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RESEARCH ARTICLE

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# Nocturnal cardiac autonomic regulation in Parkinson's disease

**Abstract** Diminished heart rate (HR) variability has been reported in patients with early phase Parkinson's disease (PD) using standardized cardiovascular reflex tests. However, limited data exist on HR variability during sleep; thus the present study was performed to investigate the characteristics of HR variability during different sleep stages. The HR variability of 21 newly diagnosed and untreated PD patients and of 22 control subjects was evaluated by using time domain, frequency domain and non-linear methods and by analyzing HR reactions to body movements during the different sleep stages (non-REM stages S1–4 and the REM stage). The nocturnal cardiac autonomic control was disturbed in PD patients compared to controls both during sleep and waking. HR reactions to body movements were decreased especially during REM sleep referring to defective sympathetic cardiovascular control. High frequency spectral power of HR variability was attenuated in the patients in waking and during non-REM sleep but not during REM sleep suggesting that parasympathetic cardiovascular control is also affected in early PD. However, the variance of R-R intervals during non-REM sleep was significantly increased in PD patients. Especially during this sleep stage the patients also moved more than the controls. HR variability is decreased not only in waking but also during sleep in PD patients. However, the increased variance of HR during non-REM sleep refers that in early phase of PD cardiovascular system is still able to react to changing body circumstances. Furthermore, our findings suggest that the indicators measuring the dominant sympathetic or parasympathetic activity of each given sleep stage are the most sensitive measures in revealing disturbed nocturnal ANS function.

**Key words** autonomic nervous system · Parkinson's disease · sleep · heart rate variability

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## Introduction

In addition to motor symptoms, patients with Parkinson's disease (PD) are known to suffer from other manifestations such as disturbances of autonomic nervous system (ANS) and sleep, even in the early phase of the disease and before commencement of antiparkinsonian medication [2, 12, 13, 19, 34–36]. The most common ANS disorders are cardiovascular manifestations, such as orthostatic hypotension and cardiac arrhythmias, bladder dysfunction, constipation, and sweating disturbances [23, 25, 31]. Of the latter, complaints such as light and fragmented sleep, with an increased number of awakenings, are reported by about 60–90 % of PD patients [34]. Motor phenomena such as nocturnal immobility, rest tremor, eye-blinking, and periodic and non-periodic limb movements in sleep, restless legs syndrome, myoclonus, and respiratory dysfunction in sleep are also encountered in PD patients [1, 34].

In early PD, standard cardiovascular reflex tests based on short-time heart rate (HR) and blood pressure responses to various stimuli have established cardiovascular ANS changes which are of varying degree and may

be subtle in a single patient [11, 19, 35]. As the disease advances, an increasing number of the patients, however, develop abnormalities in these tests [15].

In healthy subjects cardiovascular ANS control including HR regulation is known to vary considerably in relation to sleep stages [29], while little is known of cardiovascular function in PD patients during sleep. Disturbed HR reactions to nocturnal body movements have been detected [8, 9, 32] and HR variability has been reported to be diminished more during the night than during the day [26]. In these series the patients were mostly under antiparkinsonian medication and the ANS measures were not analyzed in relation to various sleep stages.

This study was designed to investigate the nocturnal cardiovascular ANS regulation and its association with the sleep stages in early PD in patients without any antiparkinsonian medication. Cardiac autonomic function was specifically evaluated in each sleep stage using both time and frequency domain methods as well as nonlinear methods for HR variability evaluation, and by analyzing HR during sleep movements.

