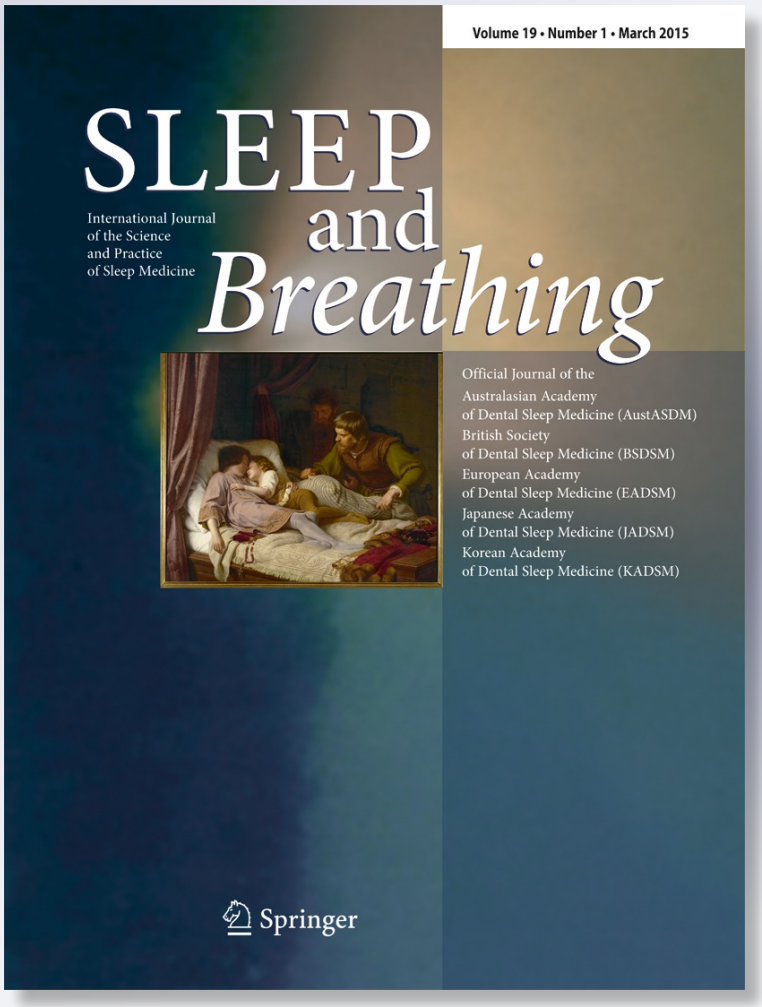
Obstructive sleep apnea should be treated in patients with idiopathic pulmonary fibrosis

Charalampos Mermigkis, Izolde Bouloukaki, Katerina Antoniou, Georgios Papadogiannis, Ioannis Giannarakis, Georgios Varouchakis, et

Sleep and Breathing
International Journal of the Science and Practice of Sleep Medicine

ISSN 1520-9512
Volume 19
Number 1

Sleep Breath (2015) 19:385-391
DOI 10.1007/s11325-014-1033-6



Springer

Sleep Breath (2015) 19:385–391
DOI 10.1007/s11325-014-1033-6

ORIGINAL ARTICLE

Obstructive sleep apnea should be treated in patients with idiopathic pulmonary fibrosis

Charalampos Mermigkis · Izolde Bouloukaki · Katerina Antoniou · Georgios Papadogiannis · Ioannis Giannarakis · Georgios Varouchakis · Nikolaos Siafakas · Sophia E. Schiza

Received: 8 April 2014 / Revised: 16 June 2014 / Accepted: 7 July 2014 / Published online: 16 July 2014

Abstract
Study objectives The most recent idiopathic pulmonary fibrosis (IPF) guidelines include obstructive sleep apnea (OSA) among the IPF-associated comorbidities. Furthermore, they recognize the paucity of studies related to continuous positive airway pressure(CPAP) treatment in this patient group and call for intensive research in this field. Our aim was to assess the effect of CPAP treatment on sleep and overall life quality parameters, morbidity, and mortality in IPF patients with OSA.
Methods Ninety-two treatment-naive, newly diagnosed, consecutive IPF patients underwent overnight-attended polysomnography (PSG). In those patients with an apnea-hypopnea index (AHI) of ≥15, therapy with CPAP was initiated. Patients were divided into poor and good CPAP compliance groups. All subjects completed multiple quality-of-life and sleep instruments before CPAP initiation and at 1 year after the start of CPAP treatment.
Results The good CPAP compliance group (37 patients) showed statistically significant improvement in all quality-of-life and sleep instruments after 1 year's CPAP treatment. The poor CPAP compliance group (18 patients) showed significant changes of smaller strength only in a minority of the used instruments. During the 24-month follow-up period after CPAP initiation, three patients from the CPAP poor compliance group died, whereas all patients from the good CPAP compliance group remained alive.
Conclusion Early OSA recognition and treatment is crucial in a fatal disease such as IPF. Effective CPAP treatment in IPF patients with OSA results in a significant improvement in daily living activities and quality of sleep and life. Good CPAP compliance appears to improve mortality.

