

Heart Rate Variability during Sleep-Related Wake Phases in REM Sleep Behavior Disorder

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Abstract

Autonomic dysfunction can be observed in people with neurodegenerative diseases. This study explores heart rate variability (HRV) in idiopathic rapid eye movement (REM) sleep behaviour disorder (iRBD), RBD patients with Parkinson's disease (PD-RBD), and control group (CG). The focus is on wake states before and after sleep, acquired during overnight polysomnography.

A total of 18 CG, 20 iRBD, and 20 PD-RBD subjects, underwent polysomnographic exams with at least 6 hours of sleep. A 5-min ECG signal was obtained during the two awake phases, and analysed for time, frequency, and non-linear indexes. Non-parametric statistical analysis was employed to evaluate intra-group behaviours.

Significant differences were found in time and frequency domain indexes, in PD-RBD and iRBD groups, associated with an increased HRV in the wake after sleep compared to wake before sleep onset ($p < 0.05$ to $p < 0.0001$). Similarly, in the same groups, a significant reduction in nonlinear indexes was found during the last wake stage ($p < 0.01$), but not in CG. As such, RBD may cause an increase in parasympathetic activities in both phases, regardless the presence of Parkinson's disease.

1. Introduction

Autonomic dysfunction refers to a state in which involuntary bodily functions such as heart rate, blood pressure, or body temperature are altered. This dysfunction may be localized or systemic [1]. The systemic autonomic dysfunction is associated with a specific group of neurodegenerative disorders also known as α -synucleinopathies. This group includes Parkinson's Diseases (PD), multiple system atrophy and dementia with Lewy bodies, which is linked to Rapid Eye Movement (REM) sleep behaviour disorder (RBD) [2].

RBD is a sleep disorder in which patients experience nightmares and the loss of normal muscle atonia typical of the REM phase, which causes abnormal and potentially dangerous movements while sleeping. Approximately 90% of people with idiopathic RBD (iRBD) develop α -synucleinopathies over time, with PD accounting for 70% of these cases [3]. Some studies were carried out to explore the autonomic imbalance in these patients, by assessing the heart rate variability (HRV) during sleep. Indeed, HRV has a direct relationship with the autonomic nervous system activation and reflects the balance between the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) activity [4].

In the scientific literature, time domain, frequency domain, and nonlinear indexes were explored to investigate HRV and its association with neurodegenerative and sleep disorders, such as iRBD or PD [5,6]. In [6], a reduction in HRV was observed in iRBD patients during wake stage in response to arousals stimulation or periodic limb movements, when compared to control group (CG). This study selected wake epochs without any standardization, so including wake before sleeping, after sleep, during day or night. Other studies reported a reduced HRV in iRBD, which conversely is increased from non-REM to REM stage in CG [7].

According to such studies, HRV varies in different sleep phases, thus we hypothesize that different wake states could also exhibit different HRV values according to the presence of RBD and PD, which has never been explored so far. Indeed, to the best of our knowledge, no study focused on HRV in wake states when separated by a sleep period within affected people (i.e., in RBD with and without PD) or CG. As such, this study is aimed at filling that gap, by investigating changes in HRV across these groups in different wake phases, namely immediately before sleep onset and after sleep end.

1. Methodology

1.1. Study population

Three groups of participants were included in this study: 18 CG (age: 59 ± 8 years, 61% female), 20 iRBD (age: 68 ± 9 years, 15% female) and 20 RBD affected by PD (PD-RBD) (age: 73 ± 5 years, 35% female). Inclusion criteria were that subjects should not have any cardiological or neurological disorder and should not be under any treatment that might impact on heart rate. The diagnosis of PD and RBD was done following the international guidelines of the Movement Disorder Society and the International Classification of Sleep Disorders (ICSD-3), respectively. Participants were recruited from the AIMS accredited Italian Sleep Medicine Centers of Cagliari and Genova, which in turn received ethical approval from their respective local ethical committees.

1.2. HRV analysis

To perform HRV analysis, the ECG signal was extracted from polysomnography (PSG) data during wakefulness, before and after a sleep period of at least 6 hours. To maintain homogeneity, a single 5-minute ECG epoch in each of the two wake states was examined for all participants. All the ECG signals were upsampled to 512 Hz (in case of lower sampling frequency) and then R-peak detection was performed by a wavelet-based ECG delineator [8], followed by automatic R-peak refinement and correction, adopting the same approach used in [9].

To measure HRV, time-domain, frequency-domain, nonlinear, and complexity-based indexes were computed. The *time-domain indexes* included mean of normal RR intervals (NNmean), standard deviation of the NN intervals (STDNN), root mean square of the differences between adjacent NN intervals (RMSSD), the standard deviation of the differences between successive NN intervals (SDSD), number and percentage of adjacent NN-interval pairs with differences greater than 50 ms (R50 and pR50, respectively). *Frequency-domain indexes* included the spectral power in three frequency bands, obtained by computing the area under the power spectral density in very low frequency (aVLF) [0.0033 0.04], low frequency (aLF) [0.046 0.158] and high frequency (aHF) [0.158 0.4] bands; furthermore, LF and HF contributions were assessed in terms of normalized units and their balance, respectively as:

$$nLF = aLF / (aLF + aHF) \quad (1)$$

$$nHF = aHF / (aLF + aHF) \quad (2)$$

$$LF/HF \text{ ratio} = aLF / aHF \quad (3)$$

Nonlinear indexes included two entropy measures, i.e., sample entropy (SE) and approximate entropy (AE), along with Poincare plots. Poincare plots visually analyse HRV by plotting the spread of consecutive heart rate values. Two indexes can be extracted: SD1, which shows short-term variability spread along the first principal component, and SD2, which indicates long-term variability, which is perpendicular to SD1.

Lastly, *complexity indexes* were included, in particular the Lempel-Ziv complexity (LZC) and Kolmogorov complexity (KC). To measure both complexity indexes, the discrete-time signal was converted into a binary and ternary sequence.

1.3. Statistical Analysis

Statistical analysis was adopted to assess if any potential HRV difference might occur when comparing the two examined wake states, i.e., wake before sleep (WBS) and wake after sleep (WAS), within the same group. As such, three different analyses were carried out, i.e., WBS vs. WAS in CG, WBS vs. WAS in iRBD, and WBS vs. WAS in PD-RBD. To this aim, pairwise non-parametric Wilcoxon rank sum test was used. In order to prevent type-1 error, Bonferroni correction was applied, and results with $p < 0.0025$ were highlighted in all the performed tests, whereas $p < 0.05$ was considered for uncorrected statistical significance.

2. Results

Figure 1 shows the comparison across the two wake states (i.e., WBS vs. WAS) for time-domain indexes. It can be observed that all time domain indexes (except NNmean) increased during WAS compared to WBS for the diseased groups (iRBD and PD-RBD). Specifically, RMSSD, SDSD, R50 and pR50 were significantly higher ($0.01 < p < 0.0005$) in WAS in iRBD and PD-RBD group. This was not observed in the CG group. Moreover, we also see significant increase ($0.002 < p < 0.0001$) in SDNN during WAS for all the groups i.e., CG, iRBD and PD-RBD.

Figure 2 shows the results for frequency-domain analysis within each group across two wake states. Similarly, significant increases were observed for aHF and aLF values during WAS compared to WBS in diseased groups, but not in the CG. A similar finding emerged also in LF/HF ratio, but only for PD-RBD, and in aVLF, which was found to be higher in WAS compared to WBS for all groups. Conversely, an opposite behaviour was observed in nHF for PD-RBD, where WAS values were lower than WBS, even if not statistically significant according to Bonferroni correction.

Nonlinear analysis in Figure 3 indicated a significant decrease for both entropies during WAS compared to WBS. These differences were found in SE for both PD-RBD and iRBD, and in AE for all groups. Conversely,

significant increases were found in SD1 and SD2 during WAS compared to WBS (SD1 for all groups, SD2 for both PD-RBD and iRBD).

Finally, in Figure 4, all the complexity indexes showed a significant increase during WAS compared to WBS in PD-RBD and iRBD. Conversely, no significant differences were observed across the two wake states for the CG.

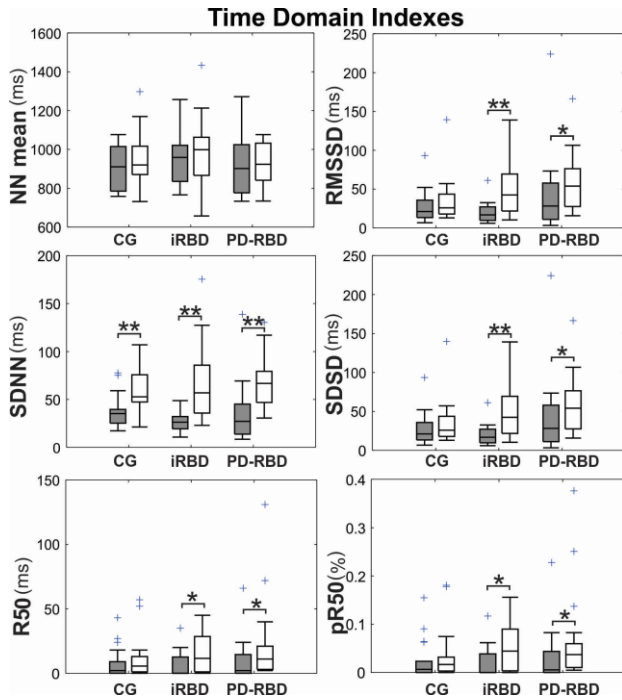


Figure 1. Time domain indexes during wakefulness before (WBS, grey) and after (WAS, white) sleep for all the analysed groups ($p < 0.05$ (*) $p < 0.0025$ (**)).

3. Discussion and Conclusion

This study revealed significant variations in HRV indexes during awake periods before and after sleep in different groups. The increase in SDNN index during WAS compared to WBS indicated a normal sympathovagal activity, i.e., increased PNS activity and decreased SNS activity. Notably, iRBD and PD-RBD groups showed increases in PNS-modulated time-domain indexes within the WAS, suggesting a dominant PNS effect due to the presence of RBD. Frequency-domain analysis indicated varied PNS and SNS activity patterns, potentially revealing autonomic imbalances in PD-RBD subjects, possibly due to the coexistence of PD.

Nonlinear analysis showed decreased entropies, implying less adaptive ANS function and potential cardiovascular concerns for the affected groups.

The complexity analysis exhibited significantly increased complexity measures for the affected groups

during WAS, indicating intricate physiological interactions in response to RBD. This higher complexity

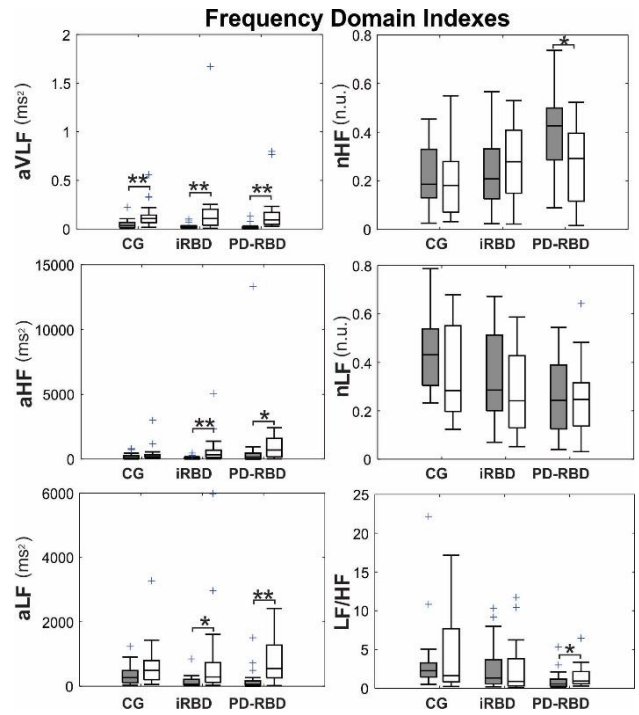


Figure 2. Frequency domain indexes during wakefulness before (WBS, grey) and after (WAS, white) sleep for all the analysed groups ($p < 0.05$ (*) $p < 0.0025$ (**)).

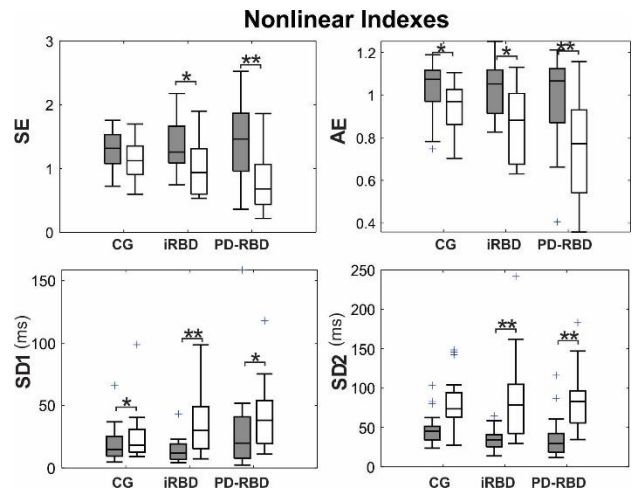


Figure 3. Non-linear indexes during wakefulness before (WBS, grey) and after (WAS, white) sleep for all the analysed groups ($p < 0.05$ (*) $p < 0.0025$ (**)).

might signify a flexible cardiovascular system adapting to RBD-induced physiological demands. However, the paradoxical pattern of increased complexity alongside reduced short-term irregularity and complexity in the HRV data could point towards ANS modulations in RBD patients. These findings align with prior research

exploring HRV response upon awakening, highlighting potential cardiovascular vulnerability during morning awakening [10,11]. Overall, the study reveals the intricate interplay between PNS and SNS and their impact on HRV patterns in individuals affected by RBD and associated neurodegenerative diseases.

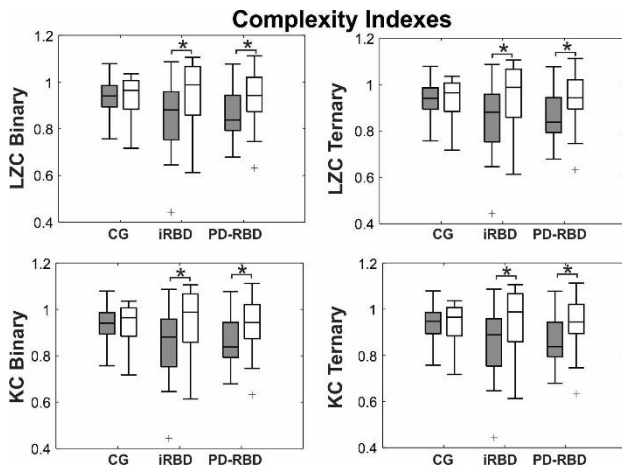


Figure 4. Complexity indexes during wakefulness before (WBS, grey) and after (WAS, white) sleep for all the analysed groups ($p < 0.05$ (*) $p < 0.0025$ (**)).

This study presents a few limitations. First, it did not consider the severity of the disease, which might affect HRV. The second limitation is the unavailability of PD patients who did not have RBD as potential participants.

Nonetheless, this preliminary study suggests that HRV could be a valuable digital biomarker for RBD also during different wakefulness states. More specifically, this study highlights the dominance of PNS activity during awakening in people affected with RBD compared to CG.

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