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Bound to supine sleep: Parkinson's disease and the impact of nocturnal immobility

Sommerauer, M ; Werth, E ; Poryazova, R ; Gavrilov, Y V ; Hauser, S ; Valko, P O

Abstract: BACKGROUND Impaired nocturnal mobility is a well-known problem in Parkinson's disease (PD), and clinical experience suggests a predominance of supine body position during sleep. However, this assumption - and potential consequences - still awaits objective validation by a polysomnography-based and adequately controlled study. METHODS Clinical and polysomnographical analysis of 80 consecutive PD patients and 80 control subjects carefully matched for age, sex, body mass index and apnea-hypopnea index. RESULTS PD patients slept twice as much in supine position than control subjects ($62.2 \pm 32.9\%$ vs. $34.2 \pm 28.5\%$, $p < 0.001$). In PD, but not in control subjects, more supine sleep correlated with fewer changes in body position ($\rho = -0.434$, $p < 0.001$). Longer PD disease duration was an independent predictor of more supine sleep in multiple linear regression analysis ($\beta = 0.389$, $p < 0.001$); conversely, more supine sleep was associated with higher apnea-hypopnea index and daytime sleepiness. CONCLUSIONS We confirmed that supine sleep is common in PD, and increases with longer disease duration. Our findings indicate that supine sleep may contribute to the overall disease burden by deteriorating sleep-disordered breathing and daytime vigilance.

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Author Declaration

Parkinsonism & Related Disorders is committed to proper scientific conduct and the protection of animal and human research subjects. Submission of this manuscript implies compliance with the following ethical requirements. Please affirm that you are representing all of the authors in stating compliance with these policies by checking the box at the end of this section.

1. Studies with human subjects must have been conducted in accordance with the Declaration of Helsinki. All persons must have provided informed consent prior to being included in the study.
2. Studies with animal subjects must have been conducted in accordance with the Guide for the Care and Use of Laboratory Subjects as adopted by the US National Institutes of Health and/or according to the requirements of all applicable local, national and international standards.
3. Protocols with animal or human subjects must have been approved by the relevant local committee(s) charged with ensuring subject protection. Studies that entail pain or distress will be assessed in terms of the balance between the distress inflicted and the likelihood of benefit.
4. The authors declare that the manuscript is original, that it is not being considered for publication elsewhere, and that it will not be submitted elsewhere while still under consideration for Parkinsonism & Related Disorders or after it has been accepted by Parkinsonism & Related Disorders.
5. All authors have seen and approved the manuscript in the form submitted to the journal. The authors declare that they have conformed to the highest standards of ethical conduct in the submission of accurate data and that they acknowledge the work of others when applicable.
6. All sources of financial support for the work have been declared in the Acknowledgements section of the manuscript. Any additional conflicts of interest must also be declared. Please include declarations of any consultancy or research funding received from relevant companies from three years prior to performance of the research until the time of manuscript submission. If the research is supported by internal funds, that should be stated as well.

To indicate compliance with the preceding declaration and that you have obtained agreement from all of the authors of this paper to declare their compliance as well, please place an x here: X

In cases of uncertainty please contact an editor for advice.

Dear Dr. Bonifati

Thank you for giving us the opportunity to submit a revised version of our manuscript. We also would like to thank the three reviewers for their thoughtful comments, which helped to improve the quality of the manuscript. Our responses to the reviewers' concerns are written in *italics*, and the changes in the manuscript are highlighted with red font. We hope you will now find the current version suitable for publication.

I again certify that all coauthors have seen and agree with the contents of the manuscript. It is not under review at any other publication.

Thank you again for reconsidering our manuscript for publication.

Reply to reviewers' comments

Reviewer #1

Sleep disorders are such complex problems that one must be careful in deducing too much, especially from a single, retrospective study. Your study appears to have been well done and the ms is well written. I have some reservations and suggestions.

We thank Reviewer #1 for this encouraging comment and the helpful suggestions.

In the highlights section, I suggest noting on the first line that this was a retrospective study. This indicates to the reader that you were unable to control for many variables that might be important.

We added a statement that this was a retrospective study.

In the introduction, I suggest deleting the statement that "nocturnal immobility is recognized as a disease-defining feature." Perhaps you mean "common disease feature?" I am not aware of any criteria for defining PD that include nocturnal immobility.

We changed the wording according to the reviewer's suggestion.

I applaud your matching PD and controls for BMI and AHI, but, as you know, there are many other items you might have chosen. Your mean ages were the same. Did you purposely match for age? Please state.

Thank you for this comment. We understand that perfect matching is not feasible. For this study, we deliberately matched the two groups for age, sex, BMI and AHI, because we believe these four factors most likely impact the distribution of different body positions during sleep.

You state that one body position you measured was "upright." Did some subjects sleep upright in a bed? Please clarify

The used sensor is able to detect "upright" body position, i.e. when sitting or standing up; however, no sleep in this position was detected in this study. We apologize for this confusion and have now clarified this issue in the Methods section.

You state that "probably only few conditions lead to such a pronounced increment in supine..." Unless you have data to support this, I suggest deleting. I suspect that many neurological and orthopedic disorders are associated with this, and, in the U.S., pediatricians now have babies sleep on their backs to avoid SIDS. This might possibly lead to most adults learning to do this.

We deleted this statement, as we indeed lack any supporting data.

