Non-Linear Dynamic Analysis of RR Signals in Patients with and without Excessive Daytime Sleepiness

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Abstract

Linear and non-linear measures applied to heart rate variability (HRV) can be used to quantify modulation of the sympathetic and parasympathetic branches of the autonomic nervous system. RR signals were obtained from the ECG recorded during five Maintenance of Wakefulness (MWT) and Multiple Sleep Latency (MSLT) tests alternated throughout the day from patients suffering sleep disturbance. Two different end-points were considered: Study A, excessive daytime sleepiness (EDS) versus without daytime sleepiness (WDS); Study B, Pre-CPAP versus Post-CPAP (continuous positive airway pressure therapy) in EDS. Measures obtained from spectral analysis (PSD), time-frequency representation (TFR), auto-correntropy (ACORR) and auto-mutual-information function (AMIF) were applied to describe autonomic nervous system activity and RR regularity. Statistical differences between EDS and WDS groups were found in MSLT events. During MSLT, the parasympathetic activity and RR regularity in EDS were affected by CPAP therapy. Non-linear measures obtained from EDS in Post-CPAP differed from Pre-CPAP (p-value<0.05) and tended to be similar to WDS.

1. Introduction

Sleep-related breathing disorders are common causes of excessive daytime sleepiness, a socially and clinically relevant problem. An excessive daytime sleepiness (EDS) is a symptom that can have many different causes, not only sleep deprivation. Mechanisms responsible for daytime sleepiness are still largely unknown.

EDS, with subjects falling asleep at unusual times of the day and during activities where vigilance is required, represents a troublesome symptom in patients with sleep-related breathing disorders (SRBD) [1,2]. Moreover, the reduced cognitive performance reported in patients with SRBD may not only depend on their typical nocturnal intermittent hypoxia, but may also be related to EDS [3]. The pathogenesis of EDS in SRBD is still ill defined. In this context, SRBD may affect autonomic modulation of the cardiovascular system, by interfering with autonomic influences responsible for cardiovascular regulation, leading to a kind of autonomic arousal [4,5].

A previous study [1] has shown that the phasic and tonic autonomic changes induced by SRBD might represent sensitive additional markers of the concomitant perturbation of sleep quality and, thus, of the occurrence of daytime sleepiness in patients with SRBD. Among various symptoms associated with this condition, the most prevalent is EDS.

In the present work, linear and nonlinear signal processing techniques were applied to RR series for the assessment of drowsiness in patients suffering sleep disturbance who undergoing the maintenance of wakefulness test (MWT) and multiple sleep latency test (MSLT). In the clinical practice, the MSLT and MWT are frequently used to measure the time elapsed from the start of a daytime nap period to the first signs of sleep, called sleep latency [6-9].

Measures based on time-frequency representation (TFR) and power spectral analysis (PSD) were applied to RR series in awaking state in order to quantify modulation of the sympathetic and parasympathetic branches of the autonomic nervous system. Auto-mutual information function (AMIF) and auto-correntropy (ACORR) were used to describe the complexity and regularity of the RR time series. Finally, statistical analysis was performed in order to characterize patients with excessive daytime sleepiness (EDS) and without daytime sleepiness (WDS). Furthermore, the patients of the EDS group were analyzed before and after the CPAP (continuous positive airway pressure) therapy.

2. Materials and methods

2.1. Analyzed database and preprocessing

The analyzed database belongs to the Multidisciplinary

Sleep Disorders Unit of the Hospital Clínic (Barcelona, Spain). This database contains data recorded from 40 patients: EDS group, 20 patients with excessive somnolence (MWT < 20 min and MSLT < 8 min); WDS group, 20 patients without somnolence (MWT > 20 min and MSLT > 8 min). RR series (interval between consecutive heartbeats) were obtained from the ECG recorded during five MWT and five MSLT alternated throughout the day. The MSLT and MWT consisted of a series of five nap opportunities during the day beginning approximately two hours after morning awakening. The MSLT measures the propensity for falling asleep in a comfortable situation, lying in bed in a dark and quiet room, with explicit permission to fall asleep. The MWT assesses resistance to fall asleep. Subjects were sitting in a bed and were instructed to stay awake.

