

# Nocturnal Hypoxia and Sleep Disturbances in Cystic Fibrosis

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**Summary.** Disrupted sleep and nocturnal hypoxia are common in cystic fibrosis (CF). However, the predictors of nocturnal hypoxia in CF are still controversial. In order to identify the risk factors for nocturnal desaturation and sleep disturbances, we carried out a clinical and polysomnographic investigation of CF patients. We studied 30 clinically stable CF cases with clinical lung disease (mean age = 12.8; mean FEV1 = 65.2), 10 CF cases without significant lung disease (mean age = 13.3; mean FEV1 = 99.8), and 20 controls (mean age = 15.5). Patients were evaluated by spirometry, 6-min walk test, the Shwachman–Kulczycki (S–K) score, and full overnight polysomnography. Cases with clinical lung disease had lower body mass index, forced vital capacity, and S–K scores. During sleep, five CF cases with clinical lung disease (15%) had SaO<sub>2</sub> <90% during more than 30% of total sleep time and 11 cases (36.6%) had a nadir SaO<sub>2</sub> below 85%. FEV1 values for CF cases with clinical lung disease were related to nadir SaO<sub>2</sub> ( $P < 0.03$ ) and to mean SaO<sub>2</sub> ( $P = 0.02$ ). A receiver operating characteristic (ROC) analysis determined FEV1 at 64% to be predictive of nocturnal desaturation as defined by minimum SaO<sub>2</sub> <85% (sensitivity = 92.3%; specificity = 77.3%) or SaO<sub>2</sub> <90% for 30% of sleep time (sensitivity = 81.8%; specificity = 85.2%). Frequency of impaired sleep was not different in CF cases with (N = 2) and without significant lung disease (N = 5,  $P = 0.53$ ). Sleep architecture was not significantly different between the two groups. Sleep apnea was present in three CF cases with clinical lung disease and in one case without significant lung disease. In summary, desaturation during sleep can be predicted by FEV1 <64% with good sensitivity and specificity. There are no significant differences in sleep architecture between clinically stable CF cases with and without significant lung disease. **Pediatr Pulmonol.** 2009; 44:1143–1150. © 2009 Wiley-Liss, Inc.

**Key words:** cystic fibrosis; sleep apnea; polysomnography; hypoxia; FEV1; SaO<sub>2</sub>.

## INTRODUCTION

Cystic fibrosis (CF) is a common inherited chronic progressive illness with high morbidity and mortality. Over the past 50 years, the use of antibiotics, mucolytic agents, physiotherapy, nutritional support, and the creation of specialized reference centers have dramatically improved survival.<sup>1–3</sup> Despite great variability in the severity of pulmonary involvement, even in homozygous patients, repeated infections and progressive deterioration of lung function are still a major concern.<sup>4,5</sup> Hypoxia during sleep can occur in stable CF patients who are not hypoxic during the day.<sup>6</sup> It has been suggested that reduced ventilation during rapid eye movement (REM) sleep accounts for most of the sleep hypoxemia in CF although upper airway obstructive pathology may also contribute.<sup>7</sup> Hypoxia can lead to clinical complications, such as pulmonary hypertension and right ventricular failure in CF.<sup>8,9</sup> Experimental evidence suggests that hypoxia could exacerbate lung inflammation and influence the bacterial profile in the CF lung.<sup>3,10</sup> Impaired neurocognitive function and daytime sleepiness have been attributed to nocturnal hypoxemia and disturbed sleep in

these subjects.<sup>11</sup> Furthermore, disrupted sleep and nocturnal hypoxemia have been related to poor quality of life in CF.<sup>12</sup> Thus, sleep disturbances are important and need to be addressed in these patients.

To date, questions remain about the predictors for nocturnal desaturation in patients with CF. Daytime SaO<sub>2</sub>, lung function parameters, and clinical scores of disease

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severity have all been suggested as potential predictors of oxygen desaturation during sleep.<sup>13,14</sup> Though nocturnal hypoxia is considered to be common and its identification relevant for the management of CF, clear guidelines for its investigation are not yet available. Polysomnography can adequately identify patients with sleep desaturation and has the advantage of diagnosing unsuspected cases of obstructive sleep apnea. It can also guide the selection of patients for nocturnal oxygen supplementation and determine the optimal inspired oxygen concentration for nocturnal oxygen therapy.<sup>15</sup> Furthermore, it has been properly pointed out that reports about the pattern of sleep architecture in CF patients are scarce.<sup>14</sup>

The aim of this study was to evaluate clinical, respiratory, and sleep parameters in CF cases with and without significant lung disease and to determine the best predictors of nocturnal desaturation in these patients.