## Methods

### Subjects

Investigations were conducted with 21 consecutive untreated patients (7 women and 14 men, age 41–74 years, mean 58.2 years) referred to the Department of Neurology and subsequently diagnosed to have idiopathic PD fulfilling the Parkinson's Disease Society Brain Bank [4] clinical criteria. Patients with manifestations of other central or peripheral nervous system disorders and patients with any other disease or medication known to affect the ANS were excluded. The clinical disability of the PD was graded by the Hoehn and Yahr staging [14] and the Unified Parkinson's Disease Rating Scale (UPDRS) [7]. The mean Hoehn and Yahr stage was 1.5 and the total UDPRS score was 25.8 ± 11.7. The mean duration of the PD was 1.8 ± 2.0 years. The clinical follow-up was continued after the study trial period, the mean follow-up being 3 years, and the PD diagnosis remained valid. None of the patients had 2 or more abnormal test results in daytime standardized cardiovascular reflexes. None of the patients reported sleeping difficulties. The control group consisted of 22 healthy age-matched subjects (12 women and 10 men, age 42–84 years, mean 55.6). One patient and two control subjects were excluded from the study due to a lack of sleep (duration of the S1 and/or S2 sleep of less than one hour and no signs of REM- or slow wave sleep stages S3–4). One additional patient was excluded due to periodic sleep apnea (apnea-hypopnea index 5 per hour). The final study group thus consisted of 19 patients and 20 controls. All patients and controls gave their informed consent. The study was approved by the local Ethics Committee of the Medical Faculty, and was carried out according to the principles of the Declaration of Helsinki.

### Recordings

All subjects underwent polysomnography for one night including an electroencephalogram with C3/A2, C4/A1, O1/A2 and O2/A1 tracings, a submental electromyogram, electro-oculograms, electrocardiogram (ECG), airflow with nasal thermistore, body movement recording with a static charge sensitive bed and oxygen saturation recordings. Sleep stages (non-REM stages S1–4 and REM stage) were scored off-line using the standard criteria in 30 s epochs [28]. R-R intervals were checked manually after automatic detection of the R-spikes from the electrocardiogram and all R-R intervals were included in the analysis. However, in some occasional cases where no R-spikes could be detected or an ectopic beat occurred, the erroneous or missing R-spike was substituted with a point dividing the R-R interval equally.

### Sleep movement related HR analysis

Phasic and tonic HR variability time domain measures were evaluated in relation to spontaneous body movements during sleep [10]. The body movement ratio (Rbm), i. e. the ratio of the mean RR interval before to the shortest one after body movements, represents an index of phasic HR increase induced by body movements. The sleep-wakefulness ratio (Rs/w) was considered as an index of tonic heart rate decrease induced by sleep, calculated as the ratio of the mean RR interval before body movements to the mean RR interval during wakefulness.

### HR variability analysis in different sleep stages

Instead of using only segments of R-R intervals considered as representative of each sleep stage, all data with the same sleep stage including all corresponding R-R intervals were pooled into one segment before analysis; thus, the data represent the particular sleep stage.

### Time domain measures of HR variability

Three parameters were calculated as time domain measures of HR variability: the standard deviation of R-R intervals (SDNN), the square root of the mean squared differences of successive R-R intervals (rMSSD) and the pNN50, i. e. the percentage number of the consecutive R-R interval changes greater than 50 ms [6].

### Frequency domain measures of HR variability

Both fast Fourier transformation (FFT) and autoregressive modelling (AR) were used for the spectral analysis of HR variability. Before FFT the R-R intervals were converted to a smoothed instantaneous HR time series at 4 Hz, and an exact Hamming window was applied. For the AR the parameters of the model and the variance of the driving white noise were estimated by means of the recursive Levinson Durbin algorithm and the optimal order was chosen according to the Akaike information criteria [21]. The spectral components were determined visually for each subject in three frequency bands: 0.15–0.40 Hz for the high frequency (HF); 0.04–0.15 Hz for the low frequency (LF); and 0.003–0.04 Hz for the very low frequency (VLF) band. Both absolute and normalized HR variability power values (i. e. in percentage of the total power minus the VLF component), according to Task Force [33] and the LF/HF ratio were calculated.

### Non-linear measure of HR variability

The fractal dimension (FD) was calculated by using a customized Mandelbrot-ε-blanket method [24, 27]. In this method the length of the HR curve is defined as a maximum of 25 times with different scales. When plotting the lengths versus the scale on a log-log scale from the slope of the best fitting straight line, the FD can be computed.

