy deposited independently on each band.

In this work, mother wavelets of the cubic spline type are used, which, due to their morphological characteristics, are the most adequate for biological signals. On the other hand, they constitute a base in the mathematical sense.

The coherence is defined as the cross-spectrum, normalized to an individual power spectrum. It is used to identify frequency bands within which two time series are covered, and to determine the time and frequency intervals in which two phenomena have a strong interaction.

For coherence calculation between EEG and ECG wavelet decomposition bands, the steps below were followed:

- To determine micro-awakening, about 10 seconds of the EEG signal was taken together with the corresponding ECG portion – these portions of EEG and ECG corresponding to sleep Phases I and II, without artifacts. Channels C3 and C4 of the EEG were chosen. For each patient, 10 similar micro-awakenings were used.

- Both signals EEG and ECG were decomposed with wavelet pass bands separating them in 6 octaves. This is always possible because both signals are sampled at the same frequency (349 Hz).

- The coherence wavelet method was applied between the 36 pairs of EEG and ECG bands.

Statistics

In order to establish the correlation between the micro-awakening frequency values and the maximum correlation frequency, the Pearson regression coefficient was calculated for the analysis of the results. F- and t-tests were used to compare mean and standard deviation at the significant values of α = 0.05 and 0.01, respectively.

RESULTS

The group of studied patients (n = 25) consisted of 16 males and 9 females, ages between 26 and 78 years (54 ± 16 years), and body mass index (BMI) between 21.6 and 54 kg/m^2 (29 ± 7 kg/m^2). Table 1 shows the results patient by patient.

The coherence between EEG alpha band and ECG high frequency band showed a periodic pattern with a distinctive frequency establishing the maximum synchronisation between both of them.

Table 1 shows the synchronization frequency in hertz (Hz) and the maximum correlation times between EEG and ECG for each individual; these are the mean values for all synchronization frequencies for each patient without considering the kind of breathing event.

Table 1: Demographic data. Ages are expressed in years and body mass index (BMI), in kg/m^2

Patient	Age	BMI	Severity	Arousals/ hour	Maximum Correlation Frequency (Hz)	Time (seconds)
P1	32	23	N	3	0.48	2.08
P2	74	31.4	N	4.8	0.41	2.4
P3	49	26.6	N	13.8	0.49	1.1
P4	60	25	M-L	16.8	0.55	1.81
P5	36	23.2	M-L	17.4	0.48	2.08
P6	69	29.2	M-L	19.2	0.57	1.75
P7	50	38	M-L	21.6	0.53	1.88
P8	26	21.6	M-L	24	0.55	1.8
P9	44	23.8	M-L	30	0.55	1.81
P10	67	29	M-L	30	0.59	1.69
P11	76	30.3	M-L	33	0.53	1.88
P12	45	28.2	M-L	40	0.53	1.86
P13	30	24.4	M-L	45	0.58	1.72
P14	59	33.8	S	45	0.64	1.56
P15	28	54	S	45	0.59	1.69
P16	68	24.2	S	46.2	0.57	1.75
P17	50	27.7	S	46.8	0.62	1.61
P18	54	23.9	S	60	0.65	2.08
P19	28	37.5	S	60	0.68	1.47
P20	59	37.2	S	60	0.61	1.6
P21	78	23.9	S	63.6	0.64	1.56
P22	65	29	S	75	0.71	1.4
P23	61	39.1	S	76	0.66	1.51
P24	78	23.9	S	79.2	0.65	1.53
P25	50	27.7	S	81.6	0.7	1.42

N: normal subject; M-L: slight-moderate; S: severe.

If we plot maximum correlation frequency as a function of micro-awakening/hour (arousals), we obtain a good correlation, with Pearson's coefficient of 0.817. Figure 1 shows graphic data.

Figure 2 shows the same graph, but for slight-moderate (A) and severe (B) groups of patients. Figure 2A indicates that spectral frequencies are between 0.5 and 0.6 Hz for slight-moderate group, while in the severe cases, they are between 0.6 and 0.7 Hz.

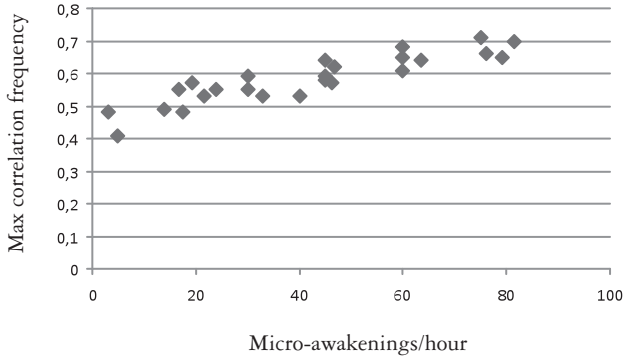

Figure 1: Synchronization frequency and micro-awakenings/hour correlation plot in the whole group.

