Sleep Oxygen Desaturation Predicts Survival in Idiopathic Pulmonary Fibrosis

Likurgos Kolilekas, M.D.^{1,2}; Effrosyni Manali, M.D.³; Katerina A. Vlami, M.D.¹; Panagiotis Lyberopoulos, M.D.¹; Christina Triantafyllidou, M.D.^{1,4}; Konstantinos Kagouridis, M.D.¹; Katerina Baou, M.D.¹; Sotirios Gyftopoulos¹; Konstantinos N. Vougas, Ph.D.⁵; Anna Karakatsani, M.D., M.P.H., Ph.D.¹; Manos Alchanatis, M.D.³; Spyros Papiris, M.D., Ph.D.¹

¹Second Pulmonary Department, Attikon University Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece; ²Seventh Pulmonary Department, Sotiria Hospital for Chest Diseases, Athens, Greece; ³First Department of Respiratory Diseases, Sotiria Hospital for Chest Diseases, Medical School, National and Kapodistrian University of Athens, Athens, Greece; ⁴Sixth Pulmonary Department, Sotiria Hospital for Chest Diseases, Athens, Greece; ⁵Genomics and Proteomics Research Units, Center of Basic Research II, Biomedical Research Foundation, Academy of Athens, Athens, Greece

Background: Recent studies suggest poor sleep quality in patients with idiopathic pulmonary fibrosis (IPF). However, so far, the impact of IPF-related sleep breathing disorders (SBDs) on survival has not been extensively studied.

Methods: In a cohort of 31 (24 males) treatment-naïve, newly diagnosed consecutive IPF patients, we prospectively investigated the relationship of SBD parameters such as apnea-hypopnea index (AHI), maximal difference in oxygen saturation between wakefulness and sleep (maxdiff SpO₂), and lowest sleep oxygen saturation (lowest SpO₂) with clinical (survival, dyspnea, daytime sleepiness), pulmonary function, submaximal (6-min walk test [6MWT]) and maximal exercise variables (cardiopulmonary exercise test [CPET]), and right ventricular systolic pressure (RVSP).

Results: Sleep oxygen desaturation exceeded significantly that of maximal exercise ($p < 0.001$). Maxdiff SpO₂ was inversely related to survival, DLCO%, and SpO₂ after 6MWT, and directly with dyspnea, AHI, and RVSP. The lowest SpO₂ was directly related to survival and to functional (TLC%, DLCO%) as well as submaximal and maximal exercise variables (6MWT

distance, SpO₂ after 6MWT, peak oxygen consumption/kg, SpO₂ at peak exercise), while an inverse association with dyspnea score, AHI, and RVSP was observed.

Conclusions: Our findings provide evidence that intermittent sleep oxygen desaturation significantly exceeds that of maximal exercise and is associated with survival in IPF patients. Furthermore, they imply the existence of a link between lung damage and apnea events resulting to the induction and severity of intermittent sleep oxygen desaturation that aggravate pulmonary arterial hypertension and influence IPF survival.

Commentary: A commentary on this article appears in this issue on page 603.

Keywords: Idiopathic pulmonary fibrosis, sleep disordered breathing, sleep oxygen desaturation, survival, exercise limitation and testing

Citation: Kolilekas L; Manali E; Vlami KA; Lyberopoulos P; Triantafyllidou C; Kagouridis K; Baou K; Gyftopoulos S; Vougas KN; Karakatsani A; Alchanatis M; Papiris S. Sleep oxygen desaturation predicts survival in idiopathic pulmonary fibrosis. *J Clin Sleep Med* 2013;9(6):593-601.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep breathing disorders are frequent in idiopathic pulmonary fibrosis. The aim of the study was to examine the relationship between SBDs and clinical and functional parameters of IPF, and to evaluate the impact of SBDs on survival in IPF.

Study Impact: Our data indicate that sleep oxygen desaturation and apnea-hypopnea index affect negatively survival in IPF patients and that sleep in IPF is a process mimicking maximal exercise, arising an important question: if CPAP treatment can modify disease progression in IPF.

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrosing interstitial pneumonia of unknown cause associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP).¹ The disease is always lethal, and its natural history is characterized by either rapid or slow deterioration of respiratory function, often accelerated by the unpredictable development of acute exacerbations.¹ Pharmacologic therapy is lacking, and all patients will die from respiratory failure or complicating comorbidities such as coronary vascular disease, pulmonary hypertension, gastroesophageal reflux disease (GERD), and obstructive sleep apnea (OSA).^{1,2}

Obstructive sleep apnea and more generally, sleep breathing disorders (SBDs) that include increased sleep fragmentation, decreased slow wave and REM sleep, as well as sleep oxygen desaturation characterizing poor sleep quality, are frequent in IPF.^{2,3} Poor sleep quality has been shown to further influence quality of life in IPF patients who already suffer from an impaired quality of life due to low energy levels, fatigue, and exer-

tional dyspnea.^{4,5} The latter, is the most prominent and disabling symptom in IPF and is attributed to several factors including deranged lung mechanics, gas exchange abnormalities, pulmonary vascular disease, myocardial dysfunction, and peripheral muscle weakness.⁶ Moreover, exertional dyspnea and oxygen desaturation during exercise are parameters that negatively influence the outcome in IPF.^{6,7}

In the present study we hypothesized that sleep oxygen desaturation and eventually OSA or their physiological consequences also have a negative impact on IPF survival. To examine this hypothesis we prospectively investigated the relationship of several SBD parameters with clinical and pulmonary function variables as well as with right ventricular systolic pressure (RVSP).

METHODS

Subjects

We prospectively recruited 31 consecutive patients referred to our department's Outpatient Interstitial Lung Disease Unit over a period of one year. Written informed consent was obtained from each patient. All patients fulfilled the criteria of both previous and—as retrospectively evaluated—new guidelines of the American Thoracic Society, European Respiratory Society and the American College of Chest Physicians for the diagnosis of IPF.¹ Of 31 patients, only 6 were diagnosed using lung biopsy; the other 25 were diagnosed by fulfilling typical clinico-radiographic criteria. Secondary causes of lung fibrosis were excluded based on history, absence of relevant occupational or environmental exposures, clinical examination, and serology tests. The study was approved by the Medical Ethics Committee of Attikon University Hospital, National and Kapodistrian University of Athens, Greece. Written informed consent was obtained from each subject.

Dyspnea

Chronic exertional dyspnea was assessed at presentation by the responsible physicians (LK, EM) using the modified Medical Research Council (mMRC) chronic dyspnea self-administered questionnaire consisting of 6 questions about perceived breathlessness.⁶

Pulmonary Functional Tests (PFTs)

PFTs were performed either at diagnosis or after a short interval not exceeding 10–15 days from the 6MWT and the CPET. Specifically, forced expiratory volume at the first second (FEV₁), forced vital capacity (FVC), total lung capacity (TLC), and single-breath carbon monoxide diffusing capacity (DLCO) were assessed by MasterScreen Body apparatus (Erich Jaeger GmbH, Würzburg, Germany) according to the ERS/ATS Guidelines. All measurements were expressed as both percent of predicted normal and as absolute values.⁶

6-Minute Walk Test

The 6MWT was done according to the ATS guidelines.⁸ The test was performed along a measured corridor in our department. Participants were encouraged to cover as much distance as possible. Oxygen saturation was measured at the beginning and at the end of the 6-MWT.

CPET

The CPET was performed using a standardized protocol in accordance with the American Thoracic Society/American College of Chest Physicians (ATS/ACCP) statement.⁹ We excluded patients taking β -blockers; all others were encouraged

to take their medication as usual. On arrival at the exercise suite, patients were connected to a 12-lead electrocardiogram (Cardio Card, Oxycon Pro). Oxygen saturation was measured by digital pulse oximetry (AutoCorr BCI), and blood pressure was assessed by a sphygmomanometer. Calibrations were performed according to the instructions of the manufacturers. All patients underwent a maximal or symptom-limited cardiopulmonary exercise test with an electromagnetically braked cycle ergometer (Ergometrics 900, Erich Jaeger GmbH, Würzburg, Germany) using a ramp protocol. All tests were monitored continuously with 3 leads: II, V1, and V5. The protocol included: 3 min of sitting rest, 3 min of unloaded cycling (at 60 ± 5 revolutions/min), followed by a progressively increasing work rate in a ramp fashion and 3 min of recovery. The work rate increment for each ramped exercise test was individualized on the basis of each patient's pre-test activity level (range, 8 to 25 Watts/min). The duration of the test was symptom-limited. Cardiopulmonary data were collected and analyzed with an exercise metabolic unit (Oxycon Pro Erich Jaeger GmbH, Würzburg, Germany). The following parameters were recorded: heart rate (HR), minute ventilation, tidal volume (TV), peak oxygen consumption (VO₂ peak), peak oxygen consumption/kg (VO₂ peak/kg), %VO₂ predicted, minute ventilation-carbon dioxide production relationship (VE/VCO₂ slope), VE/VCO₂ slope at anaerobic threshold, respiratory rate (RR), total ventilation (VE), oxygen pulse (O₂P), oxygen saturation at peak exercise (SpO₂ peak), anaerobic threshold (AT), breathing reserve (BR), heart rate recovery (HRR), and heart rate reserve (HRRes).

Polysomnography

All participants underwent full-night polysomnography (PSG) according to standard techniques, including sleep staging by monitoring of central and occipital channels of electroencephalogram (C4-A1, C3-A2, O1-A2, O2-A1), electrooculogram and electromyograms (submental and anterior tibialis). Airflow was monitored by combined thermistor and nasal pressure transducer signals. Electrocardiogram and heart rate were monitored using the standard limb leads. Respiratory efforts were monitored with piezoelectric transducers placed around the chest and the abdomen. Arterial oxygen saturation (SpO₂) was measured continuously by pulse oximetry using a finger probe. Body position was assessed with a body position sensor. All variables were recorded by a computerized system (Alice 5, Philips Respironics, USA). Manual scoring was done in all cases, according to the American Academy of Sleep Medicine recommendations.^{10,11} Apnea was defined as the reduction in airflow $\geq 90\%$ of baseline, lasting ≥ 10 s. It was classified as an obstructive apnea when associated with the presence of an inspiratory effort, as central apnea in the absence of an inspiratory effort, or as mixed apnea if inspiratory effort was absent in the initial part of the event and present at the final part. Hypopnea was defined as the reduction in baseline airflow or in thoracoabdominal movement $\geq 30\%$ with $\geq 4\%$ desaturation, lasting ≥ 10 s. The apnea-hypopnea index (AHI) was calculated as the number of apnea and hypopnea events per hour of sleep. All PSGs were scored by the registered sleep technologist of our laboratory (SG) and reviewed by the responsible authors (LK, KAV).

CPAP titration was done manually under the surveillance of a technician.

Based on the monitoring of oxygen saturation during sleep the following parameters were furthermore calculated for each patient:

1. The maximal difference in oxygen saturation between wakefulness and sleep (maxdiff-SpO₂) evaluated as stated in previous publications.^{12,13}
2. The lowest sleep oxygen saturation (lowest SpO₂)

Questionnaires

All patients completed the Epworth Sleepiness Scale (ESS) before performing PSG.¹⁴

Echocardiography

Trans-thoracic echocardiography was performed in all patients. Right atrial pressure was estimated on the basis of the inferior vena cava size and movement on respiration. The simplified Bernoulli equation was used to calculate right ventricular systolic pressure (RVSP).¹⁵ An RVSP value < 35 mm Hg was considered normal.¹⁶

Survival

During the time of data acquisition of the present study, 10 of 31 patients succumbed to IPF. All deaths were attributable to the disease, as verified by the death certificates. Finally, 21 of the 31 patients who were still alive at the reporting of this work were censored for survival analysis.

Statistical Analysis

Data are presented either as mean $\pm$ standard deviation ($\pm$ SD) or as median with interquartile range. The Mann-Whitney test is used for 2-group comparison. The Pearson and Spearman correlation coefficients were both utilized to describe the relationships between variables, since the first one shows a strong bias towards linear relationships while the other one presents a more generic behavior towards any relationship. Having calculated both coefficients, we can distinguish the relationships tending to be linear from the non-linear ones. The factors of the current study were individually evaluated for relevance to the overall survival through Cox proportional hazards models. More specifically, each of these models were evaluated by 3 independent and asymptotically equivalent tests, the Wald test, the Likelihood ratio test and the Score (logrank) test, each calculating a p-value for the null hypothesis that the factor coefficients are equal to zero. A mean p-value was calculated by averaging the p-values of the aforementioned tests, and this was used as the final criterion for the determination of relevance to the overall survival. Lowest SpO₂ during sleep and SpO₂ peak during CPET were checked for normality with the Kolmogorov-Smirnov test of normality, and having been found normally distributed, they were compared for difference in their mean values with the paired t-test.

All statistical analysis was carried out using R and SPSS. A cox proportional hazard modelling was performed utilizing the 'Survival' R-package. The nonparametric Spearman correlation coefficient was calculated by using SPSS v.13.0.0 (Chicago, IL). A p-value $\leq$ 0.05 was considered significant.¹⁷

Table 1—Demographic, anthropometric, and clinical data of the study population

Variables (n)	Values
Age, years (31 pts)	67.96 ($\pm$ 7.88)
Sex (M/F)	24/7
BMI (kg/m ²)	28.66 ($\pm$ 4.3)
Neck circumference, cm (30 pts)	40.25 ($\pm$ 4.19)
Smoking history	
Ex-smokers	18 (58.1)
Nonsmokers	12 (38.7)
Current smokers	1 (3.2)
MRC chronic dyspnea score	
0.0	2 (6.5)
1.0	9 (29)
2.0	13 (41.9)
3.0	5 (16.1)
4.0	2 (6.5)
GERD	
No	6 (19.3)
Yes	25 (80.7)
AHI	
< 5	3 (9.7)
5-15	12 (38.7)
> 15	16 (51.6)
Epworth Sleepiness Scale	
Score < 10	22 (78.6)
Score > 10	6 (21.4)
RVSP (N = 31)	
< 35 mm Hg	15 (48.4)
$\geq$ 35 mm Hg	16 (51.6)
Oxygen supplementation at home	0
Oxygen supplementation after enrolment	2

Pts, patients; BMI, body mass index; MRC, medical research council; GERD, gastroesophageal reflux disease; AHI, apnea-hypopnea index; RVSP, right ventricular systolic pressure. Values are expressed as mean $\pm$ SD, or absolute numbers and percentage of total.

RESULTS

Epidemiological, Functional, Exercise Capacity, and Sleep Characteristics of the Study Group

Thirty one patients (77.4 % male) with a mean age (SD) of 68 (7.88) years and body mass index (BMI) of 28.66 (4.3) were studied and followed-up for a mean time of 495.39 (266.07) days and a median time of 530 days. Seven patients (22.6%) had moderate to severe dyspnea, with MRC scores of 3 and 4. Smoking habits and further anthropometric and clinical data of the study group are shown in **Table 1**. More than two-thirds of patients presented with GERD; all of them received specific treatment after enrollment. Patients walked during the 6MWT a mean distance of 375.60 (159.07) m or 58.9% (24.26%) of predicted distance and desaturated at a minimum SpO₂ of 89.6% (4.90%). On CPET the mean value of VO₂ peak/kg was 17.21 mL/kg/min (4.37) and the minimum SpO₂ was 88.96% (6.05%). The severity of functional impairment as well as exercise capacity profile of the study group at submaximal and maximal exer-

Table 2—Functional and exercise testing characteristics of the study group

TESTs	Variables (units)	Patients number	Mean $\pm$ SD
PFT	FEV ₁ (L)	30	2.13 $\pm$ 0.48
	FEV ₁ % pr	30	80.7 $\pm$ 14.7
	FVC (L)	30	2.61 $\pm$ 0.64
	FVC % pr	30	77.6 $\pm$ 17.06
CPET	TLC (L)	29	3.9 $\pm$ 0.87
	TLC % pr	29	63.97 $\pm$ 11.94
	DLCO (mmol/min/kPa)	28	3.67 $\pm$ 1.32
	DLCO % pr	29	43.77 $\pm$ 15.96
	TIF (FEV ₁ /FVC %)	30	82.18 $\pm$ 5.37
	VO ₂ peak (ml/min)	25	1,393.24 $\pm$ 389.36
	VO ₂ peak %	25	79.28 $\pm$ 17.43
	VO ₂ peak (mL/min/kg)	25	17.21 $\pm$ 4.37
	AT (mL/kg/min)	22	10.98 $\pm$ 5.67
	Oxygen pulse (mL/beat)	25	10.17 $\pm$ 2.67
6MWT	Oxygen pulse %	25	82.44 $\pm$ 18.46
	SpO ₂ peak	25	88.67 $\pm$ 6.01
	VE peak (L/min)	25	65.61 $\pm$ 19.31
	VE peak %	25	82.64 $\pm$ 17.73
	BR peak %	25	23.84 $\pm$ 16.93
	VE/VCO ₂ slope	24	41.25 $\pm$ 12.17
	Heart rate reserve (pm/min)	25	14.76 $\pm$ 14.63
	Heart rate recovery (bpm)	25	16.00 $\pm$ 8.45
	Distance (m)	30	375.60 $\pm$ 159.07
	SpO ₂ before %	30	95.5 $\pm$ 2.13
	SpO ₂ after %	30	89.6 $\pm$ 4.90

PFT, pulmonary function testing; pr, predicted; CPET, cardiopulmonary exercise testing; 6MWT, 6-min walk test; TLC, total lung capacity; DLCO, diffusion capacity of the lung for carbon monoxide; TIF, Tiffeneau index; SpO₂, oxygen saturation; VO₂ peak, oxygen uptake at peak exercise; AT, anaerobic threshold; VE, peak minute ventilation at peak exercise; BR, breathing reserve; VE/VCO₂ slope, slope of minute ventilation-carbon dioxide production relationship; HR, heart rate.

cise testing is shown in **Table 2**. Regarding sleep characteristics, 12 patients (38.7%) had mild OSA, and 16 patients (51.6%) had moderate to severe OSA. Sleep architecture (as shown in **Table 3**) was disrupted and characterized by S2 sleep disturbed by hypopneas and obstructive apneas, decreased REM sleep, an increased arousal index and wake time after sleep onset with a sleep efficiency of 83.55% (IQR 72.82%-92.6%). More precisely, mean S2 sleep (SD) represented 91.31% (6.1%) of total sleep time (TST), mean S1 sleep 3.36% (2.7%) of TST, mean REM sleep 5.13% (5%) of TST, and mean slow wave sleep (SWS) 0.21% (1.16%) of TST. In the study population, the mean time of sleep with SpO₂ < 90% was estimated at 17.13% (25.9%) of TST. Lowest SpO₂ during sleep was 84% (IQR 78%-87%). The mean value (SD) of maxdiff SpO₂ during sleep was 10.32% (5.83%). Six patients (21.4%) had an ESS > 10. The mean value of the lowest SpO₂ during sleep was 82.52 (7.54), while the mean value of SpO₂ peak during CPET was 88.67 (6.01). When both variables were compared, the difference in their means was found to be statistically significant (p value < 0.001).

Table 3—Interquartile ranges (25%-75%) of the sleep characteristics of the study group (31 pts)

Sleep characteristics	25	50	75
AHI	6.70	15.30	20.90
RDI	7.40	17.40	26.67
AHI/NREM	7.10	17.70	26.80
AHI/REM	0.00	2.60	24.00
Obstructive index	1.92	4.20	10.87
Hypopnea index	2.90	6.50	15.70
Mixed index	0.00	0.00	0.20
Central index	0.00	0.20	1.00
MDA / sec	19.27	20.95	25.15
Snoring Number	29.75	147.5	319.25
Sleep latency min	13.75	19.5	28.87
REM latency min	0.00	121.00	236.75
Sleep efficiency %	72.82	83.55	92.6
TST min	243.5	306.5	331.5
WASO min	12.62	34.25	77.12
S1 sleep min	4.37	7.00	8.87
S2 sleep min	233.62	282.25	319.25
Slow wave sleep min	0	0	0
REM sleep min	0	14	24.25
Min SpO ₂ %	78.00	84.00	87.00
Mean SpO ₂ %	88.5	90.5	92.0
Average SpO ₂ %	91.00	93.00	95.00

AHI, apnea-hypopnea index; RDI, respiratory disturbance index; MDA, mean duration apnea; TST, total sleep time; WASO, wake time after sleep onset; SpO₂, oxygen saturation.

Survival Plot and Correlations between Sleep Architecture Characteristics and Survival and Clinical, Functional, Physiological Exercise Testing, and Pulmonary Hypertension Variables of the Study Population

The cumulative Kaplan-Meier survival plot for the study population is shown in **Figure 1**. Survival was associated with SpO₂ peak during CPET exercise (p = 0.032 HR = 0.764, CI [95%] = 0.584-0.999) as well as with RVSP calculated by Doppler echocardiography (p = 0.001 HR = 1.1, CI [95%] = 1.036-1.167). Among sleep characteristics, the maxdiff SpO₂ was inversely related to survival (p = 0.011 HR = 1.142, CI [95%] = 1.031-1.265) (**Figure 2**), DLCO% and SpO₂ after 6MWT and directly with MRC, AHI, and RVSP (**Table 4**). Lowest SpO₂ was directly related to survival (p = 0.009 HR = 0.897, CI [95%] = 0.827-0.972) (**Figure 3**) and to functional (TLC%, DLCO%), physiological exercise testing parameters (6MWT distance, SpO₂ after 6MWT, VO₂ peak/kg, SpO₂ peak) and inversely with MRC score, AHI, and RVSP (**Table 5**). AHI itself was not related to survival in IPF patients when the entire study population was examined. After excluding the subgroup of IPF patients that were assigned to treatment with CPAP for OSA, AHI was found to be significantly correlated with decreased survival, (p = 0.043, HR = 1.02, CI [95%] = 1.001-1.048) (**Figure 4**). It is of note that all outcome correlations were further adjusted for lung volumes and resting SpO₂, and we found that none of them contributed in a statistically significant way (p < 0.05).

Figure 1—Survival of 31 patients with usual interstitial pneumonia/idiopathic pulmonary fibrosis (UIP/IPF)

All patients were followed until death (uncensored $n = 10$) or until reporting of the study (censored $n = 21$). Shown are cumulative Kaplan-Meier survival plot, sample size, and survival (median survival = 525 days).

Table 4—Statistically significant correlations (either Pearson r or Spearman r) of maximal fall of oxygen saturation during sleep (maxdiff SpO_2) with functional, clinical, exercise testing, and sleep variables of the study group ($n = 31$)

Variables	Pearson r	Pearson r , p value	Spearman r	Spearman r , p value
DLCO%	-0.388	0.037	-0.373	0.046
SpO_2 a 6-MWT	-0.365	0.047	-0.338	0.068
MRC	0.382	0.034	0.269	0.143
AHI	0.461	0.009	0.479	0.006
RVSP	0.702	< 0.001	0.598	< 0.001

DLCO%, diffusion capacity of the lung for carbon monoxide per cent predicted; SpO_2 , oxygen saturation; a, after; 6-MWT, 6 min walking test; MRC, medical research council; AHI, apnea-hypopnea index; RVSP, Right ventricular systolic pressure. Correlation is significant at $p \leq 0.05$.

to the initial Cox proportional hazards models. Furthermore, AHI in this group of IPF patients was significantly correlated with neck circumference ($r = 0.45$, $p = 0.013$) and hip diameter ($r = 0.38$, $p = 0.039$), but not with BMI. Among the clinical, functional, exercise physiological, and pulmonary hypertension parameters, the only significant correlations of AHI found were with $\text{VO}_{2\text{peak}}$ and $\text{VO}_{2\text{peak/kg}}$ from CPET.

When IPF patients with excessive daytime sleepiness were compared with those that presented lower ESS scores no significant difference was noticed regarding survival, pulmonary function, submaximal and maximal exercise variables, RVSP, or BMI (data not shown).

DISCUSSION

The main finding of the present study is that in IPF patients, intermittent sleep oxygen desaturation exceeds that of maximal

Figure 2—Maximal fall in saturation of oxygen during sleep

Kaplan-Meier survival curves for various values of maximal fall in saturation of oxygen (maxdiff SpO_2) during sleep, as predicted by the respective statistically significant Cox proportional hazards model for the entire study population ($n = 31$). Correlation is significant at $p \leq 0.05$.

Figure 3—Lowest oxygen saturation during sleep

Kaplan-Meier survival curves for various values of lowest saturation during sleep (lowest SpO_2), as predicted by the respective statistically significant Cox proportional hazards model for the entire study population ($n = 31$). Correlation is significant at $p \leq 0.05$.

exercise and is associated with survival. Both sleep oxygen desaturation variables (maxdiff SpO_2 , lowest SpO_2) we studied were related to lung damage, as reflected by functional parameters (TLC%, DLCO%), sleep apnea events, exercise oxygen desaturation, dyspnea, and right ventricular systolic pressure. These results imply a link between lung damage and apnea events in the induction and severity of intermittent sleep oxygen desaturation and a role of the later on aggravating pulmonary arterial hypertension and its negative effect on IPF survival.

Table 5—Statistically significant correlations (either Pearson *r* or Spearman *r*) of lowest oxygen saturation during sleep with functional, clinical, exercise testing, and sleep parameters of the study group (*n* = 31)

Variables	Pearson <i>r</i>	Pearson <i>r</i> , p value	Spearman <i>r</i>	Spearman <i>r</i> , p value
TLC%	0.294	0.121	0.396	0.033
DLCO%	0.467	0.01	0.489	0.007
6-MWT distance	0.463	0.01	0.494	0.005
SpO ₂ b 6-MWT	0.502	0.005	0.572	< 0.001
SpO ₂ a 6-MWT	0.55	0.002	0.573	< 0.001
MRC score	-0.477	0.007	-0.417	0.019
VO ₂ peak/kg	0.286	0.147	0.377	0.05
SpO ₂ peak	0.291	0.141	0.402	0.037
AHI	-0.465	0.008	-0.542	0.002
RVSP	-0.732	< 0.001	-0.662	< 0.001

TLC, total lung capacity; DLCO, diffusion capacity of the lung for carbon monoxide; 6-MWT, 6-min walking test; SpO₂, oxygen saturation; b, before; a, after; MRC, medical research council; VO₂ peak, oxygen uptake at peak exercise; AHI, apnea-hypopnea index; RVSP, Right ventricular systolic pressure; Correlation is significant at *p* ≤ 0.05.

So far nocturnal hypoxemia in idiopathic pulmonary fibrosis has been associated with decreased energy levels and impaired daytime social and physical functioning.¹⁸ To the best of our knowledge, this is the first study supporting the negative impact of sleep desaturation on survival in a population of pure IPF patients. Moreover, our findings are consistent with the results of a recent retrospective study, in which a mixed ILD population (including IPF patients) was studied by overnight oximetry, showing that an elevated nocturnal desaturation index is predictive of mortality.¹⁹

An advantage of our study is the use of formal polysomnography. We showed that sleep oxygen desaturation was linked to the severity of the underlying lung damage of IPF and the coexistence of OSA, as disclosed by the relationship between both desaturation parameters used with both DLCO% and AHI. The significantly greatest magnitude of the sleep lowest SpO₂ compared to that of maximal exercise emphasizes the fact that sleeping in IPF is a stressful “practice,” even more intense to that of maximal exercise, both conducted under hypoxemic conditions. The relevance of exercise oxygen desaturation in the clinical course of IPF patients has become clearly evident in several studies where oxygen desaturation, even mild, proved a good predictor of mortality.^{20,21} The mechanisms linking both intermittent nocturnal and exercise oxygen desaturation with survival may be related to the pathogenetic role of pulmonary hypoxic vasoconstriction in the development or worsening of pulmonary arterial hypertension (PH) disproportionate to the severity of the underlying IPF.²² Several studies have shown that PH and its markers (such as pulmonary vascular resistance) and markers of cardiac stress (such as the levels of brain natriuretic peptide) predict survival in IPF.^{23,24} In this study, both oxygen desaturation indices investigated were correlated with the RVSP measured with Doppler echocardiography, thus providing the link between intermittent oxygen desaturation and

Figure 4—Apnea-hypopnea index

Kaplan-Meier survival curves for various values of apnea-hypopnea index (AHI) as predicted by the respective statistically significant Cox proportional hazards model for IPF patients of the study population not receiving treatment with continuous positive airway pressure (CPAP) (*n* = 25). Correlation is significant at *p* ≤ 0.05.

pulmonary hypertension as well as its associated mortality. The potential mechanisms linking sleep and exercise oxygen desaturation with the development of PH may relate to different mechanisms, such as the hypoxia-mediated endothelial dysfunction²⁵ and the rise in arterial endothelin-1 levels—a potent mediator of pulmonary vascular remodelling²⁶—as well as to the resetting of peripheral chemoreceptors due to hypoxia and the resulting lowering of the hypoxic drive, which might aggravate sleep oxygen desaturation by delaying arousal.²⁷ Furthermore, the desaturation-reoxygenation sequence characterizing intermittent hypoxia constitutes a major stimulus, even more potent than continuous hypoxia, which leads to oxidative stress, systemic inflammation, and generalized vascular endothelial damage adversely affecting myocardial function.^{25,28}

The present study also shows that SBDs and especially OSA is common in IPF extending previous observations.^{2,3} This rate of occurrence is even higher from the 10% of OSA encountered in chronic obstructive pulmonary disease (COPD), rendering the term “overlap” syndrome even more appropriate for the coexistence of OSA and IPF.^{29,30} This high occurrence, however, is not related to the BMI of the population studied, which appears even lower of that of previous publications.^{2,3} Furthermore, it cannot be attributed to the treatment effect of corticosteroid use because all were treatment-naïve patients. Factors other than obesity are implicated in the disturbed sleep architecture in IPF, such as the interaction between pharyngeal patency and lung volume. Prior studies have showed that during both wakefulness and sleep, there is increased pharyngeal collapsibility and airway resistance when lung volume is reduced.^{31,32} Moreover, the lung volume dependence appears to be more pronounced in patients with OSA, probably due to loss of caudal traction on upper airway and subsequent airway instability.^{33,34} This effect of decreased lung volume during sleep may be even more

important in supine subjects with restrictive disorders such as IPF.^{35,36} Another implicated factor could be the rapid, shallow breathing pattern characterizing these patients, considered to be a reflex response to stiff lungs mediated by vagal afferents. The decrease of rapid, shallow breathing pattern during sleep, especially during REM sleep, may worsen hypoxemia, which in turn leads to sleep fragmentation and impairment of sleep quality.¹³ In fact, in the study group, both lung volumes and saturation during sleep were decreased.

Another finding of the present study is that sleep architecture presented impaired efficiency characterized by a predominance of S2 sleep, a decrease of REM sleep, and an increase in the arousal index. Sleep disturbances, no matter how common or severe in IPF, were not found to cause excessive daytime sleepiness, with only one-fifth of our patients showing high ESS scores. We could speculate that IPF patients report important tiredness and fatigue more often than excessive daytime sleepiness. In the literature, daytime sleepiness in OSAS patients is suggestive of hyperglycemia and hyperinsulinemia.³⁷ However, when IPF patients with excessive daytime sleepiness were compared with those with lower ESS scores, no significant difference was noticed regarding survival, pulmonary function, submaximal and maximal exercise variables, RVSP or BMI.

To further understand the significance of SBDs in IPF, we examined the associations of SBDs parameters with clinical, functional, submaximal and maximal exercise testing parameters. We found that AHI, the most representative of SBD parameters, was not related to the majority of clinical and physiological parameters of severity, such as the MRC chronic dyspnea scale and the dynamic and static lung volumes. Among the exercise parameters, AHI was only related to cardiopulmonary exercise testing. Data on the relationships of sleep disordered breathing and its physiological derangements with exercise are scarce. Based on the literature, there is evidence that the distance walked at 6MWT in severe OSA is related to BMI but not to AHI.³⁸ As far as cardiopulmonary exercise testing is concerned, OSA patients have a decrease of peak oxygen uptake and an increased cardiovascular response related to the severity of OSA.³⁹ Despite the importance of exercise in the evaluation of severity and outcome in IPF, no data exist as far as we know on the impact of OSA on exercise capacity of these patients. The present study shows an association of AHI with peak oxygen uptake in IPF, and to the best of our knowledge demonstrates for the first time in the literature that among SBD parameters, it is the lowest saturation during sleep that best correlates with clinical, functional and physiological parameters of disease severity and outcome. It is already known that hypoxemia during sleep induces brainstem depression and is one mechanism leading to sleep disordered breathing.¹² Desaturation during sleep has been well studied in chronic respiratory diseases such as COPD and lymphangioleiomyomatosis (LAM), but it has been poorly studied in IPF.^{40,41} It was shown that patients with mild daytime hypoxemia may be particularly vulnerable to desaturation during sleep because they often reside on the steep portion of the oxyhemoglobin dissociation curve. COPD-OSA overlap syndrome patients have more pronounced nocturnal hypoxemia and are at increased risk of death.⁴⁰ As far as interstitial lung disease is concerned, a single study more than 20 years ago, pointed out that oxygen desaturation during sleep was less se-

vere than during exercise.⁴² In the present study population, saturation at rest and wakefulness were significantly related with the lowest saturation during sleep. The fact that the lowest SpO₂ was related to major parameters known to reflect ventilatory impairment, exercise limitation, extent of disease, and pulmonary hypertension in IPF⁶ could provide further explanation on the prognostic significance of this parameter in IPF.

The major clinical implication of our findings would be the management of oxygen desaturation in combined IPF and OSA patients with continuous positive airway pressure (CPAP), seeking for a survival benefit. Based on the latest guidelines,¹ IPF patients with severe resting hypoxemia are advised to use long-term oxygen therapy, based partly on indirect information from patients with obstructive lung disease.⁴³ So far, CPAP treatment is shown to have a beneficial impact on hospitalizations and survival of OSA and of COPD-OSA “overlap” patients, while data for combined IPF and OSA are completely lacking.^{44,45} In our study population, only four patients were treated with CPAP, and they were all alive at the reporting of the study. No significant conclusions could be drawn yet because of the very small number of patients treated, although one could speculate that CPAP in this group of patients might relate to the survival benefit.

Our study has a number of limitations, the most important being the moderate number of patients included, reflecting the rarity of the disease in Greece—3.4 cases per 100,000 inhabitants.⁴⁶ However, it is a prospective, single-center study, based on a well-selected group of newly diagnosed IPF patients; none had received treatment for IPF.

In conclusion, in IPF, intermittent sleep oxygen desaturation exceeds significantly that of maximal exercise and is associated with survival. Both sleep oxygen desaturation variables studied were related to lung damage, sleep apnea events, exercise oxygen desaturation, dyspnea, and right ventricular systolic pressure. Moreover, our results imply the existence of a link between lung damage and apnea events in the induction and severity of intermittent sleep oxygen desaturation that aggravate pulmonary arterial hypertension and influence IPF survival. Further studies are needed to clarify this issue and underlying pathophysiological mechanisms.

ABBREVIATIONS

6MWT, 6 minute walking test
 AHI, apnea-hypopnea index
 AT, anaerobic threshold
 ATS/ACCP, American Thoracic Society/American College of Chest Physicians
 BR, breathing reserve
 BMI, body mass index
 CPET, cardiopulmonary exercise testing
 COPD, chronic obstructive pulmonary disease
 CPAP, continuous positive airway pressure
 ESS, Epworth Sleepiness Scale
 FEV₁, Forced expiratory volume at the first second of expiration
 FVC, Forced vital capacity
 GERD, gastroesophageal reflux disease
 HR, heart rate

HRR, heart rate recovery
 HRRes, heart rate reserve
 IPF, idiopathic pulmonary fibrosis
 IQR, interquartile range
 LAM, lymphangioleiomyomatosis
 Lowest SpO₂, lowest oxygen saturation during sleep
 Maxdiff SpO₂, maximal difference in oxygen saturation between wakefulness and sleep
 VE/VCO₂ slope, Slope of minute ventilation-carbon dioxide production relationship
 MRC, Medical Research Council
 OSA, obstructive sleep apnea
 O₂P, oxygen pulse
 SpO₂ peak, oxygen saturation at peak exercise
 VO₂ peak, peak oxygen consumption
 VO₂ peak/kg, peak oxygen consumption/kg
 PSG, polysomnography
 PFTs, pulmonary function tests
 PH, pulmonary hypertension
 RR, respiratory rate
 RVSP, right ventricular systolic pressure
 SpO₂, saturation of oxygen
 DLCO, Single-breath carbon monoxide diffusing capacity
 SBDs, sleep breathing disorders
 TLC, total lung capacity
 VE, total ventilation
 TV, tidal volume
 UIP, usual interstitial pneumonia

REFERENCES

1. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. *Am J Respir Crit Care Med* 2011;183:788-824.
2. Lancaster LH, Mason W, Parnell JA, et al. Obstructive sleep apnea is common in idiopathic pulmonary fibrosis. *Chest* 2009;136:772-8.
3. Mermigkis C, Stagaki E, Tryfon S, et al. How common is sleep disordered breathing in patients with idiopathic pulmonary fibrosis. *Sleep Breath* 2010;14:387-90.
4. Krishnan V, McCormack MC, Mathai SC, et al. Sleep quality and health related quality of life in idiopathic pulmonary fibrosis. *Chest* 2008;134:693-8.
5. Swigris JJ, Kuschner WG, Jacobs SS, Wilson SR, Gould MK. Health-related quality of life in patients with idiopathic pulmonary fibrosis: a systematic review. *Thorax* 2005;60:588-94.
6. Manali ED, Lyberopoulos P, Triantafyllidou C, et al. The Medical Research Council chronic dyspnea scale: relationships with cardiopulmonary exercise testing and 6-minute walk test in idiopathic pulmonary fibrosis patients. *BMC Pulm Med* 2010;10:32.
7. Lama VN, Flaherty KR, Toews GB, et al. Prognostic value of desaturation during a 6MWT in Idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003;168:1084-90.
8. ATS Statement: Guidelines for the 6 minute walk test. *Am J Respir Crit Care Med* 2002;166:111-7.
9. ATS/ACCP Statement of cardiopulmonary testing. *Am J Respir Crit Care Med* 2003;167:211-77.
10. Iber C, Ancoli-Israel S, Chesson A, Quan SF. *The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specifications*. 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007.
11. Kushida CA, Littner MR, Morgenthaler T, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. *Sleep* 2005;28:499-521.
12. Perez-Padilla R, West P, Lertzmann M, Kryger MH. Breathing during sleep in patients with interstitial lung disease. *Am Rev Respir Dis* 1985;132:224-9.
13. Bye PT, Issa F, Berthon-Jones M, Sullivan CE. Studies of oxygenation during sleep in patients with interstitial lung disease. *Am Rev Respir Dis* 1984;129:27-32.
14. Johns MW. A new method of measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep* 1991;14:540-5.
15. Fisher MR, Forfia PR, Chamera E, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med* 2009;179:615-21.
16. Gallie N, Hooper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2009;30:2493-537.
17. R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL <http://www.R-project.org/>. J. 2011.
18. Clark M, Cooper B, Singh S, Cooper M, Carr A, Hubbard R. A survey of nocturnal hypoxemia and health related quality of life in patients with cryptogenic fibrosing alveolitis. *Thorax* 2001;56:482-6.
19. Corte TJ, Wort SJ, Talbot S, et al. Elevated nocturnal desaturation index predicts mortality in interstitial lung disease. *Sarcoidosis Vasc Diffuse Lung Dis* 2012;22:41-50.
20. Flaherty KR, Andrei AC, Murray S, et al. Idiopathic pulmonary fibrosis: prognostic value of changes in physiology and six-minute-walk test. *Am J Respir Crit Care Med* 2006;174:803-9.
21. Lama VN, Martinez FJ. Resting and exercise physiology in interstitial lung diseases. *Clin Chest Med* 2004;25:435-53.
22. Corte TJ, Wort SJ, Wells AU. Pulmonary hypertension in idiopathic pulmonary fibrosis: a review. *Sarcoidosis Vasc Diffuse Lung Dis* 2009;26:7-19.
23. Corte TJ, Wort SJ, Gatzoulis MA, Macdonald P, Hansell DM, Wells AU. Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic lung disease and suspected pulmonary hypertension. *Thorax* 2009;64:883-8.
24. Corte TJ, Wort SJ, Gatzoulis MA, et al. Elevated Brain natriuretic peptide predicts mortality in interstitial lung disease. *Eur Respir J* 2010;36:819-25.
25. Lévy P, Pépin JL, Arnaud C, et al. Intermittent hypoxia and sleep-disordered breathing: current concepts and perspectives. *Eur Respir J* 2008;32:1082-95.
26. Trakada G, Nikolaou E, Pouli A, Tsiamita M, Spiropoulos K. Endothelin-1 levels in interstitial lung disease patients during sleep. *Sleep Breath* 2003;7:111-8.
27. Mokhlesi B, Tulaimat A, Faibussowitsch I, Wang Y, Evans AT. Obesity hypoventilation syndrome: prevalence and predictors in patients with obstructive sleep apnea. *Sleep Breath* 2007;11:117-24.
28. Neubauer JA. Invited review: physiological and pathophysiological responses to intermittent hypoxia. *J Appl Physiol* 2001;90:1593-9.
29. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:1230-5.
30. Chaouat A, Weitzenblum E, Krieger J, Ifouna T, Oswald M, Kessler R. Association of chronic obstructive pulmonary disease and sleep apnea syndrome. *Am J Respir Crit Care Med* 1995;151:82-6.
31. Sériès F, Cormier Y, Desmeules M. Influence of passive changes of lung volume on upper airways. *J Appl Physiol* 1990;68:2159-64.
32. Sériès F, Marc I. Influence of lung volume dependence of upper airway resistance during continuous negative airway pressure. *J Appl Physiol* 1994;77:840-4.
33. Hoffstein V, Zamel N, Phillipson EA. Lung volume dependence of pharyngeal cross-sectional area in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1984;130:175-8.
34. Onal E, Leech JA, Lopata M. Relationship between pulmonary function and sleep-induced respiratory abnormalities. *Chest* 1985;87:437-41.
35. Heinzer RC, Stanchina ML, Malhotra A, et al. Lung volume and continuous positive airway pressure requirements in obstructive sleep apnea. *Am J Respir Crit Care Med* 2005;172:114-7.
36. Tagaito Y, Isono S, Remmers JE, Tanaka A, Nishino T. Lung volumes and collapsibility of the passive pharynx in patients with sleep disordered breathing. *J Appl Physiol* 2007;103:1379-85.
37. Nena E, Steiropoulos P, Papanas N, et al. Sleepiness as a marker of glucose deregulation in obstructive sleep apnea. *Sleep Breath* 2012;16:181-6.
38. Alameri H, Al-Kabab Y, BaHammam A. Submaximal exercise in patients with severe obstructive sleep apnea. *Sleep Breath* 2010;14:145-51.
39. Przybylowski T, Bielicki P, Kumor M, et al. Exercise capacity in patients with obstructive sleep apnea syndrome. *J Physiol Pharmacol* 2007;58:563-74.
40. Kent BD, Mitchell PD, McNicholas WT. Hypoxemia in patients with COPD: cause, effects and disease progression. *Int J Chron Obstruct Pulm Dis* 2011;6:199-208.
41. Medeiros P Jr, Lorenzi-Filho G, Pimenta SP, Kairalla RA, Carvalho CRR. Sleep desaturation and its relationship to lung function, exercise and quality of life in LAM. *Respir Med* 2012;106:420-8.
42. Midgren B, Hansson L, Eriksson L, Airikkala P, Elmqvist D. Oxygen desaturation during sleep and exercise in patients with interstitial lung disease. *Thorax* 1987;42:353-6.
43. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med* 1980;93:391-8.

44. Marin JM, Carrizo SJ, Vicente E, et al. Long term cardiovascular outcomes in men with obstructive sleep apnea-hypopnea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;365:1046-53.
45. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea syndrome: the overlap syndrome. *Am J Respir Crit Care Med* 2010;182:325-31.
46. Karakatsani A, Papakosta D, Rapti A, et al; Hellenic Interstitial Lung Diseases Group. Epidemiology of interstitial lung diseases in Greece. *Respir Med* 2009;103:1122-9.

ACKNOWLEDGMENTS

Drs. Kolilekas and Manali contributed equally to this work. This work has been supported by the Thorax Foundation Athens Greece, and by the Research Program "Kapodistrias" of the National and Kapodistrian University of Athens, Greece. Institution at which the work was performed: Attikon University Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece. Trial registry: Attikon University Hospital; No: 280/27-7-10. Financial Support: National and Kapodistrian University of Athens, Greece, Thorax Foundation Athens Greece. Dr. Kolilekas has been the primary investigator, participated in clinical and laboratory evaluation of all patients, in the collection and interpretation of data, in reviewing all PSG scorings and drafted the manuscript. Dr. Manali equally contributing to the principal investigator participated in gathering and evaluating clinical information and in writing the manuscript. Dr. Vlami performed night polysomnography, reviewed all PSG scorings

and participated in the interpretation of data. Dr. Lyberopoulos performed pulmonary function testing and cardiopulmonary exercise testing and participated in the interpretation of data. Drs. Triantafyllidou, Kagouridis and Baou participated in gathering and evaluating clinical information. Dr. Vougas did the statistical analysis. Mr. Gyftopoulos participated in cardiopulmonary exercise testing and in scoring night polysomnography studies. Drs. Karakatsani and Alchanatis participated in the critical review of the manuscript. Dr. Papis conceived the study, participated in its design and coordination and critically revised and rewrote the final version of the manuscript. All authors read and approved the final manuscript.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication September, 2012

Submitted in final revised form November, 2012

Accepted for publication December, 2012

Address correspondence to: Spyros Papis, Professor of Medicine and Head, 2nd Pulmonary Department, Attikon University Hospital, 1 Rimini Street, 12462, Haidari, Greece; Tel: +30 210 5832361; Fax: +30 210 5831184; E-mail: papis@otenet.gr

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.