Sleep Quality and Associated Daytime Consequences in Patients with Idiopathic Pulmonary Fibrosis

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Key Words

Idiopathic pulmonary fibrosis • Pittsburgh Sleep Quality Index • Functional Outcomes of Sleep Questionnaire • Fatigue Severity Scale • Polysomnography

Abstract

Objective: The aim of this study was to describe sleep quality and associated daytime consequences in idiopathic pulmonary fibrosis (IPF). **Subjects and Methods:** Fifteen patients with IPF and 15 control subjects matched on age and anthropometric variables were included in the study. Sleep quality and its daytime consequences were assessed by clinical interview, the Pittsburgh Sleep Quality Index (PSQI), the Functional Outcomes in Sleep Questionnaire (FOSQ), the Fatigue Severity Scale (FSS), the Epworth Sleepiness Scale and attended all-night polysomnography. **Results:** Polysomnography revealed a decrease in sleep efficiency and slow wave sleep, and an increase in stage 1 sleep and arousal index in IPF patients compared to controls. Daytime tachypnea persisted during sleep. Oxygen saturation below 90% was observed during 34.3 ± 37.3% of the total sleep time (TST). Quality of sleep and daytime function were moderately to significantly impaired based on the PSQI and FOSQ. The total FOSQ score was negatively correlated with TST with oxygen saturation below 90% ($p = 0.01$, $r = -0.62$). FSS scores were correlated with TST at oxygen saturation below

90% and mean oxygen saturation during sleep ($p = 0.002$, $r = 0.74$, and $p = 0.007$, $r = -0.66$, respectively). **Conclusions:** Our data suggest significant sleep disruption and consequent impairment of physical and social functioning in patients with IPF. In the absence of effective treatments for IPF, the improvement of sleep quality should be a primary therapeutic goal.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common form of the idiopathic interstitial pneumonias. It is thought to affect about 30 persons per 100,000 people in the general population and perhaps as many as 175 per 100,000 people in the age group of 75 years and above. The outlook for patients with IPF is poor; the symptoms of breathlessness and cough are usually progressive and about 50% of patients die within 3 years of diagnosis [1–3]. The response to currently recommended treatments in terms of survival is disappointing [1].

Due to a paucity of studies in patients with a confirmed diagnosis of IPF, significant gaps remain in our understanding of how IPF affects the quality of sleep. Previous studies in patients with interstitial lung diseases, including some patients with IPF, have shown noctur-

nal hypoxemia, sleep fragmentation, increase in stage 1 and reduction in rapid eye movement (REM) sleep in the presence of severe lung fibrosis [4, 5]. To the best of our knowledge there are no studies investigating quality of sleep based on clinical (interview, sleep questionnaires) and polysomnographic data.

Due to the rapidly progressive nature of the disease, sleep quality impairment may be markedly underdiagnosed in IPF patients. The aim of this study was to identify sleep quality impairment and associated daytime consequences in a pure IPF population. Early recognition and treatment of such problems may reduce morbidity and improve quality of life in these patients.

Subjects and Methods

Subjects

Fifteen patients with IPF (11 male and 4 female, median age 66.3 ± 9.5 , range 42–80 years) evaluated at the Pulmonary Department of Sismanoglion General District Hospital during the period of February 2006 to December 2007 participated. Patients were eligible for the study if they had histologically proven IPF (usual interstitial pneumonia) on surgical lung biopsy or, in the absence of surgical biopsy, fulfillment of the recent American Thoracic Society and European Respiratory Society criteria [1]. None of the patients were under treatment for IPF or nocturnal oxygen therapy. Three of the included IPF patients had arterial hypertension, 2 diabetes and 2 coronary disease. For comparison and statistical evaluation of results, 15 age- and body mass index (BMI)-matched normal subjects formed the control group (11 males and 4 females, median age 62.7 ± 9.9 , range 44–78 years). The control subjects did not have any history of pulmonary disease, were not receiving any medication which could affect sleep quality, and had normal spirometry findings and chest radiography.

The patients had an interview by a sleep specialist and completed the Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Index (PSQI), the Functional Outcomes in Sleep Questionnaire (FOSQ) and the Fatigue Severity Scale (FSS). Overnight polysomnography (PSG) was performed in all subjects as part of the research protocol, as none of the included subjects had an indication for a PSG according to the currently existing criteria.

The Scientific Ethics Committee of Sismanoglio Hospital approved of the study protocol, and all participants gave informed written consent.