RR series were filtered by replacing artifacts or ectopic beats if deviate more than a 15% tolerance of the mean value of the previous twenty beats. These unevenly sampled signals were processed using cubic spline interpolation and sampled at 4 Hz. For each MWT and MSLT test, a sequence of 180 s of time series $RR(t)$ in the awaking state was selected 30 s after test started. Windows belonging to tests in which the patient fell asleep in less than 180 s were not included in this study.

2.2. Spectral analysis

TFR based on Choi-Williams distribution (CWD) is calculated by convoluting the Wigner distribution (WD) and the Choi-Williams (CW) exponential, [10].

The functions, instantaneous power (*IP*) and instantaneous frequency (*IF*), were obtained from $\mathrm{CWD}_{RR}(t,f)$, and the spectrum was divided into the characteristic frequency bands of the $RR(t)$: VLF, <0.04 Hz; LF, 0.04-0.15 Hz; HF, 0.15-0.4 Hz; TB, total-frequency band. *IP* was calculated as the area under the curve of the $\mathrm{CWD}_{RR}(t,f)$ at each instant. In each of the considered bands, this value was normalized by the total power. *IF* was defined as the mean frequency of the spectrum at each instant [11]. The mean value (*m*) was calculated on the TFR functions along the time.

Also the known frequency domain analysis based on the power spectral density (PSD) using Yule-Walker AR method was applied. The maximum order of the AR model was fixed to 20th. The normalized powers LF and HF and the rate LF/HF were calculated [12].

2.3. Auto-mutual information and Auto-correntropy function

AMIF is a metric to estimate both linear and nonlinear dependences between two time series [13,14], x_t and $x_{t+\tau}$. It can be regarded as a nonlinear equivalent of the correlation function. AMIF is calculated by the distribution of the probability amplitudes of $x_t = RR(t)$ and $x_{t+\tau} = RR(t+\tau)$, and the joint probability of these time series, based on Shannon entropy.

$$AMIF\_Sh(\tau) = \sum_{x_t,\, x_{t+\tau}} P\{x_t, x_{t+\tau}\}\, log_2\left(\frac{P\{x_t, x_{t+\tau}\}}{P\{x_t\}P\{x_{t+\tau}\}}\right) \quad (1)$$

Probabilities and joint probabilities were computed on the basis of a quantization in 5 bits. This function describes how the information of a signal (AMIF value at τ=0) decreases over a prediction time intervals (AMIF values at τ>0). Increasing information loss is related to decreasing predictability, and increasing complexity of the signal [15].

AMIF was also defined from Rényi entropy as in (2).

$$AMIF\_Re_q(\tau) = \frac{1}{q-1} log_2 \sum_{x_t,\, x_{t+\tau}} \frac{P^q\{x_t, x_{t+\tau}\}}{P^{q-1}\{x_t\}P^{q-1}\{x_{t+\tau}\}} \quad (2)$$

In this work, AMIF was calculated using a discrete time delay $0 \le \tau \le 100$ samples for different values of the control parameter of Rényi entropy: q = {0.1, 0.2, 0.5, 2, 3, 5, 10, 30, 50, 100} and $q \to 1$ using (4). AMIF was normalized by its maximum value that corresponds to τ=0.

ACORR is a similarity measure of signals that generalizes the autocorrelation function to nonlinear spaces.

$$\hat{V}(\tau) = \frac{1}{N}\sum_{t=1}^{N} \frac{1}{\sqrt{2\pi}\sigma} e^{-\frac{(RR(t)-RR(t-\tau))^2}{2\sigma^2}} \quad (3)$$

where σ is the size of the kernel determined in this study by Silverman's rule [16] of density estimation.

AMIF and ACORR were applied to $RR(t)$ time series (TB) and to $RR(t)$ filtered in the frequency bands: VLF, <0.04 Hz; LF, 0.04-0.15 Hz; HF, 0.15-0.4 Hz.

Several measures were defined on the AMIF and ACORR along the time delay τ: *m*, mean value; *maxL*, first relative maximum; *min*, absolute minimum; *FD*, first derivative.

2.4. Statistical analysis

Two different end-points have been considered: Study A, comparing excessive somnolence (EDS) versus without somnolence (WDS) groups; Study B, comparing pre-CPAP versus Post-CPAP therapy in a subgroup of 10 EDS patients. For both studies, measures obtained from each MWT (MWT1, MWT2, MWT3, MWT4, MWT5) and MSLT (MSLT1, MSLT2, MSLT3, MSLT4, MSLT5) were independently analyzed.

A non-parametric test, U of Mann-Whitney test, was applied and a significance level p-value <0.05 was taken into account. Measures that satisfy this condition were considered for building the discriminant function. The leaving-one-out method was performed as validation method.

3. Results and discussions

3.1. Study A

The present study has permitted to characterize EDS and WDS groups only during MSLT with statistically significant difference. Table 1 shows the linear and non-linear measures which were able to classify both studied groups.

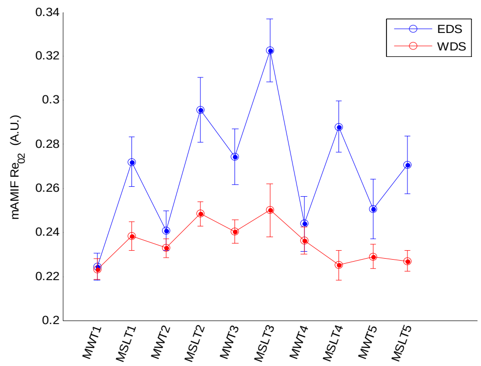
The TFR measure *mIP*(*HF*) that describes the autonomic parasympathetic nervous system activity (HF band) have presented higher values in EDS group than WDS group, with p-value=0.003 in MSLT3. EDS group presented a higher (p-value<0.05) heart rate variability (*stdRR*) during MSLT1 and MSLT4.

Table 1. Study A: Linear and non-linear measures able to statistically differentiate between WDS and EDS groups.

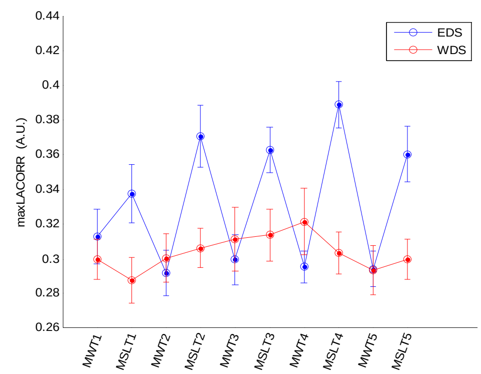
Measures	p-value	WDS (%)	EDS (%)	WDS (mean± std)	EDS (mean± std)
stdRR (*ms*)					
MSLT1	0.041	75	60	39.1±3.37	51.2±5.55
MSLT4	<0.0005	85	75	27.5±1.84	44.7±3.32
LF norm (*n.u.*)					
MSLT5	0.047	60	80	36.0±2.5	29.7±1.7
mIP(*HF*) ($x10^{-6}$)					
MSLT3	0.003	95	60	6.49±0.541	12.5±1.87
$mAMIF\_Re_{0.2}(TB)$					
MSLT3	<0.0005	90	75	0.250±0.012	0.323±0.015
MSLT4	<0.0005	90	75	0.225±0.007	0.288±0.012
MSLT5	0.008	90	60	0.227±0.005	0.271±0.013
$maxLAMIF\_Re_{0.1}(VLF)$					
MSLT3	0.0025	90	80	0.381±0.013	0.466±0.019
MSLT4	<0.0005	75	75	0.352±0.013	0.431±0.015
$mAMIF\_Sh(LF)$					
MSLT3	0.0023	90	75	0.344±0.015	0.416±0.014
MSLT5	0.0033	80	65	0.317±0.008	0.376±0.015
$mAMIF\_Re_5(HF)$					
MSLT1	<0.0005	100	70	0.371±0.004	0.406±0.008
MSLT3	<0.0005	90	70	0.387±0.009	0.436±0.011
maxLACORR(*TB*)					
MSLT1	0.027	80	60	0.287±0.014	0.338±0.017
MSLT2	0.006	90	65	0.306±0.012	0.371±0.018
MSLT3	0.008	65	75	0.314±0.016	0.363±0.014
MSLT4	<0.0005	85	80	0.303±0.012	0.389±0.014
MSLT5	0.002	80	60	0.299±0.012	0.361±0.017

The non-linear measures that describe the regularity of the *RR*(*t*) have evidenced more regularity behavior in EDS group than WDS group, with p-value<0.05 for all MSLT tests. Observing the results, it can be noted that *RR*(*t*) in VLF, LF and HF bands has similar regularity behavior when the groups are compared (p-value<0.005), this means higher values of *maxL* and *m* in EDS group.