Keywords Idiopathic pulmonary fibrosis · Obstructive sleep apnea syndrome · CPAP therapy · Quality of life and sleep · IPF mortality

Introduction

Idiopathic pulmonary fibrosis (IPF) is the most frequent type among the idiopathic interstitial pneumonias, but patients with IPF have a poor prognosis (median survival, 1.5 to 4 years) because no therapy has been demonstrated to be efficacious [1–3]. All patients will ultimately die from respiratory failure, complicated by comorbidities such as coronary vascular disease, pulmonary hypertension, gastroesophageal reflux disease (GERD), and obstructive sleep apnea (OSA) [1]. Recently published studies [4–7] report a high incidence of OSA in patients with IPF, and the effective treatment of OSA has been recognized as a primary goal [8–11].

Underlying OSA in these patients may be a reason for impaired sleep quality [4–6, 9] and may consequently have a negative influence on daily activities and overall quality of life [12–14]. In addition, underlying OSA may have a negative influence on the already high rate of IPF-related morbidity and mortality. A recently published statement [1] by the American

Charalampos Mermigkis and Izolde Bouloukaki made equal contributions to this work.

C. Mermigkis · I. Bouloukaki · K. Antoniou · G. Papadogiannis · I. Giannarakis · N. Siafakas · S. E. Schiza
Sleep Disorders Unit, Department of Thoracic Medicine, University General Hospital, Medical School of the University of Crete, Heraklion, Greece

C. Mermigkis
Sleep Disorders Center, 401 General Army Hospital, Athens, Greece

C. Mermigkis · G. Varouchakis
Sleep Disorders Center, Henry Dunant Hospital, Athens, Greece

C. Mermigkis (✉)
Thrakis 61A, Vrilissia, Athens, Greece
e-mail: mermigh@gmail.com

Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) included OSA as a comorbidity in IPF for the first time and simultaneously recognized the need for studies related to the effectiveness of continuous positive airway pressure (CPAP) treatment in this population. The only published study in this field [15] reported that 6 months of effective CPAP therapy in 12 IPF patients with moderate-to-severe OSA resulted in a statistically significant improvement in the Functional Outcomes of Sleep Questionnaire (FOSQ), a specific instrument that measures the impact of excessive sleepiness due to underlying sleep disorders on multiple daily life activities. There are no other studies with larger numbers of IPF patients with OSA treated with CPAP. In addition, there are no data related to changes in morbidity and mortality in IPF patients with OSA. A recent study [16] in newly diagnosed IPF patients who underwent an in-lab polysomnography (PSG) study showed that intermittent sleep oxygen desaturation exceeds that of maximal exercise and is associated with survival. As the main clinical implication of their findings, the authors suggested that CPAP could be used for the management of oxygen desaturation in patients with IPF, seeking a survival benefit. Only four of the patients included in that study were treated with CPAP, and they were all still alive when the study was reported.

The aim of our study was to obtain data related to the improvement of the quality of sleep and life after 1 year of CPAP treatment in a relatively large group of patients with OSA and IPF taking into account the rarity of this disease [1, 17]. Such data are crucial for the determination of therapeutic options in this population, as was demanded in the recently published guidelines for IPF. [1] In addition, our study provides the first data related to morbidity and mortality during a period of 24 months after CPAP initiation based on the medical files of included patients, which are followed by the responsible pulmonary departments

Materials and methods

Subjects

One hundred one consecutive patients with newly diagnosed IPF were prospectively recruited by three Greek pulmonary departments and were asked to participate in the study. Of those, 92 (63 males and 29 females, age 70.3±7.9 years) agreed to participate and were evaluated at the sleep centers of the above pulmonary departments. Patients were eligible for the study if they had histologically proven IPF (usual interstitial pneumonia (UIP)) on surgical lung biopsy or, in the absence of surgical biopsy, they fulfilled the recent ATS, ERS, and American College of Chest Physicians criteria for the diagnosis of IPF [1] namely: (a) Exclusion of other known causes of interstitial lung disease (ILD; e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity) and (b) The presence of a UIP pattern on high-resolution computed tomography (HRCT). None of the patients were under treatment for IPF or were receiving nocturnal supplemental oxygen therapy. More than half of the patients presented with GERD, and all of them received specific treatment after enrollment. This study was approved by the ethics committee of the participating institutes, and all participants gave their written informed consent prior to screening.