Most importantly, you need to list the many weaknesses in your study. We have no information on why sleep studies were obtained, which may have been quite different in the two groups. We don't know how many were smokers, had pain syndromes, had back problems, had RBD, had breathing disorders, were obese, what medications they took, whether supine sleeping correlated with nocturia, etc etc. You don't have to list every issue you can think of, but you should mention a few since they are relevant and impossible to match for.

Thank you for these suggestions. We appreciate your concerns, and are now discussing the limitations inherent to such a retrospective study in more detail.

Most importantly, you should acknowledge that you found correlations, not cause and effect relationships. You have not provided any data to indicate that less sleeping supine is helpful. Perhaps a trial of having people sleep with something like a small ball attached to their sleep attire to make it impossible to sleep supine would be an inexpensive intervention to test your hypothesis.

I am not sure many will agree with your suggestion to include supine sleeping in studies of treatment interventions. There are so many possible things to study and your single study does not evaluate effects of reducing the time in the supine position.

We agree that our non-interventional study does not provide any evidence that improved nocturnal mobility and less supine sleep would also lead to meaningful changes in quality of life of PD patients. We understand the difference between correlation and cause and effect relationship, and have now tempered our conclusions accordingly.

However, we do believe supine sleep and nocturnal immobility should be addressed in studies on sleep quality in PD and that this issue has so far been too neglected.

Reviewer #2

The primary aim of this article is to determine body position of PD patients during sleep. This can be determined also by sleep partner report or videography. Expensive polysomnogram is not needed. Patients were selected retrospectively from referrals to a sleep lab. Since it is not routine practice to order PSG for all PD patients, presumably these PD patients had suspicion of possible sleep apnea so they were referred for PSG. The data of these patients cannot be extrapolated to all PD patients.

We absolutely agree that polysomnography is expensive and information on body position could be achieved cheaper and by other means. Indeed, among our patients, no polysomnography was actually done primarily to assess distribution of body positions during sleep. Rather we wished to benefit from the many polysomnographies that had been performed in PD patients in our department, and set out to analyze, whether PD patients really do sleep more in supine position.

We also agree that a potential referral bias cannot be excluded. However, we believe we reasonably accounted for this risk by using a rater-independent propensity score matching with inclusion of four major variables. In addition, due to the high prevalence of sleep-wake disturbances in PD and their possible diagnostic, therapeutic and medico-legal implications, polysomnography has become an integral diagnostic procedure in PD patients in our department. Thus, a significant referral bias seems quite unlikely, because polysomnography was performed in most PD patients independent of the presence or absence of (suspected) sleep apnea or any other sleep disorder.

We admit, on the other hand, that our PD population is representative for a tertiary center, and our findings cannot be generalized to all PD patients.

We added these limitations to our discussion.

Reviewer #3

This is an interesting and well written paper confirming that supine sleep is, first, more common in PD than in normal controls and second, increases with disease duration. Reported below, there are a few questions that add more information.

We thank Reviewer #3 for this appraisal of our study.

1. The multiple regression included disease type and found no influence of disease type with the akinetic-rigid form. However other type of approach could be used to determine whether there might be some association between this form and the propensity for supine position during sleep, such as cluster analyses or group comparisons.

We also calculated a group comparison (ANOVA) for association of disease type with amount of supine sleep; we did not find significant differences in this analysis (in 2 patients, disease type was missing).

type	n	mean	p
akinetic/rigid	58	62.3	
tremor dominant	15	64.4	0.821
equal	5	52.7	

2. The second question is about dopaminergic medications, in terms of type and timing of the last dose. Specifically, first, from the data is it possible to understand whether dopaminergic agonists were more often associated with propensity for supine position? Second, was there an effect of the time of the last dose of dopaminergic medication before sleep?

We calculated a group comparison (student's T-test) for differences of percent of supine sleep position between patients with and without dopamine agonists but did not find significant differences (67% versus 55%, $p=0.12$).

We also performed correlation analysis of amount of supine sleep position with levodopa equivalent dose of dopamine agonist and long acting dopaminergics at bedtime (night dose of levodopa with continuous release and long acting dopamine agonists) but did not find any significant association. However, we could not elucidate the specific time of dosing due to insufficient data in our chart review.

We added both use of dopaminergic agonists and use of long acting dopaminergics in the multivariate regression analysis, which did not change the result, and disease duration remained the only predictor of more supine sleep position.

As our study was non-interventional and PD groups with and without long acting dopaminergics (or w/o dopamine agonists) were not perfectly matched, estimations from these preliminary calculations are difficult to generalize. We included this in our limitation paragraph.

3. Did the author explore possible relation between PSG findings and time of supine position?

We did correlation analysis of all polysomnographic findings listed in Table1 and below; however, we did not find any significant correlation (Pearson's r). We summarized these negative findings in the Result section ("supine sleep position did not correlate with any sleep stage, sleep efficiency or arousal index").

Supine position [%]	Pearson's r	p
Total sleep time [min]	,035	0.756
Sleep latency [min]	,017	0.883
Sleep efficiency [%]	-,003	0.982
Wake [%]	,024	0.833
Rapid eye movement (REM) sleep [%]	-,006	0.961
Non-REM sleep 1 [%]	,065	0.571
Non-REM sleep 2 [%]	-,089	0.434
Slow wave sleep [%]	,036	0.750
Periodic limb movements in sleep [/h]	-,066	0.564

4. Finally, a graph about the correlation between disease duration and more supine sleep in PD should be added in Figure 1.

We added a scatter plot to figure 1.

We thank Reviewer #3 for the helpful comments.