Figure 1 shows the evolution of the mean value of $mAMIF\_Re_{0.2}$ and *maxLACORR* with respect to MWT and MSLT. As it can be seen in figure 1, the non-linear measures present more changes between MWT and MSLT in EDS group than WDS group. However, the values of these measures in EDS group during MWT tend to be similar to those of WDS group, presenting a non-significant statistical level.



(a)



(b)

Figure 1. Study A. Mean value and standard error: (a) $mAMIF\_Re_{0.2}$; (b) *maxLACORR*.

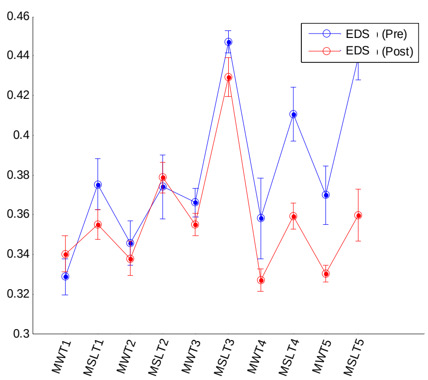
3.2. Study B

The best results of the Pre-CPAP and Post-CPAP study are shown in Table 2. Only non-linear measures, *AMIF* and *ACORR*, were able to describe the Pre-CPAP and Post-CPAP therapy. The evolution of non-linear variables was similar in the first part of the day (from MWT1 to MWT3 and from MSLT1 to MSLT3), however the statistical differences were presented during the last part of the day, after lunch time (MWT4, MWT5, MSLT4 and MSLT5), as it can be seen in figure 2. Particularly, it can be observed a more regularity behavior in Pre-CPAP than Post-CPAP during MSLT4 and MSLT5.

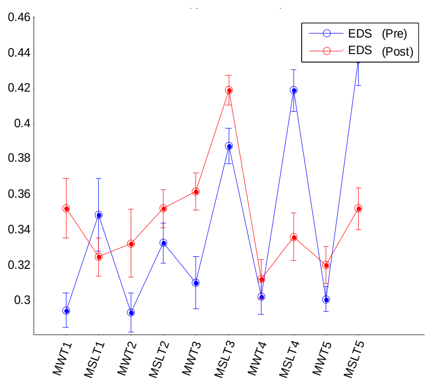
In this way, measures that describe the regularity of *RR*(*t*) in EDS group were affected by CPAP therapy, and they assumed values similar to those of WDS group in Study A.

Table 2. Study B: Non-linear measures able to statistically differentiate between Pre- and Post-CPAP in EDS group.

Measures	p-value	Pre (%)	Post (%)	Pre (mean± std)	Post (mean± std)
maxLAMIF_Re$_{0.1}$(*VLF*)					
MSLT4	0.0379	70	85	0.451±0.016	0.378±0.013
mAMIF_Sh(*LF*)					
MSLT5	0,038	70	85	0.439±0.012	0.359±0.014
maxLACORR(*TB*)					
MSLT4	0.038	70	85	0.418±0.013	0.336±0.014
MSLT5	0.026	70	70	0.436±0.016	0.352±0.013



(a)



(b)

Figure 2. Study B. Mean value and standard error: (a) *mAMIF_Sh*(*LF*); (b) *maxLACORR*(*TB*).

4. Conclusions

Autonomic parasympathetic and sympathetic nervous system activity and the regularity of the *RR*(*t*) were described by measures of TFR, AMIF and ACORR in two groups of patients in awake state. Statistical differences between EDS group and WDS group were found in MSLT events. Measures that describe the parasympathetic nervous system activity and regularity behavior of *RR*(*t*) were found to have higher values in EDS group during MSLT. Comparing Pre-CPAP and Post-CPAP therapy, statistical differences were found using measures of *AMIF* and *ACORR* in MSLT4 and MSLT5.

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