### Data analysis

Before statistical analysis the logarithmically transformed measures were adjusted for both the mean age and the mean baseline of the R-R intervals using multiple regression. The significance levels for the comparisons between the patients and control subjects were obtained by using analysis of covariance (ANCOVA) and Student's t-test. The level of statistical significance was set at $p = 0.05$.

## Results

The characteristics of the sleep patterns were similar in the PD patients and the controls (Table 1). The patients moved more frequently than the controls during sleep: during S3 there were $11.8 \pm 9.7$ movements per hour in PD patients vs. $4.6 \pm 5.9$ movements per hour in controls ($p = 0.003$, Student's t-test), during S4 $12.9 \pm 7.6$ vs. $4.9 \pm 4.5$ ($p = 0.0001$) and during SREM $15.1 \pm 9.6$ vs. $8.9 \pm 6.7$ ($p = 0.008$), respectively. One PD patient suffered from the periodic limb movement syndrome with 36 movements per hour, and three more PD patients had elevated submental EMG during REM sleep suggesting possible REM sleep behavior disorder without violence. Five PD patients had 2.4–3.5 episodes of hypopnea per hour and two of the controls had 1.7–4.2 episodes per hour during sleep ($p = 0.2680$, $\chi^2$-test).

The body movement ratio (Rbm) was decreased in PD patients during the non-REM and REM sleep stages while the sleep-wakefulness ratio (Rs/w) did not differ between the groups (Table 2). The SDNN was higher in the PD patients during non-REM sleep, especially during slow wave sleep (the S3 and S4 sleep stages) (Table 3). Other time domain measures and the FD did not differentiate the patients from the controls in any of the sleep stages.

**Table 1** Characteristics of the sleep in the PD patients and control subjects

| Variable | PD patients N = 19 | Controls n = 20 | p |
|---|---|---|---|
| Time in bed, min | 488.3 (413–584.7) | 510.9 (309.7–569) | 0.26 |
| Total sleep time, min | 345.1 (209.9–519) | 391.8 (185.4–535) | 0.26 |
| Sleep efficiency % | 77.8 (46.9–95.4) | 81.8 (49.1–95.1) | 0.34 |
| Wake after sleep onset, min | 38.0 (7.2–86.8) | 25.1 (1.4–89.9) | 0.16 |
| Sleep latency, min | 19.3 (12.8–53.8) | 20.9 (16.4–68.7) | 0.38 |
| S2 latency, min | 33.2 (6.1–76.4) | 32.1 (11.3–85.6) | 0.20 |
| REM latency, min | 110.4 (63.8–278.2) | 134.8 (56.1–229.5) | 0.97 |
| %S1 | 19.1 (8.2–39.9) | 14.5 (7.6–32.8) | 0.32 |
| %S2 | 50.3 (34.5–59.6) | 52.2 (46.5–67.1) | 0.21 |
| %S3 | 6.5 (2.8–13.2) | 6.6 (1.9–12.0) | 0.95 |
| %S4 | 8.2 (0.9–13.0) | 7.0 (1.8–16.1) | 0.66 |
| %REM | 14.7 (5.9–32.6) | 17.1 (4.6–24.8) | 0.35 |

Values are median (range)
The significance levels between the groups were obtained by Mann-Whitney U-test

**Table 2** Phasic (Rbm) and tonic (Rs/w) HRV time domain measures during different sleep stages in PD patients and control subjects

| Variable | Sleep stage | Patients n = 19 | SD | Controls n = 20 | SD | p |
|---|---|---|---|---|---|---|
| Rbm | non-REM | 1.324 | 0.008 | 1.376 | 0.012 | 0.0002 |
| | REM | 1.250 | 0.011 | 1.338 | 0.020 | 0.0001 |
| | S2 | 1.340 | 0.009 | 1.379 | 0.013 | 0.0146 |
| | S3 | 1.330 | 0.025 | 1.343 | 0.052 | 0.87 |
| | S4 | 1.355 | 0.026 | 1.339 | 0.046 | 0.77 |
| Rs/w | non-REM | 1.107 | 0.004 | 1.102 | 0.006 | 0.67 |
| | REM | 1.064 | 0.006 | 1.069 | 0.012 | 0.43 |
| | S2 | 1.105 | 0.005 | 1.104 | 0.007 | 0.91 |
| | S3 | 1.131 | 0.008 | 1.109 | 0.003 | 0.38 |
| | S4 | 1.093 | 0.006 | 1.071 | 0.020 | 0.25 |