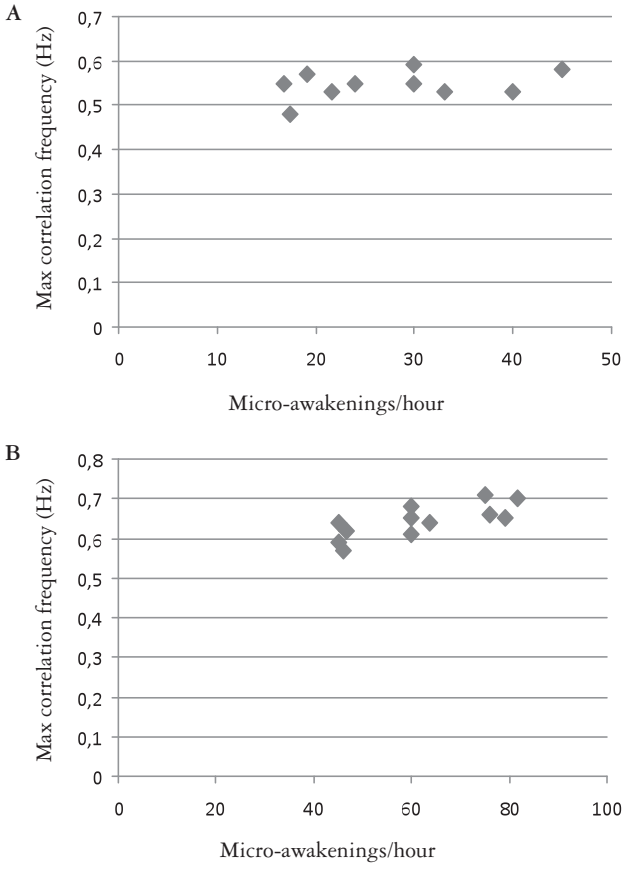

Figure 2: Synchronization frequency and micro-awakenings/hour correlation plot. A: slight-moderate; B: severe population.

Mean values were 0.546 and 0.643 Hz for slight-moderate and severe patients, respectively. To establish a level of significance of this difference, F-test for comparison of standard deviation at a level of $\alpha = 0.05$, and t-test for comparison of mean ($\alpha = 0.01$) were performed. Results show that this difference is significant.

Figure 2 also shows the existence of a virtual cut among patients with severe SDB and individuals with slight-moderated or without SDB. Such cut is represented by the value of 40 micro-awakenings/hour above which the population presenting significant myocardial activity has been grouped together.

Synchronisation times among them – the EEG alpha band and the QRS band for ECG – fluctuate between 1.5 and 2.8 seconds.

DISCUSSION

Polisomnography, in its usual interpretation, offers clear and reliable information about sleep stages and breathing events.

Nowadays, there are methods of sleep signal analysis that allow a reduction on the visual reading time of the polisomnographic tracings and let us find, in an automated way, sleep stages and disease related patterns linked to them. The regularly used methods are sleep analysis system to challenge innovative artificial networks (SASCIA), which works with neural networks, or cyclic alternating pattern (CAP)[13-15]. The use of the wavelet decomposition (WPM) plus wavelet coherence in this project helped us to evaluate simultaneous variations in the EEG signals, and in those who show an autonomic response of the organism as a result of apneas, hypopneas or limiting flow events. It makes this variations appear in the polisomnographic tracings, as for its high capability in identifying short duration changes in a synchronized way, analyzing simultaneously all the signs in the polisomnography, which could not have been possible using the Fourier transform[1] because it is insensitive to the fast changes and cannot be used in non-steady signals.

It is rather frequent to find bradi-tachycardia episodes, but only in patients with severe apnea/hypopnea sleep syndrome, relating this to the unbalances between the sympathetic-parasympathetic activity relation. In previous evaluations using CAP, it could be observed that the sympathetic activation is significantly higher during CAP events than non-CAP ones, and it is clearly related with the increase in blood pressure. Parasympathetic activity is predominant in NREM, unlike REM which has sympathetic predominance. The disappearance of the vagal predominance in NREM was observed in patients with myocardial infarction and it was proposed as a significant factor in the occurrence of nocturnal fatal events. Moreover, the obstruction of the baroreflex increment in CAP would lead to an increase in the possibilities of cardiac events[16]. Also, in association with CAP phenomena, secondary micro-awakenings responding to auditory stimuli were detected, in which a substantial cardiovascular activation was observed, coinciding with pathological situations such as SDB or periodic leg movements[17].

