The Relationship Between Sleep Disturbance and Pulmonary Function in Stable Pediatric Cystic Fibrosis Patients*

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Background: Cystic fibrosis (CF) is the most common inherited disease affecting northern European populations. It is characterized by a progressive clinical course that causes diurnal and nocturnal pulmonary and gastrointestinal symptoms.

Objectives: To determine whether clinically stable pediatric patients with CF have lower sleep efficiency than healthy control subjects, and to examine the relationship between sleep efficiency and pulmonary function.

Methods: Forty-four CF patients and 40 control subjects completed 5 days of actigraphy recordings. Additionally, sleep questionnaires were independently completed by all study participants and their parents. Pulmonary function testing was performed in all patients with CF. Multiple regression analysis was used to measure the independent correlation between sleep variables and pulmonary function.

Results: CF patients had significantly lower sleep efficiency than control subjects. The FEV1 of these patients correlated positively with sleep duration and efficiency, and negatively with the number and duration of nocturnal awakenings, age, and body mass index (BMI). The independent effect of FEV1 on sleep was first examined. Age and FEV1 were the only variables that predicted sleep duration ($R^2 = 0.3; p = 0.0007$), while FEV1 was the only variable predicting sleep efficiency ($R^2 = 0.28; p = 0.0002$). When the independent effect of sleep on FEV1 was analyzed, sleep efficiency, BMI percentile, and gender predicted FEV1 ($R^2 = 0.46; p ≤ 0.0001$). The frequency of nocturnal cough reported by patients and their parents was an independent predictor of FEV1.

Conclusions: Pediatric patients with CF and stable pulmonary function have lower sleep efficiency and more frequent nocturnal awakenings than do healthy control subjects. After adjustment for demographic characteristics, there was an independent and significant correlation between sleep parameters and FEV1, when either sleep variables or FEV1 were used as dependent variables. These findings suggest a bidirectional relationship between sleep disturbance and CF lung disease.

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Key words: cystic fibrosis; pulmonary function; sleep disturbance

Abbreviations: BMI = body mass index; CF = cystic fibrosis; Th = T helper

Cystic fibrosis (CF) is the most common inherited disease affecting northern European populations, occurring with a prevalence of 1 in 3,400 births. The phenotypic picture of CF is the result of chronic pulmonary and pancreatic disorders that develop secondary to the genetic defect. Defective ion transport along the airway epithelium and altered antimicrobial defense in the airways lead to chronic endobronchial bacterial infection with severe neutrophilic inflammation. The clinical course of CF lung disease is characterized by intermittent increases in bacterial load in the lungs, worsening airway inflammation, and progressive loss of lung function. The gastrointestinal manifestations of CF are the result of pancreatic insufficiency leading to protein and fat malabsorption, which is partially corrected by a replacement of pancreatic enzymes.

Over the past several decades, there has been a...
steady increase in the life expectancy of CF patients.\(^2\) This trend can be attributed to a better understanding of the factors that contribute to the rate of pulmonary function decline. Such factors include the roles of adequate nutrition,\(^3\)–\(^5\) early diagnosis and management of glucose intolerance,\(^6\)–\(^12\) frequency of endobronchial infections,\(^13\) and implementation of airway clearance.\(^14\) Sleep loss is known to have negative effects on mental and neurocognitive functions,\(^15\)–\(^17\) and on multiple metabolic parameters, including glucose metabolism.\(^18\)–\(^22\) It has also been associated with alterations in the normal circadian cytokine network,\(^23\) the expression of adhesion molecules,\(^24\) and the balance between cellular and humoral immune responses.\(^25\),\(^26\) Previous studies\(^27\)–\(^31\) have shown an association between sleep disturbance and CF lung disease in patients with severe airway obstruction and nocturnal hypoxemia. However, whether sleep disturbance exists in CF patients with mild-to-moderate airway obstruction, and whether it has a negative impact on the clinical course of CF lung disease are not known. Understanding the interaction between sleep disturbance and CF lung disease could have important therapeutic implications. The objectives of the present study were thus twofold, as follows: to determine whether patients with clinically stable CF and mild-to-moderate pulmonary disease had lower sleep efficiency than healthy control subjects, and to examine the relationship between sleep efficiency and pulmonary function. To accomplish these objectives, we tested the hypothesis that nocturnal pulmonary and GI symptoms contribute to sleep disturbance, which in turn may adversely affect pulmonary function. To this end, we objectively measured sleep quality in the home environment, assessed children’s perceptions of their own sleep, assessed parents’ perceptions of their child’s sleep, and explored the independent effect of sleep disturbance on pulmonary function. This study was approved by our institutional review board; an assent form was obtained from participants who were > 11 years of age.

