Assessment of Ventricular Repolarization Variability in Wake States in REM Sleep Behaviour Disorder and Parkinson's Disease

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Abstract

Idiopathic REM Sleep Behaviour Disorder (iRBD) patients exhibit autonomic dysfunction, increasing cardiovascular mortality risk. Despite this, the link to cardiovascular mortality is underexplored. This pilot study investigates the QT-variability (QTV) in iRBD and RBD with Parkinson's disease (PD-RBD) during wake before (WBS) and after (WAS) sleep.

This study included 18 control (CG), 20 iRBD, and 20 PD-RBD participants. QTV and RR variability (RRV) were derived from a 5-minute ECG epoch of polysomnography data during the two wake states. Analyses included time and frequency domain indexes, followed by non-parametric statistical analysis to assess intra- and inter-group patterns.

Significant differences in frequency domain RRV and QTV unrelated to RRV (QTVuRRV) indexes were found in WAS compared to WBS for both iRBD and PD-RBD. Moreover, iRBD and PD-RBD exhibited a significant reduction in low- and high-frequency RRV indexes and QTVuRRV compared with the CG.

In conclusion, RRV and QTVuRRV findings suggest altered autonomic regulation in iRBD and PD-RBD. However, the lack of differences in QTV indexes might suggests no significant risk of cardiovascular mortality.

1. Introduction

Idiopathic REM Sleep Behaviour Disorder (iRBD) is a condition characterized by the loss of normal muscle atonia during REM sleep, leading individuals to physically act out their dreams, which can result in potentially harmful behaviours such as kicking, punching, or jumping out of bed [1]. iRBD has been also recognized as a prodromal condition for alpha-synucleinopathies, a group of neurodegenerative disorders characterized by the abnormal accumulation of alpha-synuclein protein in the brain. These disorders include Parkinson's Disease (PD), dementia with Lewy Bodies, and Multiple System Atrophy. Research indicates that individuals with iRBD are at risk of developing one of these alpha-synucleinopathies over a period of 10-12 years, with PD being the most common conversion among them [1].

Moreover, previous evidence indicates that iRBD patients often experience autonomic dysfunction, which might be frequently manifested as alterations in heart rate variability (HRV), blood pressure regulation, and other cardiovascular parameters [1]. Indeed, autonomic dysfunction in iRBD has been deeply investigated by HRV as a measure of autonomic regulation [2–4]. However, HRV only provides information about the irregularities of autonomic function via the sinoatrial (SA) node [5], but these autonomic irregularities may elevate the risk of cardiovascular mortality [6]. In this context, QT variability (QTV) emerged as an indicator of ventricular repolarization duration variability and cardiac electrical

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instability. QTV reflects the variation of QT interval in electrocardiogram (ECG), which represents the time needed for the ventricles to repolarize after each contraction [5] . Given that the duration of the QT interval, particularly when corrected for heart rate (QTc), is commonly associated with cardiovascular risk, QTV indices have similarly been linked to cardiovascular risk in certain patient populations, highlighting its potential as a valuable tool in assessing cardiac health [5].

Despite the recognition of autonomic disturbances in iRBD, the direct relationship between these irregularities and cardiovascular mortality risk remains insufficiently explored. Thus, this pilot study focuses on investigating QTV in two distinct patient populations: iRBD and RBD associated with Parkinson's Disease (PD-RBD). The study examines QTV and HRV during two wake states: wake before sleep (WBS) and wake after sleep (WAS). By comparing QTV in these two states, the research aims to find potential variations that could indicate higher cardiovascular risk in these populations.

In this way, the study wants to highlight any possible link between QTV and cardiovascular risk that could lead to sudden cardiac deaths in iRBD and PD-RBD patients. Understanding this link could provide critical insights into the underlying mechanisms of autonomic dysfunction, leading to the development of targeted interventions to reduce cardiovascular mortality risk, ultimately improving patient's outcome.

2. Methodology

This study involved three groups of participants: 18 people in the control group (CG, average age: 59 ± 8 years, 61% female), 20 people with iRBD (average age: 68 ± 9 years, 15% female), and 20 PD-RBD people (average age: 73 ± 5 years, 35% female). Inclusion criteria were no cardiological or neurological disorders, and no treatment that could affect heart rate. Diagnoses of PD and RBD were made according to the international guidelines of the Movement Disorder Society and the International Classification of Sleep Disorders (ICSD-3), respectively. All participants went through full night polysomnography (PSG) at the Sleep Medicine Centers in Cagliari and Genova, under the ethical approval from the Ethics Committee at University Hospital of Cagliari (PG/2018/11699) and the IRB at Policlinico San Martino in Genova (IRB approval n. 105/2023 – DB id 13027).

2.1. QT Variability analysis

To perform QTV analysis, the ECG signal was extracted from PSG data during wakefulness, before and after a sleep period of at least 6 hours. To maintain homogeneity, a single 5-minute ECG epoch was examined for all participants. The detection of Q-wave onset, R-peak and T-wave end were performed by a wavelet-based ECG delineator [7], followed by automatic R-peak refinement, ectopic beat correction, and outlier rejection in QT series [5].

To measure QTV, time and frequency domain indexes were computed. The time-domain indexes included the corrected QT interval (QTc) with the Bazett's formula, the average of normal RR intervals (RRmean), the average of normal QT intervals (QTmean), the standard deviation of QT interval (SDQT), the normalized QT interval variance (QTVN), and the short-term QT interval variability (STVQT). Frequency-domain indexes included the power of QT-based tachograms (in ms^2) and RR based tachograms (in ms^2) in two frequency bands: i.e., the power at low frequencies (LF), i.e., in the range [0.04-0.15] Hz, namely QTV_{LF} and RRV_{LF}, and the power at high frequency (HF), i.e., in the range [0.15-0.4 Hz], called QTV_{HF} and RRV_{HF} hereinafter. Lastly, the time-frequency coherence between QTV and RRV was calculated to evaluate the local linear coupling of spectral components in both time and frequency domains between the QTV and RRV signals. The time-frequency spectrum of QTV was divided into two parts: QTV related to RRV (QTVrRRV) and QTV unrelated to RRV (QTVuRRV). This division was accomplished by modulating the time-frequency spectrum of QTV with the time-frequency coherence between QTV and RRV [5, 8].

2.2. Statistical Analysis

A statistical analysis was performed using the pairwise Wilcoxon signed-rank test to assess potential differences in QTV between the two wake states i.e. WBS vs. WAS, for each of the three groups (CG, iRBD, and PD-RBD) individually. Additionally, comparisons were made between the groups (CG vs. RBD, CG vs. PD-RBD, and PD-RBD vs. RBD) during WBS and WAS separately. For this purpose, the non-parametric Wilcoxon rank sum test was employed, and results with $p<0.05$ were deemed statistically significant.

3. Results and Discussion

Figure 1 illustrates the time domain indexes (i.e., RR mean, QT mean, QTc mean, SDQT, QTVN, and STVQT) across three groups during the two wake states. For RR mean, all groups showed similar medians (around 1000 ms), as well as for QT and QTc mean (approximately 400-450 ms) revealing no significant differences among all groups and across the different wake states. Similarly, also the other QTV time domain parameters (i.e., SDQT, QTVN and STVQT) did not demonstrate any significant difference across the groups and wake states, thus potentially suggesting a similar cardiovascular risk in iRBD and PD-RBD population node compared with CG [5]. However, these parameters require further investigation to capture the full picture of physiological

changes which can be done by comprehensive analysis of all relevant parameters.

Figure 2 represents the frequency domain indexes (i.e., QTV_{LF}, RRV_{LF}, QTV_{HF} and RRV_{HF}) for three groups in the two wake states. Focusing on the comparison between WBS and WAS, iRBD and PD-RBD showed higher RRV_{LF} during WAS than WBS, whereas the CG group did not present the same trend. This suggests that people with iRBD and PD-RBD might suffer from unique disruption in sympathetic and parasympathetic nervous systems. The LF band reflects both of these autonomic influences [6]. Thus, an increase in RRV_{LF} after sleep could suggest a more adaptive autonomic response to stress. Since people with iRBD [9] and PD-RBD [10] often have poor sleep quality, the increased LF variability might be a compensatory mechanism that manifests upon awakening. This shows that their autonomic nervous system is trying to manage the stress caused by disrupted sleep.

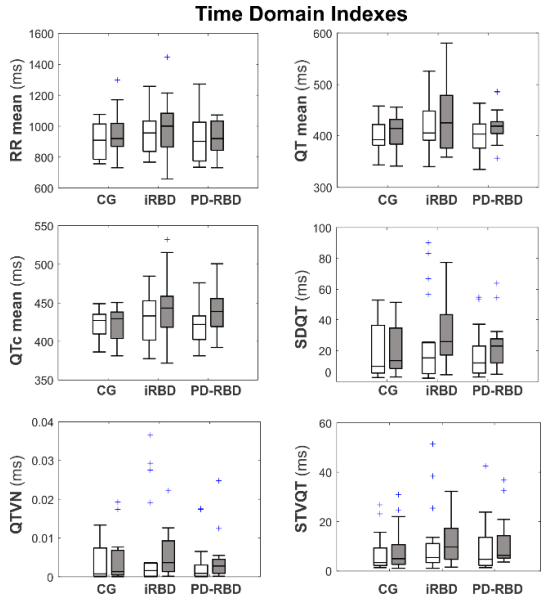

Figure 1. Time domain indexes during wakefulness before (WAS, grey) and after (WBS, white) sleep.

The analysis of wake states revealed that both the iRBD and PD-RBD groups had significantly lower RRV_{LF} during WBS compared to WAS, unlike the CG. This suggests that individuals with iRBD and PD-RBD experience autonomic imbalance. These results align with the findings from the analysis conducted across all groups.

Moreover, iRBD group showed significant decrease in RRV_{HF} compared to CG in WBS, thus indicating a decrease in parasympathetic activity. Additionally, iRBD group exhibited significantly higher RRV_{HF} during WAS compared to WBS. A similar trend was observed in the CG group but not in the PD-RBD group. This suggests that the autonomic regulation in the iRBD group is attempting to manage the physiological stress resulting from disrupted sleep. Furthermore, the sleep period is known to boost parasympathetic activity, which likely contributes to the observed increase in RRV_{HF} in the CG group. In contrast, the PD-RBD group appears to lack this compensatory response suggesting a disruption in parasympathetic activity.

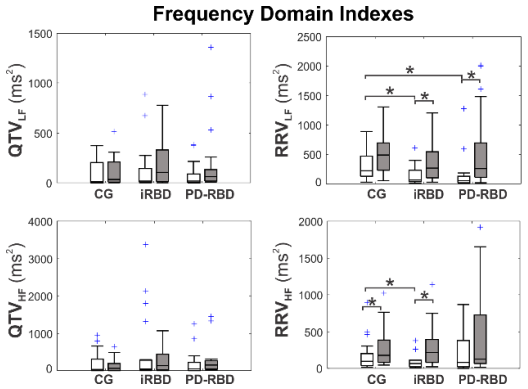

Figure 2. Frequency domain indexes during wakefulness before (WAS, grey) and after (WBS, white) sleep. Significant differences are marked by *.

Lastly, QTV_{LF} and QTV_{HF} shows no significant difference across the groups and wake states. By considering that no statistical differences were found in QTV_{LF}, QTV_{HF}, but significant differences were highlighted in RRV_{LF}, RRV_{HF}, might suggest that the population studied may not exhibit a higher risk for cardiac events, such as sudden cardiac death, based on these specific indices. Figure 3 shows the results for normalized QTVrRRV and QTVuRRV. By comparing WBS and WAS in PD-RBD group, a significantly higher $nQTVuRRV_{LF}$ and lower $nQTVuRRV_{HF}$ were observed

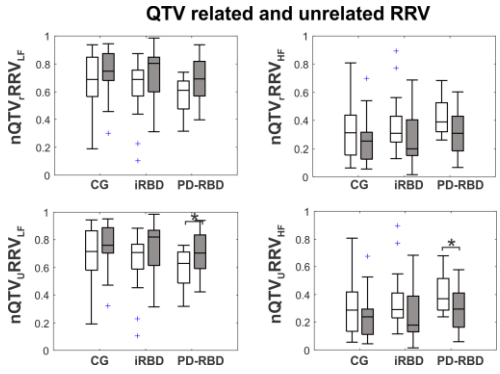

Figure 3. QTV related and unrelated to RRV during wakefulness before (WAS, grey) and after (WBS, white) sleep. Significant differences are marked by *.

after sleep. This finding indicates higher intrinsic variability and autonomic dysregulation after sleep. Despite this, there were no significant differences in

$QTVrRRV_{LF}$ and $QTVrRRV_{HF}$ between WBS and WAS, suggesting stable coupling between HRV and QTV wake states. This highlights that autonomic dysregulation in PD-RBD is more pronounced in intrinsic repolarization processes rather than in HR-modulated processes. In contrast, iRBD groups exhibited no significant differences in QTVuRRV or QTVrRRV in both LF and HF band, between WBS and WAS, nor across the groups during either wake states, suggesting the autonomic disruption is unique for the PD-RBD group.

4. Conclusion

The findings of this pilot study indicated no significant differences in basic cardiovascular parameters across CG, iRBD, and PD-RBD groups during different wakefulness states (both before and after sleep). Despite most of the time and frequency domain parameters showed no significant differences (thus suggesting no elevated cardiovascular risk specific to the iRBD and PD-RBD populations), some frequency domain metrics revealed subtle variations in autonomic responses, particularly an adaptive increase in RRV_{LF} after sleep in iRBD and PD-RBD groups, potentially compensating for poor sleep quality. Moreover, PD-RBD group exhibited specific autonomic alterations in intrinsic repolarization processes, highlighting the need for comprehensive analysis to understand these physiological changes.

This study has some limitations that should be considered. Firstly, the sample size was relatively small, which may limit generalizability of the findings. Secondly, this study does not account for potential confounding factors that could influence the RRV and QTV indexes, such as respiratory effects. Lastly, the research considered wake states only: it would be beneficial to extend the analysis to different sleep phases, particularly the REM sleep phase.

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