Different regions of the heart are differentially activated during arousal from sleep, and they may be partially influenced by different respiratory and non respiratory related sensory inputs to the neural cardiomotor centres. Cardiac arousals seem to have preceded cortical arousals, the predominant responses to arousal were respiratory rate (RR) and QT interval shortening and PR interval lengthening, although different activation patterns with potentially different arrhythmogenic potential were also observed[18]. The increase in cardiac activity during micro-awakenings is mainly a reflex activation response, which implies a decrease in the vagal tone and an increase of the sympathetic during the period of the micro-awakening[19,20].

Respiratory patterns that need correction activate the central nervous system (CNS); the autonomic nervous system is enhanced when an arousal occurs, which explains the greater increase in heart rate with EEG arousal than without arousal[21].

The slow waves determine a softer vegetative reaction, which in certain pathologic conditions may be strong enough to overcome a disturbing factor. Faster EEG activities guarantee more powerful activation of autonomic functions[22].

The techniques that used spectral analysis with time variation or fractal dimensions have analyzed variability in the cardiac frequency, but not the QRS changes in terms of analysis of signal power[23,24].

The vagal-sympathetic unbalance would be in the function of the intracardiac neuronal network with vagal-sympathetic co-activation, in which the brachicardia represents an adaptive reaction to protect the heart of hypoxia by reducing oxygen consumption. The concomitant sympathetic activation would improve contractility, optimizing systolic volume[25].

The referential signal for the detection of autonomic phenomena was developed by Pitson and Stradling[26] and consists in the analysis of the pulse transit time between the heart and the peripheral sensor placed in a finger, as it varies following the changes of arterial tension. This analysis has the objective of determining the presence of an autonomic response, called autonomic micro-awakenings, no detectable on the EEG. This signal not evaluated in our work represents a limitation to consider the results as found directly related to autonomic activation. However, the high correlation found between the EEG micro-awakenings and ECG signal characterized by the increment in power of the QRS

band is probably an expression of increment on the autonomic activity not described in the previous reading of the polisomnography.

Recently, the analysis of the cardiac frequency was used during specific intervals (e.g. micro-awakenings) using the average cardiac frequency prior to and during the event, considering likelihood ratios over 10 levels of cardiac frequency variations through an algorithm of autonomic activation identification based only in cardiac frequency changes. The model showed a lack of correlation between the visual reading of the EEG and the ECG events detected through the algorithm[27]. It is not clear whether this discrepancy in signals responded to autonomic events, as the signal was not referred to phenomena detected through pulse transit time.

Our interpretation is that the increase in the power of the QRS slow band in detriment of the fast band represents a more interesting signal in the appreciation of cardiac participation than frequency, as the latter is influenced by extra cardiac phenomena, although it would be interesting in further analysis to determine which of these two variations is more influenced by autonomic control, correlating both with PTT, which was a limitation of our work.

It does not seem possible that these results would be due to an intrinsic illness of the conduction system, but to a delay in the intraventricular conduction, modulated by a sympathetic-parasympathetic unbalance, as analyzed previously. A similar behavior is considered a predictor of the appearance of arrhythmic events and mortality in cases of myocardial infarction or congestive heart failure[28]. This circumstance might be related to the observation made in this work that the mentioned behavior is more frequently found in the most severe patients, which could be related with the clinical evolution of SDB complicated with the appearance of fatal and non fatal cardiovascular events[29].

Another possible explanation for our observation is the amplitude increase of QRS, which, even in individuals without SDB, implies an increased risk in arrhythmia production when compared to narrower QRS[30]. Polysomnographic tracings were related to sleep apneas and hypopneas of different severities with the purpose of correlating cortical activity and cardiologic response. The presence of a threshold in 40 micro-awakenings/hour shows that the correlation was significant when the presence of micro-awakenings was higher, which could mean that the sympathetic-parasympathetic unbalance requires a higher level of severity in the breathing event frequency in order to obtain higher levels of cortical activation.

CONCLUSION

This work, as far as we know, for the first time makes clear the possibility of detecting modifications of the intrinsic cardiologic activity, represented by the changes in the QRS power in the routinely polysomnographic tracing. Wavelet coherence established a mathematical relationship between fast cortical and autonomic responses, showing more severity when both reactions are observed.

In our knowledge, there are not enough data using wavelet coherence to analyze autonomical signal. Further studies in our group try to get the link among PTT, ECG and cortical activity.

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