**Materials and Methods**

**Subjects**

White CF patients ranging in age from 8 to 18 years were recruited from the CF clinic in a tertiary care center. The inclusion criteria included the following:

1. The absence of comorbidities, including diabetes mellitus, parenteral or tube feeding, use of antidepressant or hypnotic medications, and a confirmed diagnosis of asthma;
2. The absence of acute pulmonary infection requiring therapy with oral or IV antibiotics;
3. No antibiotic therapy for at least 4 weeks prior to enrollment in the study;
4. No history of lung transplantation;
5. \(\text{FEV}_1\) within 10% of previous baseline value obtained within 3 to 6 months from the study date; and
6. Adherence to the use of actigraphy for at least 4 days.

Age-matched, gender-matched, and race-matched control subjects who were free from any acute or chronic pulmonary disease or other medical conditions were also recruited.

**Actigraphy**

The actigraph (Basic Motionlogger; Ambulatory Monitoring; Ardsley, NY) is a miniature, wristwatch-like device that monitors activity levels for extended continuous periods. Previous work\(^32\)–\(^35\) has demonstrated its validity in monitoring sleep-wake patterns among infants, children, and adults. Actigraphic measures were averaged across 5 weekdays of monitoring. Actigraphic sleep measures included the following: sleep duration; sleep efficiency (ie, the percentage of true sleep time in the total sleep period), the number and duration of night awakenings lasting ≥ 5 min, and the total duration of awakenings after sleep onset.

**Daily Sleep Logs:** Daily sleep logs were completed by all participants and their parents. The measures were averaged across the monitoring period. The derived measures included the following: sleep onset; sleep duration; and awakening time.

**Survey Questionnaire**

A modified validated questionnaire consisting of 53 questions was administered to children with CF and age-matched, gender-matched, and race-matched control subjects.\(^36\),\(^37\) The questionnaire included demographic data, and questions pertaining to the child’s and parents’ medical histories. Thirty-three questions pertained to symptoms of sleep-disordered breathing, including nocturnal cough, sleep habits (eg, nocturnal use of bathroom), and symptoms of daytime sleepiness. The responses were graded as follows: never; less than once per week; one to two times per week; three to four times per week; and almost daily. To measure the degree of agreement between the responses of children and their parents, identical questionnaires were administered to parents. Both parents and children were instructed to complete the questionnaires independently.

**Pulmonary Function Testing**

All patients with CF underwent pulmonary function testing. Spirometry was performed (SensorMedics; Yorba Linda, CA) according to American Thoracic Society standards.\(^38\) Values were expressed as percentages of the predicted normal values, with adjustments made for age, sex, and height.

**Statistical Analysis**

Data from actigraphy were analyzed by \(t\) test, and \(\chi^2\) analysis was performed to measure differences in questionnaire responses between CF and control groups. For each group, \(\kappa\)-statistics were calculated to measure the degree of agreement between parents’ and children’s responses. In the CF group, multiple regression analysis was performed to measure the independent correlation between sleep variables and \(\text{FEV}_1\). In the regression analysis, male gender was coded “2” and female gender was coded “1.”
RESULTS

The study population comprised 50 CF patients and 43 control subjects. Five CF patients and three control subjects did not complete the actigraphy recording, and one participant who was thought to have CF and completed the study was later found to have been misdiagnosed. The two groups (44 CF patients and 40 control subjects) differed only in their body mass index (BMI) [Table 1]. Overall, children with CF had a mild degree of small airway obstruction (Table 2). The overall mean (±SD) FEV₁ was 74 ± 19% predicted. There was no difference between the mean FEV₁ value for females (73 ± 22% predicted) and that for males (75 ± 15% predicted).

Actigraphy

Sleep efficiency decreased with increased severity of lung disease (Fig 1). Children with CF had significantly lower sleep efficiency and more frequent awakenings from sleep compared to control subjects (Table 3). In children with CF, FEV₁ correlated positively with sleep duration and sleep efficiency, and negatively with the duration and number of awakenings after sleep onset (Fig 2).

In a regression model, which included demographic variables, age, gender, BMI expressed as a percentile, and FEV₁, age (β = −7.7; p = 0.009) and FEV₁ (β = 0.9; p = 0.02) were the only variables that predicted sleep duration (R² = 0.3; p = 0.0007), while FEV₁ (β = 0.18) was the only variable that predicted sleep efficiency (R² = 0.28; p = 0.0002).

The independent effect of sleep parameters on FEV₁ was examined in a regression model that included demographic variables, age, gender, BMI expressed as a percentile, and sleep efficiency and duration as measured by actigraphy. Sleep efficiency (β = 1.38; p = 0.0002), BMI percentile (β = 0.29; p = 0.0013), and gender (β = −10; p = 0.04) predicted FEV₁ (R² = 0.46; p < 0.0001). When sleep duration rather than sleep efficiency was entered as an independent variable, BMI percentile (β = 0.24; p = 0.02) and sleep duration (β = 0.09; p = 0.04) were the only variables predicting FEV₁ (R² = 0.28; p = 0.0012).

Survey Questionnaire

Children’s Responses: Compared to control subjects, children with CF reported more frequent awakenings with cough (p < 0.0001), more frequent awakenings for bathroom use (p = 0.005), more frