Characterization of Autonomic Dysfunction in REM Sleep Behavior Disorder

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Abstract

Goal: *This work aims at characterizing autonomic dysfunction in RBD subjects using heart rate variability (HRV) indexes computed from ECG recordings during polysomnographic studies.* ***Results:*** *RR variance (σ^2) is significantly lower in RBD both in N1 (p=0.018) and N3 (p=0.035) sleep stages. High frequency (HF) power, related to vagal control, shows a statistically significant difference between the two populations in N3 (p=0.008) and REM (p=0.028), with higher medians in the healthy subjects. Median HF power in healthy subjects reduces while moving from NREM to REM stage, whereas medians of RBD group have a similar order of magnitude in all sleep stages, always smaller than healthy controls.* ***Conclusions:*** *Results point at an overall reduction of HRV in RBD when compared to healthy controls, supported by the observed lower σ^2 and HF power, mainly in N3 and REM sleep stages. As expected, sympathetic activation in REM stage is observed in the control group, whereas RBD subjects show higher normalized HF power during sleep, possibly indicating an impaired sympathetic activation in RBD subjects.*

1. Introduction

According to Carskadon et al. [1], sleep can be defined as a reversible state in which people lose the active reactions with the surrounding environment. Sleep macrostructure is divided into rapid eye movements (REM) and Non-REM (NREM) sleep; NREM can be further subdivided into three other sleep stages (N1, N2, and N3) [2]. The first phase is N1, which constitutes 2-5% of total sleep, representing a transition between wake and sleep, except for newborns and subjects affected by narcolepsy or other neurodegenerative diseases. Its peculiar characteristic is the appearance of the Slow Eye Movements (SEM), recognizable with an electrooculogram (EOG), alongside a progressive reduction of muscular tone from the wake stage. Conversely, N2 takes up from 45 to 55% of total sleep, while N3 represents the deepest sleep stage and the more resting stage for the subject. The latter is characterized by a synchronization of the electroencephalography (EEG) traces with the presence of delta waves at high amplitudes. Of note, REM sleep is characterized by bursts of rapid eye movements which overlap with a majority of SEM, by desynchronization of the EEG, and by the appearance of rapid activity with mixed frequencies, similar to the one of an awake subject (alpha rhythm). Differently from NREM stages, in REM sleep stage a higher variability of physiological parameters is observed, like variations in arterial blood pressure, heart rate, respiration, and a drop in the body temperature. Also, healthy subjects show complete muscle atonia, i.e. a type of muscular immobility caused by the total relaxation of the muscles. Among the disorders that can influence the REM sleep stage, there is the REM Sleep Behavior Disorder (RBD). RBD has been characterized for the first time in 1986 and it is defined by the American Academy of Sleep Medicine (AASM) as "a REM sleep parasomnia characterized by the presence of dream-enactment behaviors and loss of normal REM sleep muscle atonia" [3]. Its main feature is the loss of muscle atonia typical of this sleep stage, supported by a motor activity enacting the sleep content. Possible activities range from simpler ones (like laughing, speaking, screaming, or limb movements), to more severe behaviors (like kicking or throwing punches, jumping out of bed, and running) [4]. In these last cases, if the subjects do not sleep alone, they could injure their partner. To diagnose RBD, the following criteria should be met: repeated episodes of sleep-related vocalization and/or complex motor behaviors, documented by polysomnography (PSG), or presumed, to happen during REM, given the clinical history of dream enactment; presence of REM sleep without atonia, proved by PSG; the disturbance cannot be better explained by any other sleep disorder, mental disorder, medication, or substance abuse [5]. PSG can tell if the subject has a partial or total