Methods

Polysomnography (PSG). An attended all-night PSG was performed according to established standards [6]. Multichannel recordings of the electroencephalogram (central and occipital), electro-oculogram, electromyogram, oronasal flow (by thermistor and nasal transducer), respiratory effort (by abdominal and thoracic strain gauges), oxygen saturation (pulse oximetry), snoring and body position were recorded on a computerized workstation (Alice 5, Respironics). Studies were scored in 30-second epochs following the criteria for sleep staging proposed by

Rechtschaffen and Kales [7]. The definitions of apneas and hypopneas were based on standard criteria [6]. An obstructive apnea was defined as a reduction in airflow $>90\%$ lasting at least 10 s in which there was evidence of persistent respiratory effort. A central apnea was defined as a reduction in airflow $>90\%$ lasting at least 10 s in which there was no evidence of respiratory effort. A hypopnea was defined as a reduction in airflow by 50%, with duration of at least 10 s or a reduction of airflow or respiratory effort by 30% for more than 10 s, accompanied by an EEG arousal and/or a $\geq 3\%$ oxygen desaturation. Arousals were defined as a change in EEG activity from a slower background frequency for at least 3 s [8]. Obstructive sleep apnea was considered mild if the apnea-hypopnea index was ≥ 5 per hour but <15 per hour, moderate if ≥ 15 per hour but <30 per hour, and severe if ≥ 30 per hour [7, 9].

Pulmonary Function Testing. Spirometry (forced expiratory volume in 1 s, FEV₁; forced vital capacity, FVC; FEV₁/FVC ratio), measurement of static lung volumes (total lung capacity, residual volume by body box plethysmography) and measurement of diffusing capacity (diffusing capacity of the lung for carbon monoxide by the single-breath technique) were performed (Vmax 22, SensorMedics, Yorba Linda, Calif., USA) with the patient in the seated position according to approved standards [10].

Functional Outcomes of Sleep Questionnaire (FOSQ). The FOSQ is a 30-item self-report questionnaire designed to measure the impact of excessive sleepiness on multiple activities of daily living. It comprised five dimensions: activity level, vigilance, intimacy and sexual relationships, general productivity and social outcome [11–13]. Each of these dimensions was rated on a 4-point scale. The lower the score, the greater the impact of sleepiness on daily activities.

Pittsburgh Sleep Quality Index (PSQI). Subjective assessment of sleep was determined using the PSQI. The PSQI questionnaire is a standard instrument that had been validated as differentiating 'poor' from 'good' sleep. It assessed sleep disturbances along seven dimensions: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. Each of these dimensions was rated on a 4-point scale (0–3, with 3 indicating more profound effect) and summed to give a global score. The higher the score, the greater the negative impact on sleep quality. A global score ≥ 5 indicated 'poor' sleep [14–16].

Epworth Sleepiness Scale (ESS). The ESS is currently the most used subjective test of daytime sleepiness in clinical practice. It is a simple self-administered eight-item questionnaire measuring the risk of falling asleep in eight specific situations that are commonly met. A score <10 is considered as normal. The higher the score (from 10 to 24), the greater the reported subjective daytime sleepiness [17].

Fatigue Severity Scale (FSS). In the FSS, individuals had to rate their agreement (range 1–7) with nine statements concerning the severity, frequency and impact of fatigue on daily life (physical functioning, exercise and work, family or social life). A total score of less than 36 was considered as normal. A score above that limit (maximum score 81) was suggestive of a significant negative impact of fatigue on daily life activities [18, 19].

Statistical Analysis. All data are given as mean $\pm$ standard deviation (SD). Data were examined for normal distribution using the Kolmogorov-Smirnov test. For normally distributed values (demographic, polysomnography, FOSQ, PSQI, FSS and ESS

Table 1. Demographic and pulmonary function testing data of study population

Variables	IPF patients	Controls	p value
Subjects	15	15	
Gender, male/female	11/4	11/4	
Age, years	66.3 ± 9.5	62.7 ± 9.9	0.33
BMI	27.2 ± 4.2	28.3 ± 5.1	0.54
FEV ₁ , % predicted	74.3 ± 17.4	87.1 ± 10.5	0.02
FVC, % predicted	77.4 ± 21.2	89.2 ± 9.3	0.04
FEV ₁ /FVC	94.1 ± 13.1	87.2 ± 9.3	0.1
TLC, % predicted	65.6 ± 15.7	NA	
DLCO, % predicted	56.3 ± 17.8	NA	
Resting O ₂ saturation during wakefulness, %	93.4 ± 3.5	95.2 ± 2.2	0.03

TLC = Total lung capacity; DLCO = diffusing capacity of the lung for carbon monoxide; % predicted = percentage of the predicted value; NA = not available. All data are given as mean ± SD.

data) we used the unpaired t test for statistical comparison. The Pearson correlation coefficient was employed to examine the relation between FSS and FOSQ scores and total sleep time (TST) with oxygen saturation below 90% or mean oxygen saturation during daytime or sleep (normally distributed data). A p value <0.05 was considered as statistically significant.

Results

Demographic and pulmonary function testing data are summarized in table 1. There was a statistically significant difference between IPF patients and controls regarding FEV₁ (p = 0.02), FVC (p = 0.04) and resting oxygen saturation (p = 0.03). However there was no difference between these two groups regarding age and BMI.

Clinical Interview

During the clinical interview the most common complaint was daytime fatigue, reported in all cases and also confirmed by the FSS scores. Excessive daytime sleepiness, snoring, insomnia and witnessed apneas were reported in 20, 40, 46.6 and 13.3% of the cases, respectively.

Sleep Architecture – Respiratory Monitoring

All IPF patients had tachypnea during wakefulness and sleep. The mean respiratory rate during sleep was unchanged compared to wakefulness (20.6 ± 3.9 vs. 22.9 ± 4.7 breaths/min, respectively, p = 0.13).

Table 2. PSG features in IPF patients and controls

Variable	IPF patients	Controls	p value
TST, min	290.5 ± 82.2	319.8 ± 38.4	0.23
Sleep efficiency, %	64.9 ± 17.8	78.2 ± 9.1	0.02
Arousal index	25.6 ± 14.6	12.9 ± 4.5	0.003
Stage 1, %	18.7 ± 10.2	7.4 ± 2.8	0.0003
Stage 2, %	59.5 ± 8.2	60 ± 12.5	0.9
Slow wave sleep, %	10.4 ± 11.6	16.5 ± 6.9	0.05
REM sleep, %	11.3 ± 5.9	14.9 ± 7.2	0.15
Apnea-hypopnea index	9.2 ± 6.7	7.1 ± 4.5	0.31
O ₂ saturation during sleep, %			
Mean	91.6 ± 3.8	95.3 ± 1.9	0.003
Nadir	81 ± 8.2	91.3 ± 2.9	<0.0001
TST with O ₂ saturation <90%, %	34.3 ± 37.3	0.9 ± 1.2	0.002

Data are given as mean ± SD.

On PSG we noted statistically significant differences in sleep efficiency, stage 1 sleep, slow wave sleep, arousal index, mean and nadir oxygen saturation during sleep and TST (%) with oxygen saturation below 90% between IPF patients and controls (table 2).

No statistically significant differences were found in the apnea-hypopnea index in IPF patients compared to controls (9.2 ± 6.7 vs. 7.1 ± 4.5, p = 0.31, respectively).

FOSQ, PSQI, FSS and ESS Scores

The FOSQ total, activity level, vigilance, intimacy, general productivity and social outcome scores were 13.2 ± 2.9 vs. 17.1 ± 0.9 (p = 0.0001), 2.9 ± 0.6 vs. 3.5 ± 0.4 (p = 0.004), 2.3 ± 0.9 vs. 3.1 ± 0.3 (p = 0.008), 3.1 ± 0.6 vs. 3.5 ± 0.2 (p = 0.02) and 2.9 ± 0.9 vs. 3.6 ± 0.4 (p = 0.02) in IPF patients and control group subjects, respectively (total score normal values: 16.33–19.41 and normal values of the five dimensions 3.34–3.38, 3.16–3.84, 3.84–4, 3.38–3.9, and 3.57–4). The total FOSQ score and its five dimension scores were suggestive of daytime dysfunction in IPF patients compared to controls.

IPF patients' FSS scores were suggestive of daytime fatigue with statistically significant differences compared to controls (41.5 ± 13.9 vs. 25.7 ± 7.9, respectively, p = 0.002).

PSQI scores in IPF patients were suggestive of 'poor' sleep and showed statistically significant differences compared to the control group (9.8 ± 2.3 vs. 6.4 ± 2.9, respectively, p = 0.001).

Fig. 1. Correlation of FOSQ total score and TST (%) with oxygen saturation <90%.

Fig. 2. Correlation of FSS score and TST (%) with oxygen saturation <90%.

ESS scores were higher in IPF patients (7.6 ± 2.8) compared to controls (4.9 ± 3.9), although the scores in both groups were within the normal range (0–10).

Correlation between FOSQ, PSQI, FSS and PSG or Daytime Oxygenation Parameters

The total FOSQ score was negatively correlated with TST (%) of oxygen saturation below 90% ($p = 0.01$, $r = -0.62$; fig. 1). No statistically significant correlation was observed between total FOSQ score and mean oxygen saturation during sleep.

FSS scores were correlated with TST of oxygen saturation below 90% and mean oxygen saturation during sleep ($p = 0.002$, $r = 0.74$, and $p = 0.007$, $r = -0.66$, respectively; fig. 2, 3). No statistically significant correlations were observed between total FOSQ and FSS scores and mean daytime oxygen saturation at rest.

In addition, PSQI scores showed no statistically significant correlations with nocturnal oxygenation parameters.

Discussion

This is the first study investigating sleep quality in IPF patients using attended all-night PSG and sleep quality questionnaires. Our data suggest significant sleep disruption and impairment of physical and social functioning in these patients.

Fig. 3. Correlation of FSS score and mean oxygen saturation (%) during sleep.

Previous studies found a decrease in REM sleep, marked sleep fragmentation and nocturnal hypoxemia in patients with interstitial lung disease of various etiologies (including some patients with IPF) [4, 5]. Nocturnal hypoxemia and its negative impact on health-related quality of life was also described by Clark et al. [20] in patients with IPF and pulmonary fibrosis secondary to connective tissue disorders, although sleep monitoring was performed only with overnight oximetry and not attended PSG.

The IPF terminology and the criteria for the diagnosis of IPF have been changed during the last few years and now there are strict criteria to diagnose this condition [1, 2]. Our study was designed to investigate sleep disturbances only in patients with a confirmed diagnosis of IPF, a disease with a totally different pathology and course compared to other interstitial lung diseases.

According to our data a significant sleep disruption was observed in IPF patients, with alterations in sleep macroarchitecture (decrease in stage 1 and slow wave sleep) and microarchitecture (sleep fragmentation due to an increased arousal index). An interesting feature was the sleep breathing pattern of these patients, namely the maintenance of daytime tachypnea during sleep. This finding was observed in all patients, independently of disease severity. Normal sleep is associated with a reduction in minute ventilation due to a decrease in the tidal volume and respiratory frequency. The maintenance of increased respiratory rate during sleep in IPF patients suggested that reflexes causing the rapid shallow breathing during wakefulness are active during the sleep phase as well [21–24].

Nocturnal hypoxemia parameters (mean oxygen saturation and TST % with oxygen saturation below 90%) showed a significant correlation with FSS scores. Daytime fatigue was the most common and probably the most disabling clinical symptom in our patients. Nocturnal hypoxemia and alterations in sleep macro- and microarchitecture might represent two crucial etiologic factors for daytime fatigue.

FOSQ and PSQI showed significant daytime impairment and poor sleep quality, respectively. The total FOSQ score was negatively correlated with TST of oxygen saturation below 90%. Based on these features, nocturnal hypoxemia appears to be associated with a reduction in energy levels and impairment of social and physical functioning. A ‘poor’ sleep quality and its consequences in daytime function and overall quality of life may be mark-

edly underdiagnosed in IPF patients. Despite growing awareness for the significance of sleep disturbances among healthcare providers, we suspect that treating physicians may defer sleep interview and testing in IPF patients as this disease is characterized by such a rapidly progressive course leading them to focus on more acute problems, such as dyspnea and limitations in daily activities. On the other hand the early recognition and treatment of sleep disturbances in these patients might be a primary goal since there is no effective treatment for IPF so far.

Despite the limited number of IPF patients included in our study we believe that our data will help to raise awareness of the potential sleep abnormalities in these patients and the necessity for pharmacologic and/or behavioral treatment. In addition the observed association between nocturnal oxygen desaturation parameters and daytime functional and social factors may support the recommendation of supplemental oxygen during sleep in IPF patients. Although definitive studies related to criteria for nocturnal oxygen therapy in IPF patients are lacking, such a treatment may reduce morbidity and improve patient survival, especially regarding pulmonary hypertension and cor pulmonale as a result of nocturnal hypoxemia.

Conclusions

Our data suggest significant sleep disruption and consequent impairment of physical and social functioning in patients with IPF. Significant correlations were observed between measures of nocturnal oxygen saturation and daytime functional status. In the absence of effective treatments for IPF, early recognition and treatment of sleep disturbances should be a primary therapeutic goal.

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