All included patients were interviewed by a sleep specialist. PSG was performed as part of the study protocol at the participating sleep centers and before the initiation of any therapy for IPF. Based on the PSG results, 60 of the 92 patients had features compatible with moderate-to-severe OSA (AHI, ≥15/h of sleep) and were offered CPAP treatment after a formal in-lab CPAP titration study. The patients filled out the instruments used to evaluate quality of sleep and life before CPAP initiation and at 1 year after the start of CPAP treatment.

Methods

Polysomnography

An attended all-night PSG was performed according to established standards [18]. Multichannel recordings of the electroencephalogram (frontal, central, and occipital), electrooculogram (EOG), electromyogram (EMG), oronasal flow (by thermistor and nasal pressure 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, Philips Respironics, USA). Studies were scored in 30-s epochs, following the new AASM criteria for sleep staging [18]. The definitions of apnea and hypopnea followed the new AASM standard criteria [18]. OSA was considered mild if the AHI was ≥5/h but <15/h, and moderate-to-severe if AHI was ≥15/h.

CPAP Titration Adherence and Follow-up

Patients underwent full PSG, and then CPAP was manually titrated to the correct therapeutic pressure to abolish all "visible" nocturnal OSA events, based on currently accepted guidelines [19]. All the patients received education prior to the CPAP titration night and completed a questionnaire at the end of the first night, reporting the quality of sleep during CPAP titration and any side effects. Both study groups received individual counseling during scheduled clinic appointments, at their initial sleep clinic consultation, and after the completion of the polysomnographic studies. During these

appointments, they received one-on-one counseling by a sleep physician regarding the results of their polysomnographic studies, basic information on OSA, its known effects on comorbid conditions, proper sleep hygiene, adjunctive/conservative methods to improve sleep, and the importance of treatment adherence. All patients took home a brochure describing the need for and benefits of CPAP therapy and attended a CPAP clinic, where they were given specific counseling on the proper use and maintenance of CPAP and underwent personalized, formal mask fitting by a specialized nurse. CPAP usage data included mask type (nasal or full face), number of nights on CPAP, average usage per night (hours), air leakage, and air pressure delivered. The chronological data (measured by a real-time clock and uploaded to a computer using specialized software) were obtained from the CPAP machine at each follow-up appointment. The self-reported number of nights per week and hours per night CPAP was being used, as recorded in the sleep diary, were compared with the data obtained from the CPAP machine during the first month.

In all patients who complained of a dry irritating cough that reduced their ability to use the CPAP device, heated humidification was added to the CPAP circuit, as suggested by previous studies [15, 20].

Good or poor CPAP compliance was assessed based on currently existing guidelines (good compliance for CPAP use for at least 4 h/night and 70 % of nights/week, assessed by downloads from recording devices in the CPAP units during the follow-up at the CPAP clinic). Given the known difficulties in CPAP initiation and compliance in such populations, patients were divided into groups with good or poor CPAP compliance [20].

Assessment of sleep and quality of life

Functional Outcomes of Sleep Questionnaire The FOSQ is a 30-item self-administrated questionnaire designed to measure the impact of excessive sleepiness on multiple activities of daily life. It comprises five dimensions: activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcome. Each of these dimensions is rated on a 4-point scale. Lower scores indicate greater dysfunction [21–23].

Pittsburgh Sleep Quality Index A subjective assessment of sleep was determined using the Pittsburgh Sleep Quality Index (PSQI). The PSQI questionnaire is a standard instrument that has been validated as differentiating "poor" from "good" sleep. It assesses 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 is rated on a 4-point scale (0–3, with 3 indicating a more profound effect), and the grades are summed to give a global score. The higher the score, the greater the negative impact on sleep quality. A global score of 6 indicates "poor"sleep [24–26].

Epworth Sleepiness Scale The Epworth Sleepiness Scale (ESS) is currently the most widely used subjective test of daytime sleepiness in clinical practice. It is a simple, self-administered, eight-item questionnaire that measures the risk of falling asleep in eight specific situations that are commonly encountered. A score of 10 is considered normal. The higher the score (from 10 to 24), the greater the reported subjective daytime sleepiness [27].

Fatigue Severity Scale In the Fatigue Severity Scale (FSS), individuals 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, and family or social life). A total score of less than 36 is considered normal. A score above that limit (maximum score 63) is suggestive of a significant negative impact of fatigue on daily life activities [28, 29].

Short-Form 36 Health Survey This 36-item questionnaire is a reliable and validated tool for the assessment of general (physical and mental) health and quality of life [30, 31]. The Short-Form 36 Health Survey (SF-36) encompasses eight domains—physical functioning, social functioning, mental health, role limitations due to physical problems, role limitations due to emotional problems, vitality (energy and fatigue), bodily pain, and general health perceptions—each of which is scored separately from 0 (worst) to 100 (best). The SF-36 scales are summarized into two dimensions. The first four domains make up the "physical health" dimension, and the last four form the "mental health" dimension. The scores of the two dimensions and the total SF-36 score are based on mathematical averaging of the scale components. The score ranges from 0 to 100, the best quality of life corresponding to 100 and the worst to 0.

Beck Depression Inventory This 21-item questionnaire is a widely used and well-validated self-reported inventory of depressive symptoms. [32, 33] The Beck Depression Inventory (BDI) measures the severity of depressive symptoms over the preceding week. For each item, the respondent chooses one or more options rated from 0 (absence of symptoms) to 3 (most severe level). Total scores range from 0 to 63 and represent the sum of the highest level endorsed on each item. Scores below 10 are considered normal.

Pulmonary function testing

Spirometry (FEV_1, FVC; FEV_1/FVC ratio), measurement of static lung volumes (total lung capacity (TLC) by body box

plethysmography) and measurement of diffusing capacity (diffusing capacity of the lung for carbon monoxide (DLCO) by the single-breath technique) were performed (Vmax22, SensorMedics, Yorba Linda, California, USA) with the patient in the seated position, according to approved standards [34].

Statistical analysis

All data are presented as mean ± standard deviation (SD). Data were examined for normal distribution using the Kolmogorov–Smirnov test. For normally distributed values, we used the unpaired *t* test for statistical comparison. A p value <0.05 was considered statistically significant. Kaplan–Meier survival curves were plotted and the groups were compared using the log-rank test. Statistical analyses were performed using SPSS software (SPSS, Chicago, IL, USA).

Results

Of the 92 patients who underwent overnight PSG, 14 (15 %) had an AHI within the normal range, 18 (20 %) patients had an AHI compatible with mild OSA, and 60 (65 %) patients had moderate-to-severe OSA. The subjects in the latter group were included in the study and were started on CPAP as described above. Two patients declined to use CPAP, despite intense efforts by the CPAP clinic staff, and were excluded. In addition, two other patients reported CPAP intolerance and were excluded after two weeks of unsuccessful attempts to achieve even poor compliance with CPAP use. In nine cases where there was CPAP intolerance during the titration study (mainly as a result of cough, claustrophobia and/or insomnia), short-term home CPAP acclimatization at low pressures and with the addition of heated humidification was advised. In these cases the titration was performed one week after the first attempt, this time with heated humidification. Among these patients one patient finally declined CPAP treatment and was excluded from the study group.

The differentiation into the good (37 patients) and poor (18 patients) CPAP compliance groups was made based on data from the CPAP device memory card and sleep diaries. The mean CPAP use in the good and poor CPAP compliance group based on the data from the CPAP device are summarized in Table 1.

In general, patients with moderate-to-severe OSA showed statistically significant differences in Body Mass Index (BMI) and neck circumference compared with those with no or mild OSA. No significant differences were noted in relation to pulmonary function testing values between these groups. A unique feature, in patients without OSA or with mild OSA, was a marked negative impairment in sleep macro- and micro-architecture, with low sleep efficiency, decreased percentages of REM and slow-wave sleep, an increased wake after sleep onset (WASO) time, prolonged sleep latency, and an increased arousal index. The above parameters were further deteriorated in those patients with moderate-to-severe OSA. Data concerning the demographics, pulmonary function and PSG results showed no statistical significant differences between the good and poor CPAP compliance group.

Table 1 Comparison of CPAP use between the good and poor CPAP compliance group after 1 year follow-up

CPAP compliance	Good (n=37)	Poor (n=18)	p value
CPAP (% days used a week)	80.4±5.6	59.5±6.1	<0.0001
CPAP (hours per night, on nights CPAP was used)[a]	6.3±1.4	3.2±0.5	<0.0001

Data are presented as mean ± SD

[a] This value was calculated by dividing the total hours of CPAP used by the number of days CPAP was used

The most frequent complaints cited by the 60 IPF patients with moderate-to-severe OSA were daytime fatigue (75 %), sleep onset and maintenance insomnia (67 %), and nocturnal cough (56 %). Excessive daytime sleepiness, snoring, and witnessed apneas during sleep were reported by 22, 48, and 29 % of patients, respectively.

Related to the good CPAP compliance group, statistically significant changes were noted in all of the instruments used to assess the quality-of-life and sleep variables (FOSQ, PSQI, ESS, BDI, SF-36 physical and mental component, and FSS) 1 year after CPAP initiation (Table 2). The most striking improvements were in the FOSQ (from 13.2±3.3 to 17.1±1.7; p=0.0002), which is a specific instrument for assessing the influence of sleep disorders on daily activities, and in the FSS (from 40.9±11.1 to 27.9±8.6; p=0.0007), an instrument giving insight in one of the most common but also disabling symptoms in IPF patients, namely daytime fatigue. Despite the absence of excessive daytime sleepiness based on the ESS scores, a statistically significant (p=0.04) decrease was noted even in this parameter.

Related to the poor CPAP compliance group, the only statistically significant changes, with weaker significance than in the other group, were observed in the PSQI (p=0.05), the FSS (p=0.02), the bodily pain parameter of the SF-36 physical component (p=0.04), and the vitality parameter of the SF-36 mental health component (p=0.04). Interestingly, no statistical significant changes were observed in the FOSQ.

Values of the used sleep and quality-of-life parameters before CPAP initiation showed no statistical significant differences between the good and poor CPAP compliance group with the exception of the FSS that was significant impaired in the poor CPAP compliance group (40.9±11.1 versus 51.5±10.1; p=0.004 in the good and poor CPAP compliance group, respectively).

Table 2 Values of instruments used to assess quality of life and sleep at CPAP initiation and at the 1-year time point in the good and poor CPAP compliance group

	Good CPAP compliance group (n=37)			Poor CPAP compliance group (n=18)		
	CPAP initiation	After 1 year with CPAP	p	CPAP initiation	After 1 year with CPAP	p
ESS	9.2±5.6	5.8±3.8	0.04	7.1±3.2	6.2±5.5	0.45
BDI	12.1±5.1	7.7±4.2	0.01	11.8±5.8	12.2±4.2	0.81
PSQI	10.9±4.5	5.8±4.1	0.002	10.6±4.3	7.6±4.8	0.05
FOSQ	13.2±3.3	17.1±1.7	0.0002	13.5±3.2	12.7±3.6	0.22
FSS	40.9±11.1	27.9±8.6	0.0007	51.5±10.1	41.4±15.8	0.02
SF-36 physical component	60.8±12.4	76.4±11.6	0.008	53.7±18.3	63.8±18.1	0.08
Physical functioning (PF)	62.1±22.4	75.9±11.7	0.02	51.1±29.3	47.7±21.7	0.69
Role physical (RP)	65.2±28.3	80.7±18.6	0.03	50.2±27.3	52.8±21.6	0.63
Bodily pain (BP)	64.4±27	79.7±18.6	0.04	52.4±31.3	69.2±27.8	0.04
General health (GH)	53.5±16.2	68.1±13.4	0.009	48.5±19.2	53.9±17.2	0.09
SF-36 mental health component	65.3±17.1	79.5±10.3	0.007	61.2±20.4	66.5±16.4	0.36
Vitality (VT)	61.5±15.7	72.1±13.7	0.04	52.5±19.4	63.1±16.3	0.04
Social functioning (SF)	77.2±16.8	90.6±11.6	0.01	74.4±21.6	76.1±17.8	0.78
Role emotional (RE)	63.6±23.9	80.7±13.5	0.02	56.5±29.1	66.8±22.9	0.29
Mental health (MH)	59.2±22.7	74.7±14.7	0.03	60.3±20.1	61.6±18.7	0.97

ESS Epworth Sleepiness Scale, *BDI* Beck Depression Inventory, *PSQI* Pittsburgh Sleep Quality Index, *FOSQ* Functional Outcomes of Sleep Questionnaire, *SF-36* Short-Form 36 Health Survey, *FSS* Fatigue Severity Scale

The overall survival of IPF patients with moderate-to-severe OSA showed significant differences (p=0.01) at 24 months after CPAP initiation between the good and poor CPAP compliance groups. More specifically, three patients from the CPAP noncompliant group died during the above period, whereas all patients from the CPAP good compliant group remained alive. All deaths were attributable to the disease, as verified by the death certificates. In addition, one patient out of the five that were CPAP intolerant and discontinued CPAP soon after CPAP initiation efforts, died during the 24-month period. The data are shown using Kaplan–Meier analysis in Fig. 1. A need for hospitalization due to IPF exacerbation was noted in one and six cases from the good and poor CPAP compliance groups, respectively.

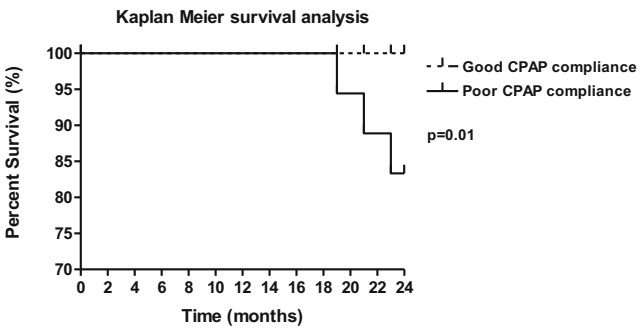


Fig. 1 Kaplan–Meier-estimated survival curves for the good and poor CPAP compliance groups (p=0.01 log-rank test)

Discussion

This is the first multicenter study to report a significant improvement in quality of life and sleep after effective CPAP treatment in a relatively large group of newly diagnosed, treatment-naive patients with IPF and comorbid moderate-to-severe OSA. In addition, it is the first to record a difference in survival rates between good and poor CPAP compliant patients. Recent guidelines [1], based on the literature of the last years,[4-7] report OSA as a comorbidity in IPF patients and stress the need for research related to the effectiveness of treatment with CPAP. It is well known that IPF remains a fatal disease with no effective therapy so far, and treatment of comorbidities, such as OSA is crucial [1, 8].

Underlying OSA may be a reason for impaired sleep quality in IPF patients [12, 13] and may consequently have a negative influence on their daily activities and overall quality of life [14–16]. In addition, the desaturation-reoxygenation sequence characterizing intermittent hypoxia constitutes a major stimulus, even more potent than continuous hypoxia, that leads to oxidative stress, systemic inflammation, and generalized vascular endothelial damage [35, 36]. A very recent study [16] reported that intermittent oxygen desaturation during sleep significantly exceeds that during maximal exercise and has a negative association with survival in IPF patients. The authors emphasize the fact that sleeping in IPF is a stressful "practice," even more intense than maximal exercise, both conducted under hypoxemic conditions. It is probably time to go one step further and to recognize that

sleep in IPF is not a restorative state but actually a marathon run with some intermittent 100-m sprints every time these patients go into REM sleep, one of the most vulnerable sleep periods. The aim of our study was not only to recognize once again that OSA is a common comorbidity in IPF patients but also to try to deal with all OSA-related deleterious effects in IPF patients by initiation of the cornerstone of treatment for OSA, namely CPAP [10].

One important message of our study was the statistically significant improvement in almost all quality-of-life and sleep questionnaires 1 year after CPAP initiation in the good CPAP compliance group. As previously reported, the main problem during CPAP initiation in IPF patients with OSA is nontolerance of CPAP or poor compliance with therapy [15, 20]. It would be easy to give up after a CPAP titration has been unsuccessful because of multiple reasons, such as cough, claustrophobia, or insomnia and to characterize these patients as ineligible to receive CPAP therapy. However, the next step is simply to accept the well-known course of the disease to disability and finally death. Well-organized sleep centers are able to deal with difficult cases like these and will attempt to overcome any difficulties. Our results showed that this is possible when IPF patients with OSA have intensive follow-up by the responsible staff in the sleep clinic. Even in patients with poor CPAP compliance, the intensive follow-up by the CPAP clinic staff was continued, in order to assess even modest positive effects on sleep and life quality.

One of the most striking features in the good CPAP compliance group was the strong statistically significant improvement in specific questionnaires, such as the FOSQ, that assess the daily effects of poor sleep caused by sleep disorders. On the other hand, the absence of improvement in the same instrument in the poor CPAP compliance group suggests that this level of CPAP use is not sufficient to accomplish significant changes, and that in such patient's regular encouragement, aiming to increase CPAP use, is crucial.

Poor sleep quality has been recognized [4–6, 9, 11] as an important issue in IPF and is further exacerbated by the coexistence of OSA. Based on the PSQI, a standard and validated instrument assessing the quality of sleep, it seems that sleep quality improves not only with good CPAP use but also in cases with poor CPAP compliance.

Daytime fatigue was the most common complaint in the included IPF patients with moderate-to-severe OSA. It is known [1, 4, 9, 12] that the cause of this symptom is multifactorial and is related not only to mood issues associated with the disease itself but also to comorbidities such as OSA. It is highly significant that, to a greater or lesser degree, a disabling feature that negatively influences any therapeutic efforts in chronic and fatal diseases like IPF was improved in both good and poor CPAP compliance patients. It should also be pointed that during the initial evaluation with quality-of-life and sleep questionnaires the only statistical significant difference between the good and poor CPAP compliance group was the FSS score. Patients of the poor CPAP compliance group had scores indicating increased negative impact of fatigue on daily life activities.

The improvements in patients with good CPAP compliance in the SF-36 physical and mental component, taken together with the positive influence in mood as assessed by the BDI, are here demonstrated for the first time. Previous studies [15] in small IPF groups with OSA did not find such positive results during the first 6 months of effective CPAP therapy. It might be the case that some complex components included in such questionnaires need more time in order to reach significance.

In agreement with previous studies [4–6], IPF patients with OSA usually do not report excessive daytime sleepiness and have normal scores on the ESS. An interesting feature of our study is the fact that ESS scores were significantly improved in the good CPAP compliance group, despite being within the normal range for this instrument. It may be speculated that IPF patients find a way to adapt to daytime sleepiness, in the same way that patients with other pulmonary diseases [37] learn, for example, to live with dyspnea and give normal scores in questionnaires for this symptom. Chronic diseases with a poor prognosis and multiple disabling and long-lasting symptoms may lead patients to a vicious cycle in which they perceive abnormal symptoms as normal. The question remains as to whether ESS is sufficiently sensitive to recognize sleepiness in patients with chronic diseases such as IPF, or whether other objective methods (probably Multiple Sleep Latency Test (MSLT)) should be used in this research field.

Finally, one very important feature was related to the survival of patients with moderate or severe OSA but with differences in their compliance with CPAP therapy. Two years after CPAP initiation, all good CPAP compliance patients were alive, and only one case of hospitalization due to acute IPF exacerbation was noted. By contrast, three patients from the poor CPAP compliance group died during the first 24 months and six needed hospitalization for acute exacerbation of IPF in the same time period. No conclusive statements can be made at this time, but these observations cannot be disregarded.

In conclusion, this is the first study to report that effective CPAP treatment in IPF patients with comorbid moderate-to-severe OSA results in a significant improvement in daily living activities, and quality of sleep and life, based on multiple scientific instruments used during the follow-up period. In addition, we have the first evidence that treatment of comorbidities such as OSA may also influence mortality in IPF, a fatal disease (IPF is not a cancer but acts like a cancer) with no effective treatment so far. We believe that the results of this study will help to raise awareness of the potential for comorbid OSA in IPF, the treatment of which may not only improve quality of life and sleep but also have positive effects in morbidity and mortality in these patients.

Conflict of interest All the authors declare that they have no conflict of interest.

References

1. An Official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management (2011) Am J Respir Crit Care Med 183:788–824
2. Olson AL, Swigris JJ (2012) Idiopathic pulmonary fibrosis: diagnosis and epidemiology. Clin Chest Med 33:41–50
3. Nathan SD, Shlobin OA, Weir N et al (2011) Long-term course and prognosis of idiopathic pulmonary fibrosis in the new millennium. Chest 140:221–229
4. Mermigkis C, Chapman J, Golish J et al (2007) Sleep-related breathing disorders in patients with idiopathic pulmonary fibrosis. Lung 185:173–178
5. Lancaster LH, Mason W, Parnell JA et al (2009) Obstructive sleep apnea is common in idiopathic pulmonary fibrosis. Chest 136:772–778
6. Mermigkis C, Stagaki E, Tryfon S et al (2010) How common is sleep disordered breathing in patients with idiopathic pulmonary fibrosis. Sleep Breath 14:387–390
7. Pihtili A, Bingol Z, Kiyan E et al (2013) Obstructive sleep apnea is common in patients with interstitial lung disease. Sleep Breath 17: 1281–1288
8. King C, Nathan SD (2013) Identification and treatment of comorbidities in idiopathic pulmonary fibrosis and other fibrotic lung diseases. Curr Opin Pulm Med 19:466–473
9. Mermigkis C, Stagaki E, Amfilochiou A et al (2009) Sleep quality and associated daytime consequences inpatients with idiopathic pulmonary fibrosis. Med Princ Pract 18:10–15
10. Mermigkis C, Bouloukaki I, Schiza SE (2013) Obstructive sleep apnea in patients with interstitial lung diseases: past and future. Sleep Breath 17:1127–1128
11. Agarwal S, Richardson B, Krishnan V et al (2009) Interstitial lung disease and sleep: what is known? Sleep Med 10:947–951
12. Krishnan V, McCormack MC, Mathai SC et al (2008) Sleep quality and health-related quality of life in idiopathic pulmonary fibrosis. Chest 134:693–698
13. De Vries J, Kessels BL, Drent M (2001) Quality of life ofidiopathic pulmonary fibrosis patients. Eur Respir J 17:954–961
14. Swigris JJ, Kuschner WG, Jacobs SS et al (2005) Health-related quality of life in patients with idiopathic pulmonary fibrosis: a systematic review. Thorax 60:588–594
15. Mermigkis C, Bouloukaki I, Antoniou K et al (2013) CPAP Therapy in patients with idiopathic pulmonary fibrosis and obstructive sleep apnea. Does it offer a better quality of life and sleep? Sleep Breath 17: 1137–1143
16. Kolilekas L, Manali E, Vlami K et al (2013) Sleep oxygen desaturation predicts survival in idiopathic pulmonary fibrosis. J Clin Sleep Med 9:593–601
17. Karakatsani A, Papakosta D, Rapti A, Hellenic Interstitial Lung Diseases Group et al (2009) Epidemiology of Interstitial lung diseases in Greece. Respir Med 103:1122–1129
18. Iber C, Ancoli-Israel S, Chesson A, Quan SF, editors (2007) 1st ed. Westchester, IL: American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specification
19. Kushida CA, Chediak A, Berry RB et al (2008) Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. J Clin Sleep Med 4:157–171
20. Mermigkis C, Mermigkis D, Varouchakis G, Schiza S (2012) CPAP treatment in patients with idiopathic pulmonary fibrosis and obstructive sleep apnea-therapeutic difficulties and dilemmas. Sleep Breath 16:1–3
21. Weaver TE, Laizner AM, Evans LK et al (1997) An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep 20:835–843
22. Reimer MA, Flemons WW (2003) Quality of life in sleep disorders. Sleep Med Rev 7:335–349
23. Gooneratne NS, Weaver TE, Cater JR et al (2003) Functional outcomes of excessive daytime sleepiness in older adults. J Am Geriatr Soc 51:642–649
24. Buysse DJ, Reynolds CF, Monk TH et al (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28:193–213
25. Backhaus J, Junghanns K, Broocks A et al (2002) Test-retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. J Psychosom Res 53:737–740
26. Carpenter JS, Andrykowski MA (1998) Psychometric evaluation of the Pittsburgh Sleep Quality Index. J Psychosom Res 45:5–13
27. Johns MW (1991) A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14:540–545
28. Hjollund N, Andersen J, Bech P (2007) Assessment of fatigue in chronic disease: a bibliographic study of fatigue measurement scales. Health Qual Life Outcome 27:5–12
29. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD (1989) The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 46: 1121–1123
30. Ware JE Jr, Kosinski M, Bayliss MS et al (1995) Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care 33:264–279
31. Martinez TY, Pereira CA, dos Santos ML et al (2000) Evaluation of the short-form 36-item questionnaire to measure health related quality of life in patients with idiopathic pulmonary fibrosis. Chest 117: 1627–1632
32. Beck AT, Beamesderfer A (1974) Assessment of depression: the depression inventory. Mod Probl Pharmacopsychiatry 7:151–169
33. Beck AT, Steer RA, Garbin MG (1988) Psychometric properties of the Beck depression inventory: twenty-five years of evaluation. Clin Psychol Rev 8:77–100
34. American Thoracic Society (1995) Standardization of spirometry. Am J Respir Crit Care Med 152:1107–1136
35. Lévy P, Pépin JL, Arnaud C et al (2008) Intermittent hypoxia and sleep-disordered breathing: current concepts and perspectives. Eur Respir J 32:1082–1095
36. Neubauer JA (2001) Invited Review: Physiological and pathophysiological responses to intermittent hypoxia. J Appl Physiol 90:1593–1599
37. Mermigkis C, Kopanakis A, Foldvary-Schaefer N et al (2007) Health-related quality of life in patients with obstructive sleep apnoea and chronic obstructive pulmonary disease (overlap syndrome). Int J Clin Pract 61:207–211