*SD* standard deviation; *Rbm* body movement ratio; *Rs/w* sleep/wakefulness ratio; The significance levels between the groups were obtained by ANCOVA

**Table 3** Standard deviation of R-R intervals (SDNN) during different sleep stages in PD patients and control subjects

| Sleep stage | Patients n = 19 | SD | Controls n = 20 | SD | p |
|---|---|---|---|---|---|
| Awake | 74.9 | 6.4 | 68.6 | 4.8 | 0.16 |
| REM | 58.4 | 4.4 | 61.6 | 4.1 | 0.68 |
| S1 | 77.8 | 5.0 | 85.1 | 4.6 | 0.28 |
| S2 | 38.8 | 4.6 | 34.8 | 4.0 | 0.05 |
| S3 | 51.9 | 4.7 | 39.5 | 3.6 | 0.034 |
| S3 + 4 | 45.3 | 5.1 | 32.2 | 3.6 | 0.031 |
| S4 | 44.8 | 5.5 | 31.9 | 3.1 | 0.029 |

*SD* standard deviation, The significance levels between the groups were obtained by ANCOVA

The normalized FFT spectral values of HRV are presented in Table 4 and the absolute values in Table 5. The normalized HF power was significantly diminished in PD patients while awake and correspondingly, the LF/HF ratio was increased (Table 4). The normalized HF power was also diminished in PD patients during non-REM sleep. During S1 sleep the normalized LF power was decreased in PD patients (Table 4). The FFT absolute spectral measures did not differ between the two groups (Table 5), although the AR VLF and LF power was increased in patients during S3 sleep (VLF power: $180 \pm 59$ in patients vs. $88 \pm 21$ in controls, $p = 0.048$; LF power respectively: $121 \pm 47$ vs. $54 \pm 14$, $p = 0.047$).

## Discussion

Our findings revealed a sleep stage related decrease in cardiac regulation in newly diagnosed PD patients. In non-REM sleep cardiovascular attenuation increased with deepening sleep. Cardiovascular dysfunction

**Table 4** Fast Fourier transformation frequency domain measures expressed as normalized units during different sleep stages in PD patients and control subjects

| Variable | Sleep stage | Patients n = 19 | SD | Controls n = 20 | SD | p |
|---|---|---|---|---|---|---|
| LF(n) | Awake | 41.1 | 1.4 | 41.3 | 1.6 | 0.89 |
| | REM | 44.8 | 1.5 | 43.0 | 1.5 | 0.64 |
| | S1 | 42.1 | 1.3 | 45.3 | 1.0 | 0.049 |
| | S2 | 44.2 | 2.1 | 40.5 | 2.2 | 0.22 |
| | S3 | 42.1 | 2.2 | 40.3 | 2.4 | 0.51 |
| | S3 + 4 | 41.3 | 1.7 | 39.2 | 2.6 | 0.48 |
| | S4 | 41.0 | 1.6 | 39.0 | 2.4 | 0.52 |
| HF(n) | Awake | 18.3 | 1.0 | 23.5 | 1.2 | 0.002 |
| | REM | 20.0 | 1.5 | 21.6 | 1.2 | 0.42 |
| | S1 | 19.6 | 1.4 | 21.0 | 1.1 | 0.48 |
| | S2 | 26.9 | 1.7 | 33.0 | 2.2 | 0.031 |
| | S3 | 30.0 | 1.5 | 35.1 | 1.9 | 0.044 |
| | S3 + 4 | 29.4 | 1.9 | 36.8 | 2.4 | 0.019 |
| | S4 | 30.3 | 2.3 | 38.4 | 2.8 | 0.029 |
| LF/HF ratio | Awake | 2.2 | 0.2 | 1.8 | 0.1 | 0.032 |
| | REM | 2.2 | 0.2 | 2.0 | 0.1 | 0.41 |
| | S1 | 2.2 | 0.2 | 2.2 | 0.1 | 0.83 |
| | S2 | 1.6 | 0.2 | 1.2 | 0.1 | 0.07 |
| | S3 | 1.4 | 0.1 | 1.2 | 0.1 | 0.11 |
| | S3 + 4 | 1.4 | 0.1 | 1.1 | 0.1 | 0.08 |
| | S4 | 1.4 | 0.1 | 1.1 | 0.1 | 0.08 |

*SD* standard deviation; *LF(n)* normalized low frequency power; *HF(n)* normalized high frequency power; The significance levels between the groups were obtained by ANCOVA

**Table 5** Fast Fourier transformation frequency domain measures expressed as absolute units ($ms^2$) during different sleep stages in PD patients and control subjects

| Variable | Sleep stage | Patients n = 19 | SD | Controls n = 20 | SD | p |
|---|---|---|---|---|---|---|
| Total power | Awake | 264 | 39 | 269 | 26 | 0.69 |
| | REM | 295 | 47 | 238 | 28 | 0.28 |
| | S1 | 323 | 32 | 363 | 28 | 0.63 |
| | S2 | 246 | 31 | 211 | 25 | 0.37 |
| | S3 | 428 | 37 | 364 | 38 | 0.23 |
| | S3 + 4 | 271 | 27 | 215 | 20 | 0.09 |
| | S4 | 342 | 42 | 276 | 26 | 0.15 |
| VLF | Awake | 65 | 10 | 58 | 6 | 0.38 |
| | REM | 61 | 10 | 48 | 6 | 0.28 |
| | S1 | 80 | 8 | 88 | 9 | 0.05 |
| | S2 | 50 | 6 | 38 | 4 | 0.09 |
| | S3 | 75 | 9 | 60 | 7 | 0.16 |
| | S3 + 4 | 50 | 8 | 35 | 4 | 0.06 |
| | S4 | 62 | 10 | 44 | 5 | 0.09 |
| LF | Awake | 81 | 15 | 87 | 9 | 0.56 |
| | REM | 105 | 17 | 82 | 11 | 0.26 |
| | S1 | 102 | 11 | 123 | 10 | 0.29 |
| | S2 | 86 | 11 | 70 | 8 | 0.22 |
| | S3 | 146 | 13 | 122 | 16 | 0.28 |
| | S3 + 4 | 90 | 11 | 71 | 9 | 0.16 |
| | S4 | 114 | 14 | 90 | 12 | 0.18 |
| HF | Awake | 36 | 6 | 49 | 6 | 0.21 |
| | REM | 47 | 9 | 41 | 5 | 0.58 |
| | S1 | 47 | 7 | 57 | 6 | 0.46 |
| | S2 | 67 | 7 | 67 | 10 | 0.89 |
| | S3 | 133 | 12 | 128 | 15 | 0.82 |
| | S3 + 4 | 83 | 9 | 77 | 8 | 0.62 |
| | S4 | 108 | 12 | 101 | 11 | 0.58 |

*SD* standard deviation; *VLF* very low frequency power; *LF* low frequency power; *HF* high frequency power; The significance levels between the groups were obtained by ANCOVA

mostly appeared in these ANS measures that reflect dominant parasympathetic or sympathetic activity of that sleep stage. However, cardiovascular responses did not appear as a constant decrease of function since the variance of HR during non-REM sleep increased.

The normalized HR variability spectral measures, which describe the relative distribution of power within the spectral components, are known to be decreased in untreated PD patients as shown by the diminished standardized daytime cardiovascular reflexes [2, 19]. In our PD patients the normalized HF power was diminished not only while awake but also during non-REM sleep. Similarly, in the present study transient/phasic HR variability time domain measure reactions to body movements were also decreased in the PD patients especially during REM stage as well as during S2-sleep agreeing with earlier findings in patients with advanced PD [8]. However, the body movement related HR reactions, which are considered to indicate sympathetically mediated control mechanisms [8], were expectedly not altered during slow wave sleep since slow wave sleep is almost solely under parasympathetic control [16, 29, 37].

