Parkinson and REM Sleep Behaviour Disorder: HRV Difference During Polysomnography

Parisa Sattar[1,2,3][a], Giulia Baldazzi[3][b], Nicla Mandas[4,3], Elisa Casaglia[2], Michela Figorilli[2], Monica Puligheddu[2][c] and Danilo Pani[3][d]

[1]*Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy*
[2]*Department of Medical Sciences and Public Health, Sleep Disorder Research Center, University of Cagliari, Cagliari, Italy*
[3]*Department of Electrical and Electronic Engineering, University of Cagliari, Cagliari, Italy*
[4]*The Hardon Academy, Scuola Universitaria Superiore IUSS Pavia, Italy*

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Abstract: Approximately 40% to 70% of patients affected by Parkinson's disease (PD) suffer from autonomic dysfunction that could be related to REM sleep behavior disorder (RBD). In this work, polysomnographic recordings were analyzed to study heart rate variability (HRV) during different sleep stages in a cohort of 20 participants, ten with Parkinson Disease with RBD (RBDpd) and ten unaffected (CG). HRV analysis was performed by considering the first 5 min epoch from each stage (i.e., wake, N2, N3, and REM), including time and frequency domain indexes, and entropy measures. Statistical analysis was carried out to assess any possible significant difference between CG and RBDpd groups, but also between the wake and REM stages in each group. Significant differences of the combined effect of RBD and PD emerged in both time and frequency domains, but also when considering nonlinear parameters during REM and awake phases. Accordingly, a comparison of wake and REM phase showed significant differences in all HRV parameters for CG that was absent in the RBDpd group. Our findings reveal the potentiality of HRV as a digital biomarker for RBDpd, by indicating distinct dysfunction of both parasympathetic and sympathetic activities in the RBDpd group, partially in line with previous studies.

1 INTRODUCTION

Parkinson disease (PD) is one of the most common neurodegenerative diseases that is often associated to cardiac autonomic dysfunction. According to the statistics, 40-70% of the PD patients experience autonomic dysfunction (Chaudhuri, Healy, and Schapira 2006). The type of autonomic dysfunction can be well understood by analyzing the sympathetic and parasympathetic activity of PD patients. Various studies have used heart rate variability (HRV) indexes to study the alterations in cardiovascular autonomic system as it is a simple and non-invasive method. Moreover, it is also one of the most promising quantitative indicators of autonomic balance based on cardiac rhythm (Acharya et al. 2006). HRV is a measure of the change in R-R intervals duration and, indirectly, of the underlying neurophysiological phenomena. Indeed, HRV is driven by the autonomic nervous system (ANS) activation, which reflects changes in parasympathetic (PNS) and sympathetic nervous systems (SNS) activities (Shaffer and Ginsberg 2017). HRV can be evaluated using time domain, frequency domain, and nonlinear measures.

Several studies have also employed HRV to explore neurodegeneration, sleep and its associated disorders such as rapid eye movement (REM) sleep

[a] https://orcid.org/0000-0002-9461-0568
[b] https://orcid.org/0000-0003-1275-4961
[c] https://orcid.org/0000-0002-6837-6608
[d] https://orcid.org/0000-0003-1924-0875

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behavior disorder (RBD) or PD (Stein and Pu 2012). HRV alterations have been investigated in PD patients during wake stage , whereas other studies also performed HRV analysis across combined non-REM stages (i.e., N1, N2, and N3) versus REM (Covassin et al. 2013). However, it is essential to identify the alteration in HRV in different non-REM phases because almost all PD patients experience tremor and altered muscle tone, that impact both REM and non-REM sleep phases. Moreover, studies also reported that PD patients have a high probability of developing RBD within 10 years after the appearance of first motor signs (Jauregui-Barrutia et al. 2010).

Interestingly, several studies on HRV revealed that PD patients without RBD have reported modulation in frequency components during wakefulness compared to healthy subjects (Ke et al. 2017; Valenza et al. 2016). Moreover, HRV analysis highlighted a stronger autonomic dysfunction according to PD severity (Devos et al. 2003). However, these studies only considered the impact of PD on HRV and did not consider the impact of the presence of RBD. On the other hand, in (Bugalho et al. 2018; Sauvageot, Vaillant, and Diederich 2011) considered both the impact of PD and RBD, reporting variation in HRV without comparing it with healthy participants.

From the aforementioned studies, it is evident that the information about the variation in HRV due the combined impact of PD and RBD was not completely described. In addition, it could also be important to analyze the SNS and PNS regulation in PD patients with RBD (RBDpd) across each sleep phase, to improve our knowledge about the development of RBD and PD. Thus, in this study we aimed at performing a preliminary evaluation of the combined effect of PD and RBD using different HRV indexes during sleep and wake stages.

2 METHODS

2.1 Participant

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. The data from 20 participants without cardiological disorders were taken from the register of the Centre of Sleep Medicine and Neurology Unit of the University Hospital of Monserrato, Cagliari, Italy. The diagnosis of RBD was based on the criteria of the International Classification of Sleep Disorders (ICSD-3).

Participants were divided into two groups: the control group (CG) was composed of ten participants, 80% females (mean age: 59.4 ± 4.9), without neurological disorders, and the affected group was composed of ten RBDpd patients, 70% females (mean age: 70.5 ± 9.4), without other neurological comorbidities. PD patients ranging between 1-3 in HY scale, and between 0-55 in UPDRS scale, were included in this study.

2.2 Heart Rate Variability Analysis

Full night video polysomnography exam was performed, using EEG and PSG Holter Morpheus by Micromed (Micromed S.p.A., Italy). Sleep RT program (Micromed S.p.A., Italy) was used to perform sleep staging and produce the hypnogram, further reviewed by an expert neurologist, in accordance with the 2013 American Academy of Sleep Medicine guidelines (van Hout 2013). ECG was recorded, resampled at 512 Hz to perform HRV analysis. The hypnogram was used to extract the ECG of wake stage (before, during and after sleep) and different sleep phases (N2, N3 and REM). To be consistent in the analysis across the different patients and sleep stages, we used the first 5-min artifact-free epoch only.

A custom implementation of a wavelet-based ECG delineator was employed to mark R-peak locations (Martínez et al. 2004) and to obtain the tachogram. An automatic tachogram correction algorithm was introduced to compensate R-peak misdetections, comparable to the commonly used approaches in the field (Mendez et al. 2009). As such, all the R-R intervals exceeding 150% of the average R-R interval were considered as associated to the presence of one or more false negatives; this condition was managed by correcting the tachogram with additional R-R intervals. Conversely, those intervals below 15% of the average R-R interval were considered as associated to the presence of a false positive; this condition was managed by automatically correcting the tachogram by discarding those extra annotations. After all, only normal-to-normal (NN) R-R intervals were maintained.

HRV analysis was first performed by using time domain indexes, i.e., mean NN interval (NNmean), root mean square of the differences between adjacent NN intervals (RMSD), percentage of adjacent NN-interval pairs with differences greater than 50 ms (pR50), and percentage of adjacent NN-interval pairs with differences greater than 20 ms (pR20).

We also evaluated HRV frequency-domain indexes. To this aim, cubic spline interpolation of the NN intervals was performed to obtain a tachogram with a proper sampling frequency of 4 Hz. The power spectrums in very low frequency (VLF) band [0.0033 0.04] Hz, low frequency (LF) band [0.046 0.158] Hz, and high frequency (HF) band [0.158 0.400] Hz were computed using the Welch's periodogram method. We also evaluated the power ratio between LF and HF (LF/HF) and between VLF and LF (VLF/LF), along with the normalized HF (nHF) and LF (nLF):

$$nLF = LF/(LF + HF) \quad (1)$$

$$nHF = HF/(LF + HF) \quad (2)$$

Finally, two nonlinear HRV indexes, i.e., approximate entropy (ApEn) and sample entropy (SE), were used to examine the irregularity of the tachogram. Both entropies calculate irregularity of a signal by exploiting two parameters (i.e., the signal length, m, and the tolerance, r). ApEn could be sensitive to the data size whereas SE is independent from data (Delgado-Bona and Marshak 2019).

2.3 Statistical Analysis

Statistical analysis was performed by using the pairwise, non-parametric Wilcoxon rank sum test for independent populations. Results were considered significant for $p < 0.05$. Statistical differences were investigated between CG and RBDpd groups, by considering each HRV parameter computed in the different sleep phases (i.e., wake, N2, N3 and REM) separately. Furthermore, pairwise statistical analysis was also carried out to investigate any possible significant discrepancy between REM and awake stages, independently in CG and RBDpd.

3 RESULTS

3.1 HRV Analysis Across the Groups

From Figure 1, we can perform a first comparison of time-domain HRV indexes across groups (i.e., CG vs. RBDpd). As can be seen, pR20 and pR50 were significantly lower in RBDpd as compared to CG group during wake phase (p<0.001 and p<0.02, respectively). Conversely, pR20 was significantly higher in RBDpd during REM phase (p<0.04). There were no significant differences in other phases or time-domain indexes.

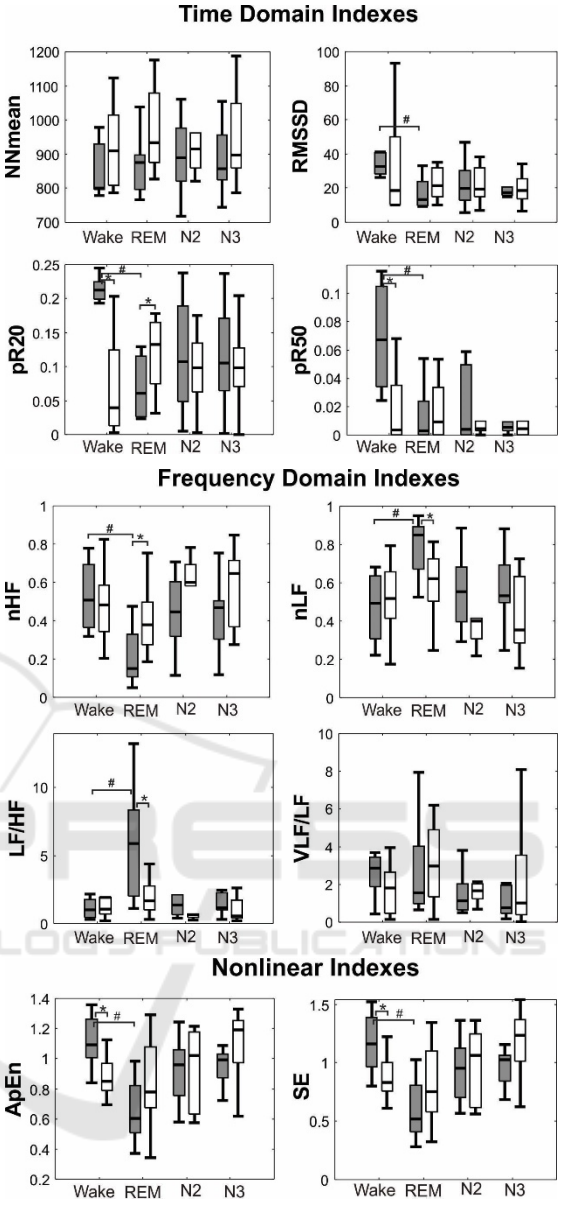

Figure 1: HRV indexes for CG (in grey) and RBDpd (in white) groups in different stages. The significant result for CG vs. RBDpd analysis is represented as (*), whereas (#) is adopted for wake vs. REM analysis.

The results of frequency-domain indexes are also shown in Figure 1. A significant decrease was observed in RBDpd group on nLF and LF/HF ratio during REM phase, compared to CG, whereas nHF was significantly higher in RBDpd compared to CG in the same phase (p<0.02 for all). No significant differences during REM phase were found during the other phases.

Finally, Figure 1 also reports the results of the nonlinear indexes. ApEn and SE both showed a

significant increase in RBDpd in comparison to CG, but only during wakefulness (p<0.01 and p<0.03, respectively).