## MATERIALS AND METHODS

### Subjects and Study Design

This was a cross-sectional study of 40 individuals, of both genders, with CF confirmed by genetic analysis and sweat test, which were divided into two groups: (i) CF with clinical lung disease ( $n = 30$ , age range 6–28 years) and (ii) CF with pancreatic insufficiency and without significant lung disease ( $n = 10$ , age range 7–22 years). All patients had a routine CT examination and the latter group had normal thin-section lung tomography and normal forced expiratory volume in 1 sec (FEV1). Patients were consecutively recruited from a reference center for the treatment of CF in Fortaleza, Brazil (mean atmospheric pressure = 757 mmHg). Inclusion criteria were: diagnosis of CF, age of 6 years or more, presence of lung disease or pancreatic insufficiency, absence of infective exacerbation on the previous 3 months, and being in a stable clinical condition, as assessed by the attending physician. Exclusion criteria were the presence of neurological disorders, craniofacial dysplasia, primary cardiac disease, and the use of sedative or antiepileptic drugs. Investigators met with no refusals from eligible patients (or from their parents, when applicable) regarding their participation in the study. Twenty age-matched individuals with no history of any chronic illness referred for polysomnography, which later showed no significant nocturnal desaturation, a Apnea–Hypopnea Index (AHI)  $< 5/\text{hr}$  and periodic limb movement (PLM) index  $< 5/\text{hr}$  were included as controls. For each participant, clinical evaluation, pulmonary function tests, and overnight polysomnography were performed within a 24-hr period. The study protocol was approved by the local research ethics committee and written informed consent was obtained in all cases.

### Clinical Evaluation

After clinical examination, a purpose-built questionnaire was used to obtain relevant demographic and clinical

data. Body mass index (BMI) was calculated as the ratio between weight (kg) and squared height ( $\text{m}^2$ ). The Shwachman–Kulczycki (S–K) score was calculated when patients were clinically stable.<sup>16</sup> It incorporates four major aspects of functional capacity: general activity, physical examination, nutrition, and chest radiographic findings, and was used as a parameter of disease severity.

Pulmonary function was assessed by spirometry (Jaeger-v4.31<sup>®</sup>). The best of three attempts was used to determine forced vital capacity (FVC) and FEV1. FVC and FEV1 were expressed as percentage of the predicted values for age, sex, and height.<sup>17</sup> Exercise capacity was evaluated measuring the distance that patients were able to walk in 6 min (6MWT).<sup>18</sup> Patients were asked to walk as far as possible upon verbal command on two occasions and the best measure was selected for analysis.

Subjective sleep quality was evaluated by the Pittsburgh Sleep Quality Index (PSQI). This questionnaire has seven components, each one dealing with a major aspect of sleep: (1) subjective quality of sleep; (2) sleep onset latency; (3) sleep duration; (4) sleep efficiency; (5) presence of sleep disturbances; (6) use of hypnotic-sedative medication; and (7) presence of daytime disturbances, as an indication of daytime alertness. Component 6 always scored 0 because patients who used hypnotic-sedative medication were not included in the study. Individuals with total PSQI score of 6 or more were considered poor sleepers.<sup>19,20</sup> Daytime somnolence was evaluated by the Epworth Sleepiness Scale (ESS), a questionnaire containing eight items that ask for expectation of dozing in eight hypothetical situations. ESS score of 10 or more indicates excessive daytime somnolence.<sup>21</sup> Slightly adapted versions of this questionnaire have been used to measure sleepiness in adolescents, and the reliability has been demonstrated.<sup>22</sup> These measures were taken concurrently.