loss of muscle atonia during REM sleep. In particular, a first-level PSG is needed, requiring the recordings of electroencephalogram (EEG) for sleep scoring, EOG for eye movements assessment, ECG for heart state and heart rate assessment, electromyography (EMG) to demonstrate abnormal muscle activity during REM sleep, usually done by recording the activity of the mylohyoid muscle, and video recordings, to correlate clinical events with the electrophysiological recordings. Analysis of heart rate variability (HRV) parameters in RBD subjects with respect to a healthy control group has already been proposed and it mainly showed reduced variability in the RBD [6,7] group. In [6], a sympathetic impairment was mainly pointed out, with lower values in the power of the low frequency (LF) band and in the sympathovagal balance LF/HF in RBD subjects than controls, but also higher ratios in REM sleep than in stage N2, and lower high-frequency (HF) power values. Bugalho et al. [7] showed a lower HRV in patients with RBD, with less variations between stages when compared with patients without RBD, especially regarding the HF measures. Recently, advanced modeling approaches for HRV indexes estimation, like the point process statistical modeling of HRV [8], have been proposed to deeply investigate the non-stationarity in HRV oscillations. Point process modeling was applied to study and characterize the presence of autonomic signatures of sleep fragmentation in recordings coming from an entire night of sleep [9]. In this work, our goal is to characterize autonomic changes in RBD subjects with respect to healthy controls by evaluating HRV indexes, computed through a point process approach, on PSG recordings.

2. Methods

2.1. Study Design and Cohort Selection

The study was approved by the Independent Ethical Committee of the Cagliari University Hospital (AOU Cagliari) and performed following the principles outlined in the Helsinki Declaration of 1975, as revised in 2000. PSG recordings were performed at the Interdepartmental Centre for Sleep Medicine of the University of Cagliari by EEG and PSG Holter Morpheus from Micromed (Micromed S.p.A., Treviso, Italy). Hypnograms have been obtained following the AASM guidelines for sleep scoring, resulting in the following subdivision: wake, N1, N2, N3, REM. The following criteria were applied to select the signals for the analysis: availability of an ECG signal in the first epoch for each sleep stage (regardless of its duration); absence of any other relevant pathology, apart from RBD; absence of arrhythmia or pacemaker. A cohort of 17 healthy controls and 22 RBD subjects who met the defined criteria was selected. For each subject, ECG waveforms were analyzed with an internally developed Pan-Tompkins-based automatic annotation software already used in previous studies [10], which extracted the times associated with the R-peak events in the signal. The resulting tachograms were manually reviewed to correct for missing beats and for beats not belonging to sinus rhythm.

2.2. Cardiovascular Data Modeling

Given the aforementioned annotations, we modeled the corresponding inter-beat-interval series using a point process approach. A point process is a binary stochastic process describing events that occur unevenly in continuous time or space. Specifically, it has been demonstrated that the stochastic structure of heartbeat intervals can be modeled as a history-dependent inverse Gaussian process [8]. The model is defined as:

$$f(t|H_{u_k},\theta) = \left[\frac{\theta_{p+1}}{2\pi(t-u_k)^3}\right]^{\frac{1}{2}} \exp\left\{-\frac{1}{2}\frac{\theta_{p+1}\left[t-u_k-\mu\left(H_{u_k},\theta\right)\right]^2}{\mu\left(H_{u_k},\theta\right)^2(t-u_k)}\right\}$$

where the average RR interval μ is obtained as a regression of the past p RR intervals (being p the order of the autoregressive model) and, along with the shape parameter of the inverse Gaussian (θ_{p+1}) and its variance (σ^2), they are all allowed to vary in time. A local maximum likelihood method is used to estimate the set of unknown parameters $\theta(t)$. The use of this probabilistic framework allows also for the estimation of indexes derived from the spectral analysis at each moment in time.

From the proposed modeling approach, considering the first epoch of each sleep stage, we extracted the following time-varying indexes: the mean RR interval (μ_{RR}), RR variance (σ^2_{RR}), the power in the LF band (0.04-0.15Hz) (LF_{RR}), the power in the HF band (0.15-0.4Hz) (HF_{RR}), the normalized LF power (LFn_{RR}), the normalized HF power (HFn_{RR}), and the ratio between LF and HF (LF/HF_{RR}) referred to as sympathovagal balance. The normalized values were obtained by dividing the corresponding power band by the sum of the LF and the HF powers in every time instant.

2.3. Statistical Analysis

To test the differences between the healthy controls and the RBD subjects, we used the Mann-Whitney U test. Continuous estimates of HRV indexes were averaged for each sleep stage and for each subject. To evaluate differences between different sleep stages, and specifically between NREM and REM sleep, for each population, the paired Mann-Whitney U test was applied. Test significance was set to a p-value < 0.05.

Table 1. Median (first;third quartiles) for the healthy controls (C) and RBD for every sleep stage. Exact p-values from the Mann-Whitney U test for between-group differences are reported. Within-group differences tested with paired Mann-Whitney U test with respect to the REM stage are indicated as follows: *:p-value < 0.1, †:p-value < 0.05, and ‡:p-value < 0.01.

HRV Feature	Group	*N1*	*N2*	*N3*	*REM*
μ_{RR} [sec]	C	0.882(0.822;0.982)	0.873(0.804;1.036)	0.982(0.848;1.111)	0.956(0.834;1.103)
	RBD	0.981(0.850;1.079)	0.855(0.784;1.011)	0.938(0.845;1.046)	1.004(0.898;1.075)
	p-value	0.060	0.198	0.403	0.179
σ^2_{RR} [sec^2 $\times 10^{-4}$]	C	2.952(0.916;4.812)	1.597(0.932;5.070)	2.628(1.165;5.875)	2.244(0.796;6.064)
	RBD	1.255(0.352;4.434)*	1.407(0.696;4.634)	1.702(0.444;4.068)	1.475(0.560;3.909)
	p-value	**0.018**	0.072	**0.035**	0.064
LF_{RR} [sec^2/Hz $\times 10^{-4}$]	C	4.232(0.843;8.877)	2.292(0.847;10.958)	3.709(0.485;19.620)	3.081(0.795;19.455)
	RBD	0.810(0.114;5.566)	0.740(0.221;3.164)	1.222(0.216;3.464)	0.806(0.135;3.940)
	p-value	**0.003**	**0.005**	**0.003**	**<0.001**
HF_{RR} [sec^2/Hz $\times 10^{-4}$]	C	1.082(0.525;2.884)	1.600(0.458;4.716)	2.833(1.023;5.171)*	0.906(0.277;2.818)
	RBD	0.841(0.201;3.366)	0.953(0.330;3.289)	0.933(0.183;2.947)	0.575(0.217;1.598)
	p-value	0.208	0.145	**0.008**	**0.028**
LFn_{RR} [n.u.]	C	0.675(0.417;0.861)	0.614(0.305;0.884)	0.512(0.150;0.837)	0.809(0.369;0.955)
	RBD	0.448(0.230;0.731)*	0.440(0.235;0.672)	0.563(0.275;0.850)	0.585(0.187;0.827)
	p-value	**0.003**	**0.015**	0.488	**0.049**
LF/HF_{RR} [a.u.]	C	2.118(0.822;6.385)	2.042(0.459;8.013)	1.505(0.177;5.295)†	4.539(0.667;28.680)
	RBD	0.900(0.300;2.775)‡	0.796(0.316;2.171)†	1.400(0.385;6.194)	1.473(0.236;4.889)
	p-value	**0.002**	**0.010**	0.524	**0.043**

3. Results

The resulting population consisted of 17 healthy controls with 11 (65%) females and median (IQR) age equal to 55 (51-62), and 22 RBD subjects with 4 (18%) females and median (IQR) age equal to 70 (66-75). Except for two RBD subjects and one control, who entered in the first REM stage before the first N3 stage, the order of occurrence of the stages was the following: N1, N2, N3, and REM, demonstrating that by selecting the first epoch for each stage, we should pay attention to the first sleep cycle for all subjects.

Exact p-values showing the results of the Mann-Whitney U test are shown in Tab. 1, together with feature distribution for each group and sleep stage.

No statistically significant differences were found for μ_{RR} between groups in any sleep stage. A statistically significant difference emerged in N1 (p-value=0.018) and in N3 (p-value=0.035) for σ^2_{RR}, with lower median values in RBD than control group for both sleep stages. LF power showed significant differences in all sleep stages (p-value$<$0.01 in NREM, $<$0.001 in REM), with lower median values in the RBD group for all sleep stages. HF power statistically differed between the two populations during N3 and REM (p-value$<$0.05) and, in both groups, REM median values were lower than NREM ones. With regards to LFn_{RR}, statistical analysis showed p-value$<$0.05 during N2 and REM, and p-value$<$0.01 during N1. Median values were higher during REM with respect to NREM sleep in both groups, and were lower for RBDs. LF/HF_{RR} results significantly differed in N1 (p-value$<$0.01), N2 and REM (p-value$<$0.05) stages. Median values were lower for the RBD subjects with respect to the healthy controls.

Within-group differences were also found when comparing NREM with REM sleep stage. In particular, control subjects showed a significant increase (+3.675) of LF/HF_{RR} during REM stage with respect to N3 (p-value=0.022), and a slight reduction of HF_{RR} (-0.4366$\times 10^{-4}$ sec^2/Hz) close to the significance level (p-value=0.055). RBD subjects showed differences in LF/HF_{RR} between N1 and REM (p-value=0.003), and between N2 and REM (p-value=0.024), with higher median values during the REM stage. Median increases were +1,736 and +1,517 from N1 and N2 to REM stage, respectively. Figure 1 shows the temporal evolution of σ^2_{RR}, LFn_{RR}, and LF/HF_{RR} in each first sleep stage for a healthy control and a RBD subject.

4. Discussions

This study investigated the differences in autonomic control during sleep, through HRV-based estimates, between healthy controls and subjects affected by RBD. Results showed a general HRV reduction in RBD subjects, with lower median variance in every sleep stage than healthy controls. Results from the spectral analysis showed a reduction of LF oscillations in all the sleep stages for the RBD group, thus suggesting a loss in the autonomic control in these patients. Also, a reduction in

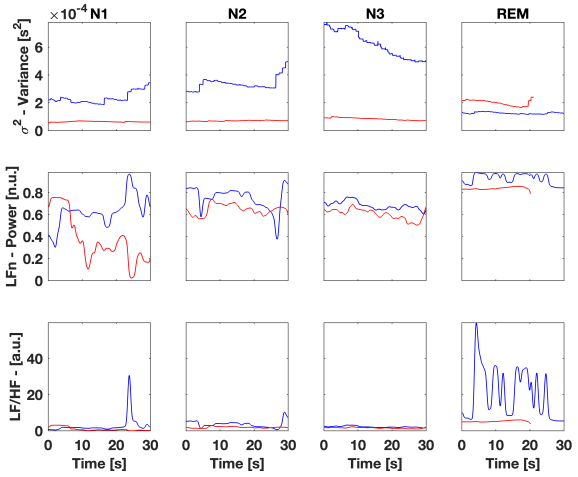

Figure 1. Temporal evolution of σ^2_{RR}, LFn_{RR}, and LF/HF_{RR} in the first 30 seconds for every sleep stage for a healthy control (blue) and a RBD subject (red).

HF content was observed in N3 and REM stages, which suggests a reduced mostly vagal activity and respiratory influence. These results are generally in agreement with those obtained in [7], in which a lower variance in all sleep stages is shown, in comparison to healthy control, as well as the findings achieved in [6], where the authors highlighted the autonomic impairment with lower values in LF_{RR}, HF_{RR} and LF/HF_{RR} for RBDs. The longitudinal characterization of HRV features during different sleep stages showed a general progressive imbalance toward the vagal activity while progressing from N1 to N2 in both populations, and a spiking sympathetic activation in the REM stage. These results are in agreement with previously published research in this field [11], which showed how NREM sleep is characterized by an increase in the vagal tone (parasympathetic activity) and a decrease in the sympathetic tone, while REM sleep shows a further increase in the same direction as NREM, except for an intermittent increase of sympathetic activity during phasic REM sleep. In particular, as shown in figure 1, healthy controls showed a progressive increase of σ^2_{RR} from stage N1 to N3, which is not observed in RBDs. Similarly, it can be observed a sudden reduction in variability during the REM stage in control subjects due to the expected sympathetic activation and bursting activity, as shown by LFn_{RR} and LF/HF_{RR}, and totally absent in RBD patients.

5. Conclusions

In conclusion, our analysis showed that subjects affected by RBD suffer from an overall autonomic dysfunction, mainly related to a reduced LF activation in the early phases of sleep and persisting in all phases, as well as a reduced HF content in the latest phases with respect to healthy controls. Furthermore, a loss in characteristic bursting sympathetic activity during REM stage can be observed for RBD patients. Further studies will explore the obtained findings on all sleep stages and in a larger cohort of subjects, paying attention if this autonomic dysfunction can be observed before the onset of the first symptoms and possibly be used as a marker for early diagnosis of RBD.

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