Highlights

- We **retrospectively** analyzed 80 PD patients and 80 matched controls by polysomnography
- PD patients slept twice as much in supine position than controls
- More supine sleep correlated with fewer changes in body position in PD
- Longer PD disease duration was an independent predictor of more supine sleep
- More supine sleep was associated with higher AHI and daytime sleepiness in PD

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**Bound to supine sleep:
Parkinson's disease and the impact of nocturnal immobility**

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Abstract

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Methods: Clinical and polysomnographical analysis of 80 consecutive PD patients and 80 control subjects carefully matched for age, sex, body mass index and apnea-hypopnea index.

Results: PD patients slept twice as much in supine position than control subjects ($62.2\pm 32.9\%$ vs. $34.2\pm 28.5\%$, $p<0.001$). In PD, but not in control subjects, more supine sleep correlated with fewer changes in body position ($\rho=-0.434$, $p<0.001$). Longer PD disease duration was an independent predictor of more supine sleep in multiple linear regression analysis ($\beta=0.389$, $p<0.001$); conversely, more supine sleep was associated with higher apnea-hypopnea index and daytime sleepiness.

Conclusions: We confirmed that supine sleep is common in PD, and increases with longer disease duration. Our findings indicate that supine sleep may contribute to the overall disease burden by deteriorating sleep-disordered breathing and daytime vigilance.

Key Words: Parkinson's disease, nocturnal immobility, supine, sleep position, sleepiness, sleep-disordered breathing

Introduction

A myriad of motor and non-motor symptoms add to the overall clinical burden in Parkinson's disease (PD), and sleep-wake disturbances are among the most frequent and significant contributors [1]. Patients often complain about difficulty turning in bed and claim to sleep mostly in supine position. However, whether PD patients do sleep more in supine position is unclear, because researchers have rarely analyzed the distribution of sleep positions in PD. In contrast, nocturnal immobility is recognized as a **common disease feature**, and an item pertaining to this symptom has been included in several clinical scales, including the Parkinson's Disease Quality of Life Questionnaire and the old and new versions of the Unified Parkinson's Disease Rating Scale [2].

Few studies reported adverse effects of nocturnal immobility on sleep quality in PD, whereas a recent polysomnography-based study failed to detect differences in the distribution of sleep positions in PD patients with and without subjectively impaired bed mobility [3, 4]. Overall, most of these studies were based only on subjective complaints and lacked appropriate control groups.

Thus, in the present study we aimed 1) at objectively comparing the distribution of distinct sleep positions and the frequency of body position changes between PD patients and carefully matched control subjects, and 2) at identifying clinical correlates and predictors of supine sleep position in PD.

Patients and methods

Subjects, clinical assessment and matching procedure

This was a retrospective chart review. In a first step, we selected 119 consecutive PD patients who received whole-night video-polysomnography (PSG) as an integral diagnostic procedure between 2004 and 2009. In order to compare their data on sleep positions and

nocturnal mobility to an adequate control group, we considered 248 consecutive non-neurological patients from our data base, in which PSG was performed during the same time for suspected sleep disorders. We used propensity score matching as a rater-independent and unbiased method to generate two groups accurately matched for age, sex, body mass index (BMI, body mass divided by the square of individual's height) and apnea-hypopnea index (AHI, number of apnea and hypopnea events per hour of sleep) [5]. By this means, we eventually included 80 PD patients and 80 matched control subjects.

Diagnostic procedure, clinical assessment and calculation of levodopa dose equivalents (LDE) are identical to previous studies [5]. We ascertained sleepiness using the Epworth Sleepiness Scale (ESS), with scores of ≥ 10 indicating excessive daytime sleepiness (EDS). The study was approved by the local Ethics Committee.

Polysomnography assessment

All patients had overnight PSG recordings, using a **multi-channel recording system (Embla, RemLogic™)**. Scoring of sleep stages and respiratory events was performed visually using standardized criteria [5]. Apnea was defined by a cessation of oro-nasal airflow longer than 10 seconds, and hypopnea by a reduction of oro-nasal airflow by at least 50% lasting more than 10 seconds and accompanied by an arousal or SaO₂ reduction of $\geq 3\%$. A body position sensor was attached by an elastic velcro strap at the level of the lower sternum **and recognized distinct body positions by virtue of different voltage outputs. This allowed for automatic detection of the following four body positions: supine, right, left, and prone. In theory, the sensor would also register upright body position, but our subjects did not sleep in this position.** We ensured adequate monitoring by comparing patient video and body position recording. As an objective measure of nocturnal immobility we used the number of changes between distinct body positions per hour.

Statistical analysis

Statistical analyses were performed using SPSS (version 21). Group data were described by means and standard deviations. For normally distributed data, we used Student's *t*-test and for non-parametric data the Mann-Whitney *U*-test. Chi-square test was used for nominal data. We calculated Pearson's *r* for correlation analysis of normally and Spearman-rho for non-normally distributed data. Stepwise multiple linear regression analysis was done including age, sex, body mass index, disease duration, Hoehn and Yahr stage, disease type, use of dopamine agonist, use of long acting dopaminergic medication, and total LDE as independent variables. Significance was accepted at $p < 0.05$.

Results

Clinical and polysomnographic findings

Demographic, clinical and polysomnographic findings are summarized in **Table 1**. PD patients slept roughly twice as much in supine position ($62.2 \pm 32.9\%$ vs. $34.2 \pm 28.5\%$, $p < 0.001$), and had fewer body position changes than controls ($4.2 \pm 7.1/h$ vs. $4.5 \pm 7.2/h$, $p = 0.04$). Lying most in supine position during sleep ($\geq 90\%$) was more common among PD patients than controls (32% vs. 6% , $p < 0.001$) (**Fig. 1A**). More supine sleep correlated with fewer body position changes in PD ($\rho = -0.434$, $p < 0.001$) but not in controls ($\rho = -0.200$, $p = 0.08$).