### Polysomnography

Standard overnight polysomnographic recordings were performed on an ALICE III<sup>®</sup> digital polygraph. Sleep studies were set to begin between 9 and 10 p.m. (lights-out) and end at 6 a.m. (lights-on). Monitored variables included electroencephalogram (EEG) ( $C_3$ ,  $C_4$ ,  $O_1$ ,  $O_2$  referenced to contralateral ear electrodes), electro-oculograms (EOG), submental electro-myogram (EMG), two-lead electrocardiogram (ECG), and pulse oximetry. Leg movements were monitored using a bilateral tibialis EMG and respiration using a nasal/oral thermocouple and nasal cannula. Body position and thoracic and abdominal movements (inductance plethysmography) were also recorded. Sleep staging was performed using a 30-sec epoch according to standard criteria. Polysomnography-derived parameters evaluated were AHI, minimum oxygen saturation ( $\text{SaO}_2$ ), mean

SaO<sub>2</sub> during sleep, percent of sleep time under 90% SaO<sub>2</sub>, sleep latency, desaturation index, sleep efficiency, REM sleep latency, amount of REM sleep (% of total sleep time), amount of non-rapid eye movement (NREM) sleep (% of total sleep time), number of arousals per hour of sleep (arousal index), and periodic leg movement per hour of sleep (PLM index). Arousal analysis and scoring of respiratory events during sleep were performed according to standard criteria.<sup>23</sup> Obstructive apneas were defined by the absence of airflow in the presence of continued respiratory effort lasting more than two respiratory cycles. The central apnea was defined by the cessation of airflow more than 10 sec, without chest and abdominal movements. Hypopneas were defined as a decrease in nasal airflow of at least 50% with a more than 3% fall in saturation an arousal, or both. Severity of sleep-disordered breathing was estimated by calculating the AHI (apneas plus hypopneas per hour of sleep).<sup>24</sup> Significant nocturnal desaturation was considered to be present if SaO<sub>2</sub> values were below 90% for at least 30% of the total sleep time and/or SaO<sub>2</sub> reached values below 85% during sleep.

### Statistical Analysis

Results are given as means  $\pm$  standard deviation (SD). Cystic fibrosis cases were grouped according to the presence or absence of lung disease and comparisons between these two groups and with non-CF normal controls were performed. Differences between groups were assessed by ANOVA, Fisher's exact test for categorical variables, Student's *t*-test for continuous variables, and Mann-Whitney test for non-parametric variables. Tukey post hoc test was used after ANOVA, when appropriate. A linear correlation analysis between FEV1 percent predicted, oxygen saturation values, and PSQI results was performed. The relations between significant nocturnal desaturation (SaO<sub>2</sub> <90% for at least 30% of the total sleep time or SaO<sub>2</sub> below 85% during sleep) and resting awake SaO<sub>2</sub> values, the S-K scores, and spirometric tests were examined by plotting receiver operating characteristic (ROC) curves. Statistical analysis was performed with the Statistic Package for Social Sciences (SPSS-16) software for Windows. Statistical significance was assumed at  $P < 0.05$ .

### RESULTS

We studied 30 CF cases with clinical lung disease (12M/18F; mean age  $12.8 \pm 6.6$ ) and 10 CF cases without significant lung disease (2M/8F; mean age  $13.3 \pm 4.7$ ). Twenty normal individuals (10M/10F; mean age  $15.5 \pm 4.3$ ) were included as controls. The three groups were similar with respect to age and gender (ANOVA,  $P = 0.25$ ; Fisher's exact test,  $P = 0.29$ , respectively). The BMI was lower in CF cases with clinical lung disease

( $17.1 \pm 2.9$ ) as compared to CF cases without significant lung disease ( $20.7 \pm 3.8$ ;  $P = 0.003$ ) and normal controls ( $21.0 \pm 2.3$ ;  $P < 0.005$ ).

Polysomnographic findings are summarized in Table 1. CF cases with clinical lung disease showed reduced sleep latency as compared to CF cases without significant lung disease as well as non-CF controls. The amount of stages 3–4 NREM sleep and REM sleep were not significantly different between cases and controls. Cases with CF and clinical lung disease had lower resting awake SaO<sub>2</sub> values ( $96.69 \pm 1.36$ ) than CF cases without significant lung disease ( $97.90 \pm 0.56$ ;  $P = 0.002$ ) and controls ( $97.65 \pm 0.48$ ;  $P = 0.002$ ). Normal controls had higher SaO<sub>2</sub> mean values during sleep than both groups of CF cases. Five CF cases with clinical lung disease (15%) had SaO<sub>2</sub> values below 90% for more than 30% of total sleep time and in 11 cases (36.6%) SaO<sub>2</sub> reached levels below 85% during sleep. Obstructive sleep apnea was found both in CF patients with clinical lung disease ( $N = 2$ ; AHI = 8 and 11/hr) and without significant lung disease ( $N = 1$ ; AHI = 11/hr). Ear, nose, and throat examination was performed in all patients. Isolated small nasal polyps were found in six cases. All patients with obstructive sleep apnea had nasal septal deviation, adenotonsillar hypertrophy, and pansinusitis. Sleep efficiency, arousal index, AHI, NREM sleep, and REM sleep were not significantly different in CF cases with or without pulmonary disease.

Individuals with CF and clinical lung disease showed lower scores of the S-K index of disease severity, in comparison to those with pancreatic insufficiency and without significant lung disease (Table 1). Cases with clinical lung disease tended to walk shorter distances than those without significant lung disease in the 6MWT. Poor sleep quality (PSQI >6) was present in five CF cases with clinical lung disease and in two cases without significant lung disease. Frequent cough was present in all cases with clinical lung disease and poor quality sleep ( $N = 5$ ). PSQI scores were not different between the two groups (Table 1). FEV1 values were not related to sleep quality as evaluated by PSQI ( $F = 2.58$ ,  $P = 0.12$ ). Excessive daytime sleepiness was present in four CF patients with clinical lung disease and was not correlated with FEV1 values ( $F = 0.28$ ,  $P = 0.59$ ). Cases with clinical lung disease and nocturnal desaturation as evaluated by sleep time with SaO<sub>2</sub> <90% presented poor sleep quality ( $P = 0.007$ ). Patients with nadir SaO<sub>2</sub> <85% presented lower FEV1 ( $P = 0.03$ ) (Table 2).

FEV1 values for CF cases with significant lung disease were related to nadir SaO<sub>2</sub> ( $F = 4.73$ ,  $P < 0.03$ ; Fig. 1) and to mean SaO<sub>2</sub> ( $F = 6.0$ ;  $P = 0.02$ ; Fig. 2). The FEV1 cutoff for oxygen desaturation during sleep was found to have the greatest ROC at 64% predicted according to both oxygen desaturation criteria used in

**TABLE 1—Clinical and Polysomnographic Measures (Mean ± SD) of 40 Cases With Cystic Fibrosis With Clinical Lung Disease (Group 1), Without Significant Lung Disease (Group 2), and Controls (Group 3)**

Variables	Group 1 (N = 30)	Group 2 (N = 10)	Group 1 vs. 2	Group 3 (N = 20)	Group 1 vs. 3, <sup>1</sup> Group 2 vs. 3 <sup>2</sup>
Gender (M/F)	18/12	8/2	0.44 <sup>3</sup>	10/10	0.56 <sup>3</sup> 0.23 <sup>3</sup>
Age (range, mean ± SD)	6–28 12.8 ± 6.61	7–22 13.3 ± 4.78	0.97 <sup>1</sup>	8–25 15.5 ± 4.33	0.23 <sup>1</sup> 0.56 <sup>1</sup>
Age at diagnosis (y)	4.63 ± 5.64	2.93 ± 2.36	0.41 <sup>2</sup>		
Duration of symptoms (y)	11.14 ± 6.42	11.49 ± 4.06	0.87 <sup>2</sup>		
BMI	17.13 ± 2.92	20.75 ± 3.81	0.003 <sup>2</sup>	21.02 ± 2.32	<0.005 <sup>2</sup> 0.96 <sup>2</sup>
FEV1	27–100 65.29 ± 24.83	85–110 99.82 ± 8.31	<0.005 <sup>2</sup>		
FVC	71.99 ± 17.96	100.70 ± 9.66	<0.005 <sup>2</sup>		
S–K scores	64.48 ± 16.22	94.0 ± 5.16	<0.005 <sup>2</sup>		
6MWT (m)	479.72 ± 69.70	528.56 ± 77.57	0.06 <sup>2</sup>		
PSQI scores	4.00 ± 3.73	3.70 ± 1.82	0.53 <sup>2</sup>		
Epworth Sleepiness Scale	5.59 ± 3.05	4.20 ± 2.65	0.21 <sup>2</sup>		
TST (min)	436.55 ± 42.26	434.86 ± 57.35	0.87 <sup>2</sup>	418.92 ± 38.65	0.16 <sup>2</sup> 0.34 <sup>2</sup>
Sleep efficiency (TST/TRT %)	94.71 ± 5.68	93.11 ± 4.53	0.21 <sup>2</sup>	95.32 ± 2.97	0.75 <sup>2</sup> 0.18 <sup>2</sup>
Sleep latency (min)	12.40 ± 5.68	22.75 ± 4.53	0.01 <sup>2</sup>	18.47 ± 10.62	0.02 <sup>2</sup> 0.27 <sup>2</sup>
REM sleep latency (min)	118.21 ± 51.54	182.25 ± 73.40	0.01 <sup>2</sup>	100.76 ± 37.20	0.16 <sup>2</sup> 0.002 <sup>2</sup>
Arousal index	8.04 ± 3.96	10.63 ± 3.76	0.06 <sup>2</sup>	8.75 ± 5.31	0.98 <sup>2</sup> 0.19 <sup>2</sup>
NREM stages 3–4 (% TST)	17.49 ± 2.22	16.90 ± 1.66	0.68 <sup>2</sup>	18.93 ± 4.08	0.19 <sup>2</sup> 0.23 <sup>2</sup>
REM sleep (% TST)	19.16 ± 6.69	15.85 ± 7.39	0.16 <sup>2</sup>	22.04 ± 4.30	0.07 <sup>2</sup> 0.004 <sup>2</sup>
SaO <sub>2</sub> mean (%)	93.03 ± 3.48	94.50 ± 1.90	0.20 <sup>2</sup>	95.75 ± 1.07	0.001 <sup>2</sup> 0.04 <sup>2</sup>
SaO <sub>2</sub> minimum (%)	84.87 ± 7.69	89.89 ± 2.08	0.05 <sup>2</sup>	91.85 ± 2.60	<0.005 <sup>2</sup> <0.12 <sup>2</sup>
Time SaO <sub>2</sub> <90% (min)	61.78 ± 128.19	3.60 ± 5.49	0.05 <sup>2</sup>	0.20 ± 0.20	<0.005 <sup>2</sup> 0.21 <sup>2</sup>
%Time SaO <sub>2</sub> <90%	15.03 ± 31.21	0.86 ± 1.32	<i>P</i> < 0.05 <sup>2</sup>	0.04 ± 0.07	0.06 <sup>2</sup> 0.99 <sup>2</sup>
Desaturation Index	10.19 ± 12.29	6.61 ± 6.50	0.39 <sup>2</sup>	4.7 ± 2.1	0.02 <sup>2</sup> 0.34 <sup>2</sup>
AHI	2.17 ± 2.50	1.92 ± 2.90	0.50 <sup>2</sup>	1.77 ± 1.21	0.82 <sup>2</sup> 0.27 <sup>2</sup>

BMI, body mass index; y, years; FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; S–K, Shwachman–Kulczycki; 6MWT, 6 min Walk test; PSQI, Pittsburgh Sleep Quality Index; TST, total sleep time; SaO<sub>2</sub>, oxygen saturation; min, minutes; AHI, Apnea + Hypopnea Index.

<sup>1</sup>Student's *t*-test.

<sup>2</sup>Mann–Whitney test.

<sup>3</sup>Fisher's exact test.

this study: minimum SaO<sub>2</sub> below 85% during sleep (sensitivity = 92.3%; specificity = 77.3%) (Fig. 3) and SaO<sub>2</sub><90% for at least 30% of sleep time (sensitivity = 81.8%; specificity = 85.2%) (Fig. 4). Data from two cases with very low FEV1 were clearly outlying the remaining data and were excluded from ROC curve analysis. Resting awake SaO<sub>2</sub> and S–K score were not good predictors of nocturnal desaturation.

## DISCUSSION

Our results show that significant nocturnal desaturation is common in young and clinically stable CF patients and can be predicted by lung function tests.

Objective evidence for a clear definition of significant hypoxia in CF is still lacking. Previously, hypoxia during sleep has been variably quantified as the minimum oxygen

**TABLE 2—Characteristics of Cystic Fibrosis Patients (n = 30) With Clinical Lung Disease According to the Presence of Nocturnal Desaturation**

Variables	SaO <sub>2</sub> <90% more than 30% TST		Nadir SaO <sub>2</sub> <85%			
	Yes (N = 4)	No (N = 26)	Yes (N = 11)	No (N = 19)		
Age (y)	17.00 ± 5.19	12.03 ± 6.46	0.22	13.77 ± 4.60	11.97 ± 7.46	0.52
Duration of symptoms (y)	12.00 ± 7.0	10.73 ± 5.9	0.73	11.52 ± 4.72	10.50 ± 6.67	0.69
BMI	17.55 ± 4.31	17.26 ± 2.95	0.97	16.76 ± 2.12	17.62 ± 3.42	0.50
FEV1	49.06 ± 10.54	70.35 ± 24.15	0.15	54.88 ± 18.5	75.73 ± 23.8	0.03*
FVC	59.33 ± 29.36	73.18 ± 15.82	0.21	63.8 ± 19.95	76.24 ± 15.06	0.10
S–K scores	53.33 ± 12.58	68.00 ± 17.04	0.17	61.67 ± 15.20	68.93 ± 18.10	0.33
6MWT (m)	445.72 ± 28.48	487.40 ± 67.31	0.30	482.62 ± 73.29	481.54 ± 61.56	0.97
PSQI scores	9.33 ± 5.85	3.20 ± 2.94	0.007**	5.44 ± 5.81	3.07 ± 1.54	0.15
Epworth sleepiness scale	5.33 ± 1.52	5.25 ± 3.19	0.96	5.33 ± 2.59	5.21 ± 3.33	0.92

BMI, body mass index; y, years; FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; S–K, Shwachman–Kulczycki; 6MWT, 6 min walk test; PSQI, Pittsburgh Sleep Quality Index.

\**P* < 0.05.

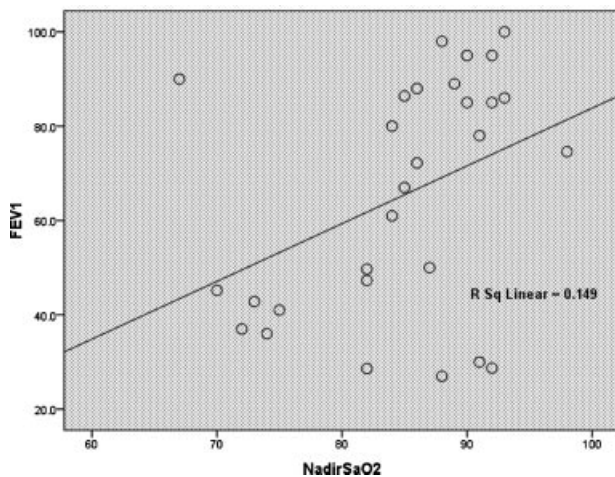
\*\**P* < 0.01.

saturation during sleep, medium oxygen saturation during sleep, percentage of time spent with oxygen saturation below 90%, or the lowest mean oxygen saturation per hour of sleep. In order to better assess the influence of clinical factors, two different criteria for nocturnal desaturation were used in this study: SaO<sub>2</sub> below 90% for more than 30% of total sleep time and/or SaO<sub>2</sub> below 85% during sleep time. These definitions are generally adopted for sleep-related oxygen desaturation and the former has been proven to be causally related to permanent pulmonary hypertension in COPD patients.<sup>25</sup>

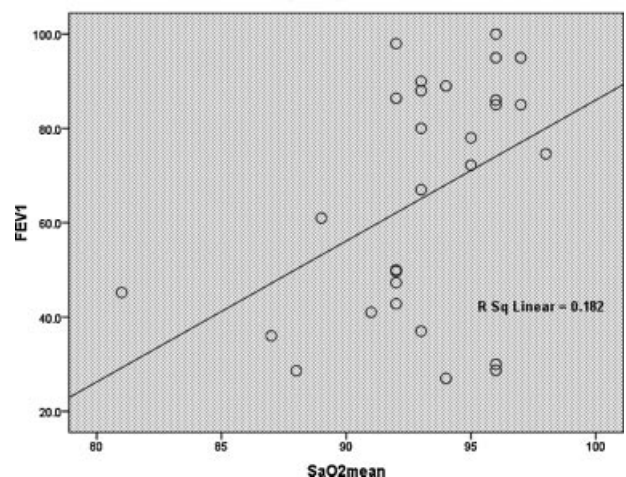
In agreement with our findings, two previous studies have suggested that an FEV1 below 64% has good sensitivity to predict hypoxia during sleep in CF, although specificity was relatively weak.<sup>26,27</sup> Additionally, FEV1 <64% has been shown to be predictive of desaturation

during flights.<sup>28</sup> A previous study using home nocturnal oxygen monitoring, without polysomnographic recording, has suggested that desaturation during sleep cannot be reliably predicted from clinical scores or awake pulmonary function in patients with CF.<sup>29</sup> One explanation for these findings could be the presence of undetected reduced sleep efficiency or increased sleep fragmentation because these results were obtained with nocturnal oxymetry.

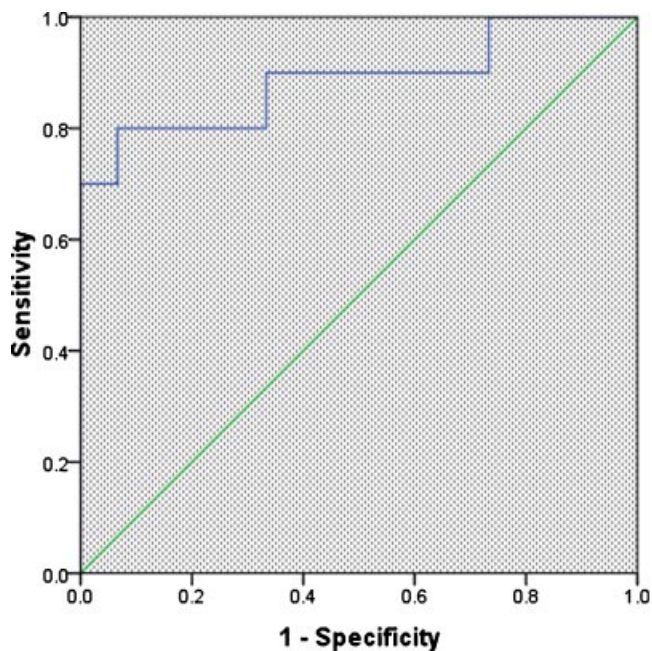
In the present study, resting awake SaO<sub>2</sub> values were not predictive of nocturnal oxygen desaturation. It should be noted that, as arterial blood gases analysis was not performed, it could still be argued that daytime PaO<sub>2</sub> may be a predictor of nocturnal desaturation despite our finding that resting awake SaO<sub>2</sub> is not. Previously, a study using oximetry identified a resting SaO<sub>2</sub> <94% to be associated with nocturnal desaturation.<sup>26</sup> Another report, using



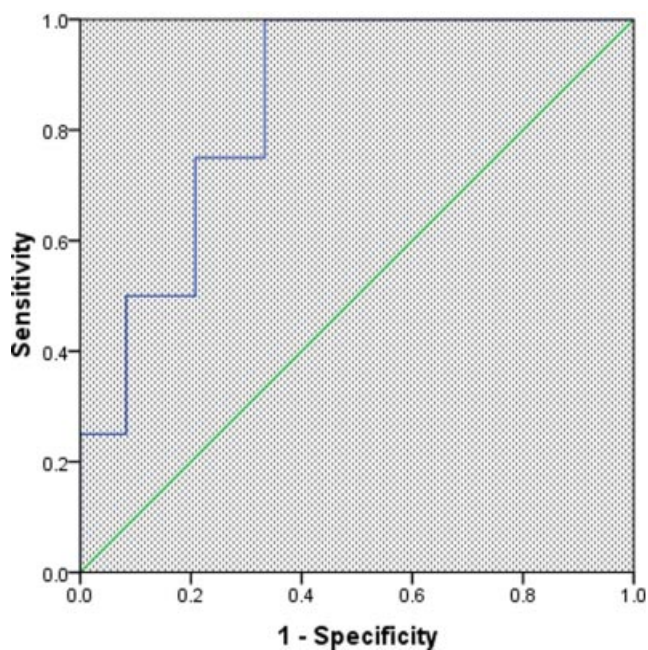
**Fig. 1. Correlation analysis between FEV1 and nadir SaO<sub>2</sub> values.**



**Fig. 2. Correlation analysis between FEV1 and mean SaO<sub>2</sub> values.**



**Fig. 3.** Receiver operator characteristic curve for predicting nocturnal desaturation (Nadir  $\text{SaO}_2 < 85\%$ ) using FEV1 values. The area under the curve was 0.81. The threshold relating to the point on the ROC curve closest to the top left corner was 64 with a sensitivity of 92.3% and specificity of 77.3%.



**Fig. 4.** Receiver operator characteristic curve for predicting nocturnal desaturation (total time below  $\text{SaO}_2 < 90\%$ ) using FEV1 values. The area under the curve was 0.81. The threshold relating to the point on the ROC curve closest to the top left corner was 64 with a sensitivity of 81.8% and specificity of 85.2%.

nocturnal oxymetry, described nocturnal desaturation in 36% of patients with an awake resting  $\text{SaO}_2 > 93\%$ .<sup>30</sup>

The mechanism for nocturnal desaturation in CF has not been fully elucidated. It could be the result of reduced respiratory drive and tidal volume and a loss of functional residual capacity, particularly during REM sleep, aggravated by respiratory muscle weakness secondary to malnutrition in these patients.<sup>7,31</sup> It has been reported that nocturnal hypoxemia could be dependent on the degree of hyperinflation, but not on respiratory muscle strength or nutritional status in CF patients (6). This is in agreement with our results that show reduced FVC and an increase in FEV1/FVC in CF patients with clinical lung disease. Further studies, with concomitant analysis of nocturnal  $\text{PCO}_2$ , are needed to clarify this issue.

The consequences of the hypoxic insult in CF have not been completely clarified. Survival rates are greatly influenced by pulmonary infective exacerbations and the role of hypoxia may be different from other chronic lung diseases, such as COPD. In COPD,  $\text{O}_2$  supplementation has been shown to improve survival and is an integral guideline in the presence of diurnal desaturation.<sup>32</sup> In some countries, it has become increasingly common to use non-invasive ventilation as first-line treatment for CF with severe hypercapnic respiratory exacerbation or for stable diurnal hypercapnia, particularly when associated with sleep disturbance.<sup>33</sup> However, the benefits from this therapeutic approach adequately have not been proven, and impact of non-invasive ventilation on pulmonary exacerbations and disease progression remains unclear. A previous report showed that in CF cases, bilevel ventilatory support (BVS) and low-flow oxygen therapy improved nocturnal oxygen saturation. An attenuation of the transcutaneous carbon dioxide observed in association with BVS suggested that the latter improved alveolar ventilation during sleep.<sup>34</sup>

To our knowledge, a comparison of sleep patterns between cases with selective pancreatic insufficiency and with the more severe forms of pulmonary disease has not been previously reported. In this study of young CF patients, sleep macroarchitecture was not strikingly different in cases with lung disease as compared to those without. Sleep macroarchitecture refers to the measures obtained from visual stage scoring of sleep EEG including sleep latency, REM latency, total sleep time, and the minutes and percentages of stages 1–4 of NREM sleep, REM, and awake.

Our patients with CF cases and lung disease showed reduced sleep latency suggesting that they may experience more sleepiness than cases without pulmonary disease. Our CF patients without lung disease showed increased REM sleep latency and reduced amount of REM sleep. However, these changes may be relatively non-specific and more related to the first-night effect. Previously, sleep architecture in CF has been investigated in a very limited

number of studies. Naqvi and coworkers have recently reported a decrease in sleep efficiency, prolonged REM latency, and reduction in percentage of REM sleep in 24 children and adolescents with CF as compared to 14 normal controls. The magnitude of sleep disruption was associated with severity of lung disease, but was not directly correlated with the degree of nocturnal hypoxemia or hypoventilation in their subjects.<sup>14</sup> It should be emphasized that our observations refer to individuals on a clinically stable condition and that severe exacerbations are likely to produce marked sleep disruption.

In this study, obstructive sleep apnea was found both in CF patients with clinical lung disease and without significant lung disease. The frequency of sleep apnea in CF is presently unknown and further large population studies are needed to clarify this issue. Based on our findings and in other report,<sup>35</sup> it seems reasonable to suggest that all patients with CF should be questioned about the occurrence of symptoms of obstructive sleep apnea, including snoring, and that full polysomnography should be performed whenever a positive history is elicited. Additionally, patients with complications of chronic hypoxemia, such as cor pulmonale and with an FEV1  $\geq 65\%$  predicted, should also be probably investigated.

## CONCLUSIONS

Significant nocturnal desaturation is common in young clinically stable patients with CF and can be predicted by an FEV1  $< 64\%$ . Polysomnography can reveal the occasional subject with obstructive sleep apnea but no major objective sleep alterations other than oxygen desaturation are found in clinically stable CF patients with and without significant clinical lung disease.

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