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RELATIONSHIPS BETWEEN CLINICAL CHARACTERISTICS AND NOCTURNAL CARDIAC AUTONOMIC ACTIVITY IN PARKINSON'S DISEASE

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Abstract

Background—The aim of the present study was to explore the association between Parkinson's disease (PD) clinical characteristics and cardiac autonomic control across sleep stages.

Methods—Frequency-domain heart rate variability (HRV) measures were estimated in 18 PD patients undergoing a night of polysomnography.

Results—Significant relationships were found between PD severity and nocturnal HRV indices. The associations were restricted to rapid eye movement (R) sleep.

Conclusions—The progressive nocturnal cardiac autonomic impairment occurring with more severe PD can be subclinical emerging only during conditions requiring active modulation of physiological functions such as R-sleep.

Keywords

Heart rate variability; Parkinson's disease; polysomnography; sleep

Introduction

Autonomic nervous system (ANS) alterations are common non-motor symptoms in Parkinson's disease (PD), occurring in up to 80% of patients (Jost, 2003). Disturbances are heterogenic and involve cardiovascular, respiratory, gastrointestinal, urogenital, sudomotor and thermoregulatory functions. Sleep difficulties are also frequent in PD. Dysregulation of

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the ANS has been reported to increase complications in PD and to affect daily functioning and quality of life (Damiano et al., 1999).

Studies investigating neurovegetative functions during wakefulness in PD have consistently reported associations between the extent of autonomic impairment and disease-related aspects such as progression and duration (Korchounov et al., 2005; Mesec et al., 1993). Further, several reports evaluating the circadian fluctuations of heart rate variability (HRV) in PD patients documented a relationship between the average 24h HRV and PD severity (Niwa et al., 2011; Haapaniemi et al., 2001). However, the persistence and nature of these associations over the sleep period are unclear.

The purpose of the current work was to explore the association between PD clinical characteristics and nocturnal cardiac autonomic activity by way of HRV measures. Given the marked ANS fluctuations in different sleep stages (Mancia, 1993), sleep stages were taken into account separately.

Methods

Participants

As a part of a larger study on sleep difficulties in PD, 18 patients (13 males; mean $\pm$ SD: 63.39 $\pm$ 7.81 y, range 52–81 y) with a diagnosis of idiopathic PD were enrolled. Patients with a diagnosis of idiopathic PD were recruited through the Department of Neurosciences at University of California-San Diego (UCSD), the San Diego Parkinson's Disease Association, community neurologists, and talks given to PD support groups.

PD severity was rated using the Hoehn and Yahr Scale (HY; Hoehn and Yahr, 1967) and the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn et al., 1987). From the UPDRS Motor scale (UPDRS III), the motor symptoms of tremor (item 20), rigidity (item 22) and hypokinesia (items 23–27, 29, 31) were derived.

None of the patients reported autonomic symptoms (such as orthostatic hypotension, sialorrhea, hyperhidrosis, or urinary incontinence). All patients were receiving antiparkinsonian therapy, with 11 patients being treated with levodopa, 7 with ropinirole, 6 with pramipexole and 2 with entacapone. To account for the various dopaminergic therapies, levodopa dosage equivalents (LDE, mg) were calculated as previously reported (Covassin et al., 2012). Patients were required to have been stable on the same antiparkinsonian medication dose for at least two months prior to participation in the study.

Exclusion criteria were as follows: clinically atypical PD, presence of any neurological disorder other than PD, deep brain stimulation, cardiovascular diseases, usage of psychotropic drugs or medications known to affect the cardiovascular or autonomic systems, and a history of alcohol or drug abuse.

The study was approved by the University of California San Diego (UCSD) Institutional Review Board and all participants signed an informed consent.

Sleep Measures

A standard regimen of polysomnography (PSG) was carried out. Sleep stages and respiratory and movement events were scored according to American Academy of Sleep Medicine (AASM) standards (Iber et al., 2007). The following sleep variables were obtained: sleep onset latency (SOL; min), wake after sleep onset (WASO; min), sleep efficiency (SE; %), amount of non rapid eye movement (NREM; sum of N1, N2 and N3 sleep stages) and rapid eye movement (R) sleep stages (min), apnea and hypopnea index

(AHI; number of apneas and hypopneas per hour of sleep), periodic limb movements in sleep index (PLMSI; number of periodic limb movements per hour of sleep). Values of AHI 10 and PLMSI 15 were used to identify sleep disordered breathing (SDB) and periodic limb movements in sleep (PLMS), respectively. The presence of REM sleep behavior disorder (RBD) was established as published elsewhere (Neikrug et al., 2011). As the overnight videos were only available for some PSGs, REM without atonia was assessed by measuring the electromyographic (EMG) score. Similarly to AASM criteria (Iber et al., 2007), a REM epoch was identified as tonic if it exhibited a higher chin EMG amplitude than the minimum amplitude detected in NREM for 50% of its duration. It was identified as phasic if, dividing each 30-sec epoch into 12 2.5-sec mini-epochs, transient bursts of muscle activity, lasting 0.1–5.0 sec and 4 times higher in amplitude than the background EMG activity, were observed in 50% of the mini-epochs. The EMG-score (%) was defined as the proportion of both phasic and tonic components, applying a cut off of 10% to indicate RBD. Moreover, the history of nocturnal abnormal behavior was assessed by administering the REM Behavior Disorder Sleep Questionnaire (RBDSQ, Stiasny-Kolster et al., 2007). Total score ranges from 0 to 13 and a score >5 is suggestive of RBD. Patients scoring both >5 on the RBDSQ and exhibiting an EMG-score >10% were classified as having RBD.

Heart Rate Variability

The electrocardiogram (ECG) was recorded overnight within the PSG and data were analyzed in 2-min segments identified within the sleep period. For an interval to be selected, the 2-min before each segment and the segment itself had to be free of body movements, arousals, apneas or hypopneas. Additionally, no sleep stage transitions could occur during either the 2-min before each segment or during the segment itself.

The interbeat intervals (IBIs; ms) from the ECG recording were first edited automatically, then visually inspected and manually corrected where necessary. The IBIs for each segment were resampled at 4 Hz to derive the IBIs data series, then a filter for detrending was applied. The power spectra in the high frequency (HF, ms^2 ; 0.15–0.4 Hz) and low frequency (LF, ms^2 ; 0.04–0.15 Hz) bands were quantified by means of the Fast Fourier Transform. The HF oscillations in IBIs mainly reflect the vagal modulation of the heart, whereas the LF fluctuations are mediated by both sympathetic and parasympathetic branches. The ratio of LF to HF powers (LF/HF) was estimated as index of sympathovagal balance. Mean IBI was also computed.

HRV measures were averaged for NREM and R-sleep periods. Average overnight values were also calculated.

The VivoSense software (Vivonoetics Inc., San Diego, CA) was used for the HRV analyses.

Study Design

Referred PD patients were interviewed and physical examination and medical history collection were performed by a physician. Recruited participants were admitted to the UCSD Clinical Translational Research Institute Gillin Laboratory for Sleep and Chronobiology and underwent one night of PSG. Sleep and wake times were set according to each patient's habits.

Statistics

Due to their skewed distribution, HRV absolute power measures were log-transformed. Correlations between HRV measures and PD characteristics were performed by Spearman's rank analysis. The relationships between HRV and sleep disorders measures (i.e., AHI, PLMSI and EMG-score) were also examined. A p-value <0.05 was considered significant.

Results

Descriptive statistics are summarized in Table 1.

Analysis of sleep measures disclosed that 13 participants exhibited an AHI 10, and 18 participants had a PLMSI 15, suggestive of SDB and PLMS, respectively. Moreover, RBD was observed in 8 patients.

Correlation analyses revealed significant negative relationships between the HF_{log} during REM and the HY ($p < 0.01$) and UPDRS total score ($p < 0.001$) (Table 2). Significant correlations were also seen with HF_{log} in R-sleep and motor symptoms, including the UPDRS III score ($p < 0.05$), rigidity ($p < 0.05$) and hypokinesia ($p < 0.01$). Conversely, there were no significant correlations with the overnight HF_{log} or the NREM HF_{log}.

The overnight LF/HF ratio was positively related to the HY staging ($p < 0.01$), UPDRS total score ($p < 0.05$), rigidity ($p < 0.05$) and hypokinesia ($p < 0.05$). Although no relationship was identified with the LF/HF ratio in NREM, the LF/HF ratio in R-sleep correlated with the HY ($p < 0.01$), UPDRS total score ($p < 0.05$), UPDRS III ($p < 0.05$), rigidity ($p < 0.01$) and hypokinesia ($p < 0.001$). The overnight IBI and LF_{log} values were not significantly correlated with any clinical parameters (data not showed). The IBI in NREM correlated with age ($\rho = -0.518$, $p < 0.05$), whilst the LF_{log} in R-sleep was found as being related to the UPDRS total score ($\rho = -0.495$, $p < 0.05$).

With regard to the sleep measures, the EMG-score correlated with age ($\rho = 0.524$, $p < 0.05$) and the PLMSI with tremor ($\rho = 0.570$, $p < 0.05$). Correlations with the other PSG parameters did not reveal any significance.

Discussion

In the present study we sought to investigate the association between cardiac autonomic activity during sleep and the PD clinical features by measuring HRV. In line with prior investigations (Haapaniemi et al., 2001; Niwa et al., 2011), we observed a progressive nocturnal cardiac autonomic dysregulation with more severe PD: the more advanced the PD, the lower the HF HRV components and the higher the LF/HF ratio, indicating more diminished vagal output and more elevated sympathovagal balance during sleep, respectively.

The associations between HRV indices and rigidity and hypokinesia suggested common pathogenetic pathways for the autonomic failure and decline of motor functions in PD, as previously proposed (Iodice et al., 2011). When NREM and R-sleep stages were examined separately, the associations between HRV measures and PD severity were only significant during R-sleep. This may be explained by the different autonomic activity seen in NREM vs. R-sleep. While NREM sleep is characterized by a parasympathetic prevalence, R-sleep is associated with an irregular autonomic activity (Mancia, 1993), with transient bursts of sympathetic activation in a context of reduced vagal tone. This autonomic pattern is reflected by the HRV profile, which displays a drop in HF components combined with an augmentation in LF activity and thus in the sympathovagal balance in R-sleep, while the reverse pattern is seen during NREM sleep (Trinder, 2007).

These results suggest that even in PD patients without clinically relevant dysautonomia, cardiac ANS impairment can occur subclinically, increase with advanced disease, and emerge only during conditions requiring an active and dynamic regulation of physiological functions such as R-sleep. As an autonomic imbalance in terms of lowered vagal tone has been identified as a marker of heightened risk of adverse outcomes (Thayer and Lane,

2007), these data may support the higher vulnerability described in PD populations at advanced stages of the disease.

A number of weaknesses need to be acknowledged. The main limitation is the small sample size which precluded regression modeling and could have lowered the statistical power resulting in a type II error. Also, the lack of a control group did not allow us to compare ANS functions with healthy subjects. Concerns may arise with regard to the high prevalence of multiple sleep disorders in our sample, which could have affected our findings. However, it should be emphasized that we performed an accurate selection of stable sleep segments for the HRV analysis, thus excluding arousals, movements and respiratory events known to influence HRV measurement. Moreover, only marginal relationships were observed between sleep disorders indices and PD clinical aspects (i.e., an increase in PLMSI with the worsening of the tremor); hence, the impact of these sleep disorders on our findings is likely negligible. Lastly, although no associations were detected between the LDE and the HRV measures, we cannot exclude the potential effects of the antiparkinsonian agents undertaken by the participants on cardiac autonomic functions. To rule out pharmacological influences, future examinations should involve untreated PD patients. In addition, longitudinal large-sample studies targeted at assessing the prognostic significance of ANS activity during sleep are warranted.

In sum, we observed significant relationships between PD severity and nocturnal HRV indices which were restricted to R-sleep. Given the sleep stage-dependent relation between HRV and clinical parameters, our study highlights the importance of examining nocturnal ANS profile according to the different sleep stages in PD patients.

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Table 1

Demographic, clinical and sleep data (mean±SD).

	Mean±SD (N=18)
<i>Demographic and clinical</i>	
Age (y)	63.39±7.81
Gender (N m/f)	13/5
Duration disease (y)	4.67±2.45
LDE (mg)	659.69±598.3
RBDSQ	4.71±3.17
HY	1.61±0.61
UPDRS total	37.28±11.08
UPDRS III	20.17±7.48
tremor	0.83±0.86
rigidity	5.39±2.85
hypokinesia	8.39±4.51
<i>PSG</i>	
WASO (min)	84.86±45.33
SOL (min)	7.19±9.62
SE (%)	80.59±9.29
NREM-sleep (min)	331.58±30.19
R-sleep (min)	46.19±30.59
AHI (N/hr)	19.68±12.67
PLMSI (N/hr)	26.07±30.13
EMGscore (%)	13.05±13.8
<i>HRV</i>	
Overnight	
IBI (ms)	1034.78±128.02
HF _{log}	2.68±0.48
LF _{log}	2.98±0.37
LF/HF	2.94±1.71
NREM-sleep	
IBI (ms)	1037.83±142.75
HF _{log}	2.88±0.65
LF _{log}	3.01±0.61
LF/HF	1.98±1.72
R-sleep	
IBI (ms)	1031.74±124.35
HF _{log}	2.47±0.49
LF _{log}	2.95±0.3
LF/HF	3.9±2.28

AHI, apnea/hypopnea index; EMGscore, electromyographic score; HF_{log}, log-transformed spectral power in the high frequency band; HRV, heart rate variability; HY, Hoehn and Yahr Scale; IBI, interbeat interval; LDE, levodopa dosage equivalents; LF_{log}, log-transformed spectral power in

the low frequency band; LF/HF, ratio of low frequency power to high frequency power; NREM, non-rapid eye movement sleep; PLMSI, periodic limb movements in sleep index; PSG, polysomnography; R, rapid eye movement sleep; RBDSQ, REM Behavior Disorder Sleep Questionnaire; SE, sleep efficiency; SOL, sleep onset latency; UPDRS, Unified Parkinson's Disease Rating Scale; WASO, wake after sleep onset.

Table 2

Spearman's correlation coefficients between HRV measures and PD characteristics.

	Overnight			NREM-sleep			R-sleep		
	HF _{log}	LF/HF	HF _{log}	LF/HF	HF _{log}	LF/HF	HF _{log}	LF/HF	
Age	0.060	0.169	0.144	-0.105	-0.047	0.076			
Duration disease	0.092	-0.188	0.036	-0.038	0.144	0.329			
LDE	0.005	-0.304	-0.139	-0.199	0.199	-0.330			
HY	-0.193	0.640**	0.016	0.364	-0.682**	0.690**			
UPDRS	-0.175	0.457*	0.002	0.109	-0.746***	0.569*			
UPDRS III	-0.054	0.379	0.062	0.075	-0.517*	0.478*			
tremor	-0.350	-0.074	-0.366	-0.051	-0.300	-0.067			
rigidity	-0.204	0.467*	-0.049	-0.125	-0.565*	0.613**			
hypokinesia	-0.018	0.580*	0.294	0.124	-0.606**	0.746***			
AHI	-0.348	-0.146	-0.282	-0.127	0.123	-0.126			
PLMSI	-0.301	0.218	-0.315	0.175	-0.247	0.141			
EMG-score	-0.455	0.218	-0.315	0.003	-0.293	0.195			

* = p<0.05,

** = p<0.01,

*** = p<0.001.

AHI, apnea/hypopnea index; EMGscore, electromyographic score; HF_{log}, log-transformed spectral power in the high frequency band; HY, Hoehn and Yahr Scale; LDE, levodopa dosage equivalents; LF/HF, ratio of low frequency power to high frequency power; NREM, non-rapid eye movement sleep; PLMSI, periodic limb movements in sleep index; R, rapid eye movement sleep; UPDRS, Unified Parkinson's Disease Rating Scale.