Correlates of supine sleep position

PD patients with EDS spent more time in supine position than those without EDS ($51.0 \pm 35.2\%$ vs. $75.4 \pm 25.0\%$, $p = 0.001$), whereas controls did not differ in this respect ($30.9 \pm 31.1\%$ vs. $38.8 \pm 23.1\%$, $p = 0.07$) (**Fig. 1B**). In PD, but not in controls, multiple linear regression analysis revealed that more supine sleep was independently associated with higher AHI ($\beta = 0.260$, $p = 0.015$ and age as second significant associate: $\beta = 0.349$, $p = 0.001$). Periodic limb movements in sleep did not correlate with supine position in either group.

Likewise, supine sleep position did not correlate with any sleep stage, sleep efficiency or arousal index, and group comparison did not reveal any difference in supine sleep between PD patients with various disease type (akinetic-rigid, tremor-dominant, equal). Finally, the use of dopamine agonists had no impact on total amount of supine position, and correlation analysis between LDE of dopamine agonists and of long-acting dopaminergic drugs at bedtime with supine position did not demonstrate any significant associations.

Predictors of supine sleep in PD

Linear regression analysis identified longer disease duration to be independently associated with more supine sleep in PD ($\beta=0.389$, $p<0.001$) (**Fig. 1C**).

Discussion

Compared to carefully matched control subjects, PD patients slept almost twice as much in supine position and less often changed nocturnal body posture. In addition, we identified longer PD duration as independent predictor of more supine sleep. These results have been expected, and may be regarded as inevitable consequences of nocturnal immobility and axial rigidity. However, more than confirming a commonplace, our study suggests relevant clinical implications of this predominance for supine sleep position, as indicated by the association with increased severity of sleep-disordered breathing and excessive daytime sleepiness.

Our knowledge about the distribution of sleep positions in general is limited, but the clinical impact of certain sleep positions has been acutely revealed by the discovery that prone sleep position is associated with a more than threefold increased risk of sudden infant death syndrome. Polysomnographic studies demonstrated that up to two thirds of patients with acute stroke spend the first nights nearly entirely in supine position, while the magnitude of supine sleep is likely to diminish following recovery [6]. In stroke patients, supine position

contributes to sleep disordered breathing (SDB) and impacts functional outcome and mortality. Application of continuous positive airway pressure (CPAP) or positional treatment is therefore increasingly advocated [7].

In this line, our results and those of many other groups confirm that SDB is the most obvious problem caused by lying in supine position. Supine position increases the risk of upper airway collapses, causes more and longer apnoeic events, and necessitates a higher pressure from CPAP devices [8, 9]. Cheyne-Stokes respiration, obstructive and central SDB all ameliorate after changing from supine to lateral sleep position. Thus, our study indicates that sleep-related respiration in PD is similarly susceptible to the adverse effects of supine position. Although the contribution of SDB to daytime sleepiness has been questioned in PD, a recent randomized placebo-controlled study in PD patients with SDB demonstrated a significant improvement of both nocturnal sleep consolidation and objective daytime sleepiness in those receiving CPAP treatment [10]. Thus, feasibility and efficacy of positional treatment – already a well established alternative to CPAP in patients with positional SDB [11] – need to be evaluated also in PD patients.

On the other hand, it is unlikely that increased SDB severity represents the sole explanation for the negative association between supine sleep and daytime sleepiness. Even healthy people with poor sleep quality spend more time in supine position than good sleepers [12], and this observation suggests a mutual influence of supine position and poor sleep quality. In our study, however, we failed to demonstrate any correlation between polysomnographic measures of sleep consolidation and amount of supine position, which is in contrast to previous studies reporting an adverse impact of nocturnal immobility on subjective sleep quality.

Our retrospective study has several limitations. Primarily, a selection bias cannot be ruled out, and polysomnography may have been differentially motivated in PD patients and controls. However, we believe we substantially reduced this risk by using a rater-independent propensity score matching with inclusion of four major variables. Moreover, due to the high

prevalence of sleep-wake disturbances in PD and their possible diagnostic, therapeutic and medico-legal implications, polysomnography has become an integral diagnostic procedure in PD patients in our department, and has thus been done largely independent of any suspected sleep disorder. Nevertheless, the potential influence on sleep position of additional features, including orthopedic comorbidity, smoking habits or nocturia, may have escaped our attention. Finally, since our study is purely observational, future work is required to confirm the clinical benefit obtained by decreased supine sleep, e.g. by using positioning device techniques such as tennis ball T-shirt or filled backpack.