Our finding of the increased variance in HR during non-REM sleep differs from a study with 24-hour ECG recording [26], reporting a decreased variance in HR with SDNN and absolute LF power both during day and night but with absolute HF power only during the night. This may be explained by the fact that their patient had more advanced PD than ours, as well as antiparkinsonian medication, which may alter HR variation values [3, 35]. Differences may also be caused by the need to exclude ECG periods with abundant artifacts in 24-hour ECG recordings. In our polygrams every R-spike was manually checked and used for the analysis.

The increased variance of HR during non-REM sleep in our study seems to be associated with the patient's increased number of movements while asleep. The hypopnea events during the S2 sleep of five PD patients and two control subjects and the periodic leg movement syndrome of one patient may further contribute to the increased variance of the HR due to the cardiac arousal [30]. This increase of HR variability indicates that in spite of mild ANS dysfunction in the early phase of PD the cardiovascular system is still able to adapt to the changing internal body circumstances.

The investigative setting and conditions in which long-term recordings of HR variations are performed

may influence the results. For example, sympathetic activity is increased while awake and during physical activity, whereas parasympathetic activity dominates at rest [16, 20, 37]. Transient physiological phenomena, such as body movements and K-complexes during sleep, seem to result in altered ANS function [29, 38], as was found in the present study as well. Also spontaneous sympathetic skin responses, the phenomenon reflecting changing internal and external body environment, have been shown to be most abundant in S4 sleep and lowest in REM sleep [22]. There are also differences in LF and HF spectral powers and their ratios during sleep stages [20, 29, 37]. In healthy subjects during deepening non-REM sleep parasympathetic activity and autonomic stability are increased appearing as increased HF spectral power in the HR spectrum. During REM sleep the regulation of ANS function becomes more labile: the tonic decrease in sympathetic activity is interrupted by irregular episodes of sympathetic activation and parasympathetic deactivation causing increased LF power in HR spectrum. Accordingly, in the present study in PD patients the HF in HR variation spectrum was changed during slow wave sleep, whereas the body movement ratio, the measure of sympathetically mediated mechanisms, attenuated during REM sleep and remained unchanged during slow wave sleep. Thus our results show that the HRV measures, which reflect the dominating ANS activity of each sleep stage, are most liable to impair in PD. Furthermore, due to the sleep stage relation of the obtained nocturnal cardiovascular dysfunction in PD our results accentuate the importance of analyzing ANS measures in different sleep stages separately.

In addition to the dopaminergic system, the degenerative process of PD also involves noradrenergic locus coeruleus, the dorsal motor vagal nucleus and the cholinergic nucleus basalis of Meynert [17]. Moreover, Lewy bodies are found in multiple areas of brain, spinal cord and in sympathetic and parasympathetic neurons [5, 17, 18]. Thus the cardiovascular autonomic control system may be injured at multiple sites in both sympathetic and parasympathetic branches. Accordingly, our study showed that both parasympathetically and sympathetically mediated cardiovascular regulation were affected depending on the given sleep stage. However, as we observed earlier in standardized daytime cardiovascular reflex tests in patients with untreated PD [19], the significant attenuation of cardiovascular reactivity at the group level as in the present study does not necessarily indicate a significant sign of autonomic failure in a single patient.

In conclusion our results showed that already at early stage in untreated PD patients a mild cardiovascular dysfunction exists during both waking and sleep. Moreover, in non-REM sleep this dysfunction increases with more deepening sleep. Furthermore, different ANS measures are altered depending on the sleep stages and some even for opposite directions. Thus sleep scoring reveals the complexity of cardiovascular regulation in PD accentuating the value of sleep scoring in examination of nocturnal ANS phenomena.

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