3.2 HRV Analysis Within Groups

Figure 1 also highlights the significant differences in HRV indexes within CG and RBDpd groups comparing wake and REM phases . The results show a significant decrease in all time-domain indexes in REM phase when compared to wake phase in CG group, except the NNmean one (p<0.001 for pR20, pR50, and p<0.002 for RMSSD).

Similarly, significant differences were also observed in CG for all frequency-domain indexes, except for VLF/LF ratio. Indeed, nHF was significantly higher in wake phase compared to REM phase (p<0.002). However, nLF and LF/HF ratio were significantly lower in wake phase as compared to REM phase in the same group (p<0.002).

For nonlinear indexes, both ApEn and SE were significantly higher in wake phase compared to REM phase in CG group (p<0.001 for both). Conversely, no significant results were found between the two phases in the RBDpd group.

4 DISCUSSION

Based on our findings, HRV seems to be a reliable digital biomarker to differentiate the PD people with RBD from the unaffected ones. We found significant differences of the combined effect of RBD and PD in time-domain, frequency-domain and nonlinear parameters between REM phase and wakefulness.

From the significant reduction of pR20 and pR50 in RBDpd group during wakefulness, we can deduce a lower PNS activity than in the CG. These results are in line with a previous study (Devos et al. 2003). Moreover, during the REM phase, the pR20 is higher in the RBDpd group, thus indicating an increased PNS activity in contrast to CG, which was not previously described in the scientific literature. Being the decrease in PNS activity also associated with stress condition, it may indicate that the wake phase is more critical/stressful for RBDpd patients than REM phase (Wang et al. 2018). In addition, for the CG, most of the time-domain indexes were significantly lower in REM phase, which implies a reduced PNS activity compared to wakefulness. This trend was absent in RBDpd group, thereby reflecting possible PNS dysfunction.

Frequency-domain analysis showed that, during REM phase, nLF decreased whereas nHF increased in RBDpd compared to CG, thus indicating alterations in SNS and PNS activity, respectively. These findings are also in agreement with previous studies (Ke et al. 2017; Valenza et al. 2016). Interestingly, the behavior of nHF also complies with the outcome of time-domain indexes, indicating dominant PNS activity in RBDpd group during wake phase, which emphasizes novel aspects of combined influence of RBD and PD compared to CG. Accordingly, the LF/HF ratio, which is a reliable measure of SNS/PNS balance, it was found considerably lower in RBDpd population compared to CG, highlighting a disrupted PNS and SNS response in RBDpd group.

Finally, the reduced value of nonlinear parameters in RBDpd suggested a lack of normal HRV during REM phase as compared to CG.

5 CONCLUSIONS

In this work, we used different HRV indexes to analyze the effect of both PD and RBD when compared to unaffected people, by considering wake, non-REM, and REM phases. From our statistical results, HRV seems to be a good digital biomarker to differentiate between these populations, by indicating distinct dysfunctions of PNS as well as SNS in the affected people. However, the study also includes a few limitations. First, the study did not consider the disease severity, which could also impact the HRV. Thus, conclusions cannot be generalized for all RBDpd patients. Second, this study only focused on the combined impact of RBD and PD. Finally, the dataset size is limited. However, this preliminary study proves that HRV is a potential digital biomarker for RBDpd which can need to be further investigated by analyzing different populations such as patients with only PD or RBD. In future works, it would be interesting to compare both the combined and individual impact of RBD and PD that can assist in early detection of phenoconversion with an increased number of participants.

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REFERENCE

Acharya, U. Rajendra, K. Paul Joseph, N. Kannathal, Choo Min Lim, and Jasjit S. Suri. 2006. "Heart Rate Variability: A Review." *Medical and Biological Engineering and Computing* 44(12):1031–51.

Bugalho, Paulo, Marcelo Mendonça, Tânia Lampreia, Rita Miguel, Raquel Barbosa, and Manuel Salavisa. 2018. "Heart Rate Variability in Parkinson Disease and Idiopathic REM Sleep Behavior Disorder." *Clinical Autonomic Research* 28(6):557–64.

Chaudhuri, K. Ray, Daniel G. Healy, and Anthony H. v Schapira. 2006. "Non-Motor Symptoms of Parkinson's Disease: Diagnosis and Management." *The Lancet Neurology* 5:235–45.

Covassin, Naima, Ariel B. Neikrug, Lianqi Liu, Jeanne Maglione, Loki Natarajan, Jose S. Loredo, Barton W. Palmer, Laura S. Redwine, and Sonia Ancoli-. 2013. "Relationships between Clinical Characteristics and Nocturnal Cardiac Autonomic Activity in Parkinson's Disease." 171(0):85–88.

Delgado-Bona, Alfonso, and Alexander Marshak. 2019. "Approximate Entropy and Sample Entropy: A Comprehensive Tutorial." *Entropy* 21(6).

Devos, D., M. Kroumova, R. Bordet, H. Vodougnon, J. D. Guieu, C. Libersa, and A. Destee. 2003. "Heart Rate Variability and Parkinson's Disease Severity." *Journal of Neural Transmission* 110(9):997–1011.

van Hout, Steven. 2013. "The American Academy of Sleep Medicine Inter-Scorer Reliability Program: Sleep Stage Scoring Richard S. Rosenberg1." *Journal of Clinical Sleep Medicine* 9(1):81–87. doi: 10.5664/jcsm.2350.

Jauregui-Barrutia, Amaia, Beatriz Tijero-Merino, Juan Carlos Gómez-Esteban, and Juan José Zarranz. 2010. "Sleep Disorders in Parkinson's Disease: REM Sleep Behaviour Disorder and Restless Legs Syndrome." *Revista de Neurologia* 50:S15-9.

Ke, Jiang Qiong, Sheng Min Shao, Yuan Yuan Zheng, Fang Wang Fu, Guo Qing Zheng, and Chun Feng Liu. 2017. "Sympathetic Skin Response and Heart Rate Variability in Predicting Autonomic Disorders in Patients with Parkinson Disease." *Medicine (United States)* 96(18):1–5.

Martínez, Juan Pablo, Rute Almeida, Salvador Olmos, Ana Paula Rocha, and Pablo Laguna. 2004. "A Wavelet-Based ECG Delineator Evaluation on Standard Databases." *IEEE Transactions on Biomedical Engineering* 51(4):570–81. doi: 10.1109/TBME.200 3.821031.

Mendez, Martin O., Anna Maria Bianchi, Matteo Matteucci, Sergio Cerutti, and Thomas Penzel. 2009. "Sleep Apnea Screening by Autoregressive Models from a Single ECG Lead." *IEEE Transactions on Biomedical Engineering* 56(12):2838–50. doi: 10.1109/TBME.2009.2029563.

Sauvageot, Nicolas, Michel Vaillant, and Nico J. Diederich. 2011. "Reduced Sympathetically Driven Heart Rate Variability during Sleep in Parkinson's Disease: A Case-Control Polysomnography-Based Study." *Movement Disorders* 26(2):234–40.

Shaffer, Fred, and J. P. Ginsberg. 2017. "An Overview of Heart Rate Variability Metrics and Norms." *Frontiers in Public Health* 5(September):1–17.

Stein, Phyllis K., and Yachuan Pu. 2012. "Heart Rate Variability, Sleep and Sleep Disorders." *Sleep Medicine Reviews* 16(1):47–66.

Valenza, Gaetano, Stefano Orsolini, Stefano Diciotti, Luca Citi, Enzo Pasquale Scilingo, Maria Guerrisi, Sabrina Danti, Claudio Lucetti, Carlo Tessa, Riccardo Barbieri, and Nicola Toschi. 2016. "Assessment of Spontaneous Cardiovascular Oscillations in Parkinson's Disease." *Biomedical Signal Processing and Control* 26:80–89.

Wang, Man Ling, Pei Lin Lin, Chi Hsiang Huang, and Hui Hsun Huang. 2018. "Decreased Parasympathetic Activity of Heart Rate Variability during Anticipation of Night Duty in Anesthesiology Residents." *Anesthesia and Analgesia* 126(3):1013–18. doi: 10.1213/ANE.0000000000002439.