Overall, our study emphasizes the need for treatment strategies that help improving nocturnal mobility and liberating PD patients from their excessive supine recumbency. Studies evaluating the effects of long-lasting dopaminergic drugs, continuous dopaminergic stimulation or deep brain stimulation **should therefore consider including supine sleep position as a possible end point when analyzing effects on sleep quality and daytime vigilance.**

References

- [1] Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol.* 2009;8:464-74.
- [2] Mutch WJ, Smith WC, Scott RF. A screening and alerting questionnaire for parkinsonism. *Neuroepidemiology.* 1991;10:150-6.
- [3] Louter M, Munneke M, Bloem BR, Overeem S. Nocturnal hypokinesia and sleep quality in Parkinson's disease. *J Am Geriatr Soc.* 2012;60:1104-8.
- [4] Louter M, van Sloun RJ, Pevernagie DA, Arends JB, Cluitmans PJ, Bloem BR, et al. Subjectively impaired bed mobility in Parkinson disease affects sleep efficiency. *Sleep Med.* 2013;14:668-74.
- [5] Sommerauer M, Imbach LL, Jarallah M, Baumann CR, Valko PO. Diminished event-related cortical arousals and altered heart rate response in Parkinson's disease. *Mov Disord.* 2015; 30:866-70.
- [6] Brown DL, Lisabeth LD, Zupancic MJ, Concannon M, Martin C, Chervin RD. High prevalence of supine sleep in ischemic stroke patients. *Stroke.* 2008;39:2511-4.
- [7] Svatikova A, Chervin RD, Wing JJ, Sanchez BN, Migda EM, Brown DL. Positional therapy in ischemic stroke patients with obstructive sleep apnea. *Sleep Med.* 2011;12:262-6.
- [8] Oksenberg A, Silverberg DS, Arons E, Radwan H. The sleep supine position has a major effect on optimal nasal continuous positive airway pressure : relationship with rapid eye movements and non-rapid eye movements sleep, body mass index, respiratory disturbance index, and age. *Chest.* 1999;116:1000-6.
- [9] Oksenberg A, Khamaysi I, Silverberg DS. Apnoea characteristics across the night in severe obstructive sleep apnoea: influence of body posture. *Eur Respir J.* 2001;18:340-6.

- [10] Neikrug AB, Liu L, Avanzino JA, Maglione JE, Natarajan L, Bradley L, et al. Continuous positive airway pressure improves sleep and daytime sleepiness in patients with Parkinson disease and sleep apnea. *Sleep*. 2014;37:177-85.
- [11] van Maanen JP, de Vries N. Long-term effectiveness and compliance of positional therapy with the sleep position trainer in the treatment of positional obstructive sleep apnea syndrome. *Sleep*. 2014;37:1209-15.
- [12] De Koninck J, Gagnon P, Lallier S. Sleep positions in the young adult and their relationship with the subjective quality of sleep. *Sleep*. 1983;6:52-9.

Table 1: Demographic, clinical and polysomnographic findings in PD patients and control subjects.

	PD patients (n=80)	Control subjects (n=80)	<i>p</i>
Matched characteristics			
Age [y]	62.9 ± 8.6	63.4 ± 12.3	0.47
Sex, female [n]	26	25	1.00
Body mass index	25.9 ± 4.4	26.3 ± 3.9	0.49
Apnea-hypopnea index [/h]	9.8 ± 15.4	10.5 ± 13.3	0.16
Clinical findings			
Epworth sleepiness scale	9.6 ± 4.4	6.4 ± 6.2	0.001
Epworth sleepiness scale ≥10	47%	36%	0.20
PD characteristics			
Disease duration [y]	8.7 ± 6.5		
Unified Parkinson's Disease Rating Scale III	24.7 ± 12.7		
Hoehn and Yahr Stage	2.4 ± 0.8		
Akinetic-rigid disease type [%]	74.4		
Tremor-dominant disease type [%]	19.2		
Total levodopa dosage equivalent [mg]	551 ± 402		
Polysomnographic findings			
Total sleep time [min]	321 ± 84	334 ± 79	0.20
Sleep latency [min]	35 ± 54	35 ± 45	0.53
Sleep efficiency [%]	76 ± 16	77 ± 16	0.57
Wake [%]	24 ± 16	24 ± 16	0.84
Rapid eye movement (REM) sleep [%]	14 ± 7	12 ± 7	0.14
Non-REM sleep 1 [%]	13 ± 8	14 ± 8	0.36
Non-REM sleep 2 [%]	37 ± 12	36 ± 10	0.85
Slow wave sleep [%]	12 ± 9	14 ± 8	0.20
Periodic limb movements in sleep [/h]	12 ± 27	17 ± 28	0.04
Sleep position characteristics			
Supine sleep position [%]	62.2 ± 32.9	34.2 ± 28.5	<0.001
Lateral sleep position [%]	33.4 ± 30.5	60.0 ± 27.7	<0.001
Prone sleep position [%]	3.6 ± 12.5	4.9 ± 12.8	0.05
Transition index [/h]	4.2 ± 7.1	4.5 ± 7.2	0.04

Figure 1 **Prevalence of supine sleep position in PD patients and control subjects and effects on daytime sleepiness**

A: Frequency and distribution in supine sleep position percentages differed significantly between Parkinson's disease (PD) patients and control subjects (Co) ($p < 0.001$).

B: PD patients (**black bars**) with excessive daytime sleepiness (EDS) had more supine sleep than those without EDS ($p = 0.001$). Control subjects (**grey bars**) did not differ in this respect ($p = 0.07$). **Error bars indicate standard deviations.**

C: PD patients with longer disease duration spent more time in supine body position ($r = 0.391$, $p < 0.001$).

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**Bound to supine sleep:
Parkinson's disease and the impact of nocturnal immobility**

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Abstract

Background: Impaired nocturnal mobility is a well-known problem in Parkinson's disease (PD), and clinical experience suggests a predominance of supine body position during sleep. However, this assumption – and potential consequences – still awaits objective validation by a polysomnography-based and adequately controlled study.

Methods: Clinical and polysomnographical analysis of 80 consecutive PD patients and 80 control subjects carefully matched for age, sex, body mass index and apnea-hypopnea index.

Results: PD patients slept twice as much in supine position than control subjects ($62.2\pm 32.9\%$ vs. $34.2\pm 28.5\%$, $p<0.001$). In PD, but not in control subjects, more supine sleep correlated with fewer changes in body position ($\rho=-0.434$, $p<0.001$). Longer PD disease duration was an independent predictor of more supine sleep in multiple linear regression analysis ($\beta=0.389$, $p<0.001$); conversely, more supine sleep was associated with higher apnea-hypopnea index and daytime sleepiness.

Conclusions: We confirmed that supine sleep is common in PD, and increases with longer disease duration. Our findings indicate that supine sleep may contribute to the overall disease burden by deteriorating sleep-disordered breathing and daytime vigilance.

Key Words: Parkinson's disease, nocturnal immobility, supine, sleep position, sleepiness, sleep-disordered breathing

Introduction

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3 A myriad of motor and non-motor symptoms add to the overall clinical burden in
4 Parkinson's disease (PD), and sleep-wake disturbances are among the most frequent and
5 significant contributors [1]. Patients often complain about difficulty turning in bed and claim to
6 sleep mostly in supine position. However, whether PD patients do sleep more in supine
7 position is unclear, because researchers have rarely analyzed the distribution of sleep
8 positions in PD. In contrast, nocturnal immobility is recognized as a common disease feature,
9 and an item pertaining to this symptom has been included in several clinical scales, including
10 the Parkinson's Disease Quality of Life Questionnaire and the old and new versions of the
11 Unified Parkinson's Disease Rating Scale [2].
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24 Few studies reported adverse effects of nocturnal immobility on sleep quality in PD,
25 whereas a recent polysomnography-based study failed to detect differences in the
26 distribution of sleep positions in PD patients with and without subjectively impaired bed
27 mobility [3, 4]. Overall, most of these studies were based only on subjective complaints and
28 lacked appropriate control groups.
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35 Thus, in the present study we aimed 1) at objectively comparing the distribution of
36 distinct sleep positions and the frequency of body position changes between PD patients and
37 carefully matched control subjects, and 2) at identifying clinical correlates and predictors of
38 supine sleep position in PD.
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Patients and methods

Subjects, clinical assessment and matching procedure

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56 This was a retrospective chart review. In a first step, we selected 119 consecutive PD
57 patients who received whole-night video-polysomnography (PSG) as an integral diagnostic
58 procedure between 2004 and 2009. In order to compare their data on sleep positions and
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1 nocturnal mobility to an adequate control group, we considered 248 consecutive non-
2 neurological patients from our data base, in which PSG was performed during the same time
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4 for suspected sleep disorders. We used propensity score matching as a rater-independent
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6 and unbiased method to generate two groups accurately matched for age, sex, body mass
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8 index (BMI, body mass divided by the square of individual's height) and apnea-hypopnea
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10 index (AHI, number of apnea and hypopnea events per hour of sleep) [5]. By this means, we
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12 eventually included 80 PD patients and 80 matched control subjects.
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16 Diagnostic procedure, clinical assessment and calculation of levodopa dose
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18 equivalents (LDE) are identical to previous studies [5]. We ascertained sleepiness using the
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20 Epworth Sleepiness Scale (ESS), with scores of ≥ 10 indicating excessive daytime sleepiness
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22 (EDS). The study was approved by the local Ethics Committee.
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25 26 27 *Polysomnography assessment*

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29 All patients had overnight PSG recordings, using a multi-channel recording system
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31 (Embla, RemLogicTM). Scoring of sleep stages and respiratory events was performed visually
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33 using standardized criteria [5]. Apnea was defined by a cessation of oro-nasal airflow longer
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35 than 10 seconds, and hypopnea by a reduction of oro-nasal airflow by at least 50% lasting
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37 more than 10 seconds and accompanied by an arousal or SaO₂ reduction of $\geq 3\%$. A body
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39 position sensor was attached by an elastic velcro strap at the level of the lower sternum and
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41 recognized distinct body positions by virtue of different voltage outputs. This allowed for
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43 automatic detection of the following four body positions: supine, right, left, and prone. In
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45 theory, the sensor would also register upright body position, but our subjects did not sleep in
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47 this position. We ensured adequate monitoring by comparing patient video and body position
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49 recording. As an objective measure of nocturnal immobility we used the number of changes
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51 between distinct body positions per hour.
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58 59 *Statistical analysis*

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Statistical analyses were performed using SPSS (version 21). Group data were described by means and standard deviations. For normally distributed data, we used Student's *t*-test and for non-parametric data the Mann-Whitney *U*-test. Chi-square test was used for nominal data. We calculated Pearson's *r* for correlation analysis of normally and Spearman-rho for non-normally distributed data. Stepwise multiple linear regression analysis was done including age, sex, body mass index, disease duration, Hoehn and Yahr stage, disease type, use of dopamine agonist, use of long acting dopaminergic medication, and total LDE as independent variables. Significance was accepted at $p < 0.05$.

Results

Clinical and polysomnographic findings

Demographic, clinical and polysomnographic findings are summarized in **Table 1**. PD patients slept roughly twice as much in supine position ($62.2 \pm 32.9\%$ vs. $34.2 \pm 28.5\%$, $p < 0.001$), and had fewer body position changes than controls ($4.2 \pm 7.1/h$ vs. $4.5 \pm 7.2/h$, $p = 0.04$). Lying most in supine position during sleep ($\geq 90\%$) was more common among PD patients than controls (32% vs. 6% , $p < 0.001$) (**Fig. 1A**). More supine sleep correlated with fewer body position changes in PD ($\rho = -0.434$, $p < 0.001$) but not in controls ($\rho = -0.200$, $p = 0.08$).

Correlates of supine sleep position

PD patients with EDS spent more time in supine position than those without EDS ($51.0 \pm 35.2\%$ vs. $75.4 \pm 25.0\%$, $p = 0.001$), whereas controls did not differ in this respect ($30.9 \pm 31.1\%$ vs. $38.8 \pm 23.1\%$, $p = 0.07$) (**Fig. 1B**). In PD, but not in controls, multiple linear regression analysis revealed that more supine sleep was independently associated with higher AHI ($\beta = 0.260$, $p = 0.015$ and age as second significant associate: $\beta = 0.349$, $p = 0.001$). Periodic limb movements in sleep did not correlate with supine position in either group.

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2 Likewise, supine sleep position did not correlate with any sleep stage, sleep efficiency or
3 arousal index, and group comparison did not reveal any difference in supine sleep between
4 PD patients with various disease type (akinetic-rigid, tremor-dominant, equal). Finally, the
5 use of dopamine agonists had no impact on total amount of supine position, and correlation
6 analysis between LDE of dopamine agonists and of long-acting dopaminergic drugs at
7 bedtime with supine position did not demonstrate any significant associations.
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14 *Predictors of supine sleep in PD*

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18 Linear regression analysis identified longer disease duration to be independently
19 associated with more supine sleep in PD ($\beta=0.389$, $p<0.001$) (**Fig. 1C**).
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27 **Discussion**

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31 Compared to carefully matched control subjects, PD patients slept almost twice as
32 much in supine position and less often changed nocturnal body posture. In addition, we
33 identified longer PD duration as independent predictor of more supine sleep. These results
34 have been expected, and may be regarded as inevitable consequences of nocturnal
35 immobility and axial rigidity. However, more than confirming a commonplace, our study
36 suggests relevant clinical implications of this predominance for supine sleep position, as
37 indicated by the association with increased severity of sleep-disordered breathing and
38 excessive daytime sleepiness.
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50 Our knowledge about the distribution of sleep positions in general is limited, but the
51 clinical impact of certain sleep positions has been acutely revealed by the discovery that
52 prone sleep position is associated with a more than threefold increased risk of sudden infant
53 death syndrome. Polysomnographic studies demonstrated that up to two thirds of patients
54 with acute stroke spend the first nights nearly entirely in supine position, while the magnitude
55 of supine sleep is likely to diminish following recovery [6]. In stroke patients, supine position
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contributes to sleep disordered breathing (SDB) and impacts functional outcome and mortality. Application of continuous positive airway pressure (CPAP) or positional treatment is therefore increasingly advocated [7].

In this line, our results and those of many other groups confirm that SDB is the most obvious problem caused by lying in supine position. Supine position increases the risk of upper airway collapses, causes more and longer apnoeic events, and necessitates a higher pressure from CPAP devices [8, 9]. Cheyne-Stokes respiration, obstructive and central SDB all ameliorate after changing from supine to lateral sleep position. Thus, our study indicates that sleep-related respiration in PD is similarly susceptible to the adverse effects of supine position. Although the contribution of SDB to daytime sleepiness has been questioned in PD, a recent randomized placebo-controlled study in PD patients with SDB demonstrated a significant improvement of both nocturnal sleep consolidation and objective daytime sleepiness in those receiving CPAP treatment [10]. Thus, feasibility and efficacy of positional treatment – already a well established alternative to CPAP in patients with positional SDB [11] – need to be evaluated also in PD patients.

On the other hand, it is unlikely that increased SDB severity represents the sole explanation for the negative association between supine sleep and daytime sleepiness. Even healthy people with poor sleep quality spend more time in supine position than good sleepers [12], and this observation suggests a mutual influence of supine position and poor sleep quality. In our study, however, we failed to demonstrate any correlation between polysomnographic measures of sleep consolidation and amount of supine position, which is in contrast to previous studies reporting an adverse impact of nocturnal immobility on subjective sleep quality.

Our retrospective study has several limitations. Primarily, a selection bias cannot be ruled out, and polysomnography may have been differentially motivated in PD patients and controls. However, we believe we substantially reduced this risk by using a rater-independent propensity score matching with inclusion of four major variables. Moreover, due to the high

1 prevalence of sleep-wake disturbances in PD and their possible diagnostic, therapeutic and
2 medico-legal implications, polysomnography has become an integral diagnostic procedure in
3 PD patients in our department, and has thus been done largely independent of any
4 suspected sleep disorder. Nevertheless, the potential influence on sleep position of
5 additional features, including orthopedic comorbidity, smoking habits or nocturia, may have
6 escaped our attention. Finally, since our study is purely observational, future work is required
7 to confirm the clinical benefit obtained by decreased supine sleep, e.g. by using positioning
8 device techniques such as tennis ball T-shirt or filled backpack.
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10 Overall, our study emphasizes the need for treatment strategies that help improving
11 nocturnal mobility and liberating PD patients from their excessive supine recumbency.
12 Studies evaluating the effects of long-lasting dopaminergic drugs, continuous dopaminergic
13 stimulation or deep brain stimulation should therefore consider including supine sleep
14 position as a possible end point when analyzing effects on sleep quality and daytime
15 vigilance.
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References

- 1
2
3 [1] Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic
4 pathophysiology and treatment. *Lancet Neurol.* 2009;8:464-74.
5
6
7
8
9 [2] Mutch WJ, Smith WC, Scott RF. A screening and alerting questionnaire for parkinsonism.
10 *Neuroepidemiology.* 1991;10:150-6.
11
12
13 [3] Louter M, Munneke M, Bloem BR, Overeem S. Nocturnal hypokinesia and sleep quality in
14 Parkinson's disease. *J Am Geriatr Soc.* 2012;60:1104-8.
15
16
17
18
19 [4] Louter M, van Sloun RJ, Pevernagie DA, Arends JB, Cluitmans PJ, Bloem BR, et al.
20 Subjectively impaired bed mobility in Parkinson disease affects sleep efficiency. *Sleep*
21 *Med.* 2013;14:668-74.
22
23
24
25
26
27 [5] Sommerauer M, Imbach LL, Jarallah M, Baumann CR, Valko PO. Diminished event-
28 related cortical arousals and altered heart rate response in Parkinson's disease. *Mov*
29 *Disord.* 2015; 30:866-70.
30
31
32
33
34
35 [6] Brown DL, Lisabeth LD, Zupancic MJ, Concannon M, Martin C, Chervin RD. High
36 prevalence of supine sleep in ischemic stroke patients. *Stroke.* 2008;39:2511-4.
37
38
39
40
41 [7] Svatikova A, Chervin RD, Wing JJ, Sanchez BN, Migda EM, Brown DL. Positional therapy
42 in ischemic stroke patients with obstructive sleep apnea. *Sleep Med.* 2011;12:262-6.
43
44
45
46 [8] Oksenberg A, Silverberg DS, Arons E, Radwan H. The sleep supine position has a major
47 effect on optimal nasal continuous positive airway pressure : relationship with rapid eye
48 movements and non-rapid eye movements sleep, body mass index, respiratory
49 disturbance index, and age. *Chest.* 1999;116:1000-6.
50
51
52
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54
55
56 [9] Oksenberg A, Khamaysi I, Silverberg DS. Apnoea characteristics across the night in
57 severe obstructive sleep apnoea: influence of body posture. *Eur Respir J.* 2001;18:340-
58
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- [10] Neikrug AB, Liu L, Avanzino JA, Maglione JE, Natarajan L, Bradley L, et al. Continuous positive airway pressure improves sleep and daytime sleepiness in patients with Parkinson disease and sleep apnea. *Sleep*. 2014;37:177-85.
- [11] van Maanen JP, de Vries N. Long-term effectiveness and compliance of positional therapy with the sleep position trainer in the treatment of positional obstructive sleep apnea syndrome. *Sleep*. 2014;37:1209-15.
- [12] De Koninck J, Gagnon P, Lallier S. Sleep positions in the young adult and their relationship with the subjective quality of sleep. *Sleep*. 1983;6:52-9.

Table 1: Demographic, clinical and polysomnographic findings in PD patients and control subjects.

	PD patients (n=80)	Control subjects (n=80)	<i>p</i>
Matched characteristics			
Age [y]	62.9 ± 8.6	63.4 ± 12.3	0.47
Sex, female [n]	26	25	1.00
Body mass index	25.9 ± 4.4	26.3 ± 3.9	0.49
Apnea-hypopnea index [/h]	9.8 ± 15.4	10.5 ± 13.3	0.16
Clinical findings			
Epworth sleepiness scale	9.6 ± 4.4	6.4 ± 6.2	0.001
Epworth sleepiness scale ≥10	47%	36%	0.20
PD characteristics			
Disease duration [y]	8.7 ± 6.5		
Unified Parkinson's Disease Rating Scale III	24.7 ± 12.7		
Hoehn and Yahr Stage	2.4 ± 0.8		
Akinetic-rigid disease type [%]	74.4		
Tremor-dominant disease type [%]	19.2		
Total levodopa dosage equivalent [mg]	551 ± 402		
Polysomnographic findings			
Total sleep time [min]	321 ± 84	334 ± 79	0.20
Sleep latency [min]	35 ± 54	35 ± 45	0.53
Sleep efficiency [%]	76 ± 16	77 ± 16	0.57
Wake [%]	24 ± 16	24 ± 16	0.84
Rapid eye movement (REM) sleep [%]	14 ± 7	12 ± 7	0.14
Non-REM sleep 1 [%]	13 ± 8	14 ± 8	0.36
Non-REM sleep 2 [%]	37 ± 12	36 ± 10	0.85
Slow wave sleep [%]	12 ± 9	14 ± 8	0.20
Periodic limb movements in sleep [/h]	12 ± 27	17 ± 28	0.04
Sleep position characteristics			
Supine sleep position [%]	62.2 ± 32.9	34.2 ± 28.5	<0.001
Lateral sleep position [%]	33.4 ± 30.5	60.0 ± 27.7	<0.001
Prone sleep position [%]	3.6 ± 12.5	4.9 ± 12.8	0.05
Transition index [/h]	4.2 ± 7.1	4.5 ± 7.2	0.04

Figure 1 **Prevalence of supine sleep position in PD patients and control subjects and effects on daytime sleepiness**

A: Frequency and distribution in supine sleep position percentages differed significantly between Parkinson's disease (PD) patients and control subjects (Co) ($p < 0.001$).

B: PD patients (black bars) with excessive daytime sleepiness (EDS) had more supine sleep than those without EDS ($p = 0.001$). Control subjects (grey bars) did not differ in this respect ($p = 0.07$). Error bars indicate standard deviations.

C: PD patients with longer disease duration spent more time in supine body position ($r = 0.391$, $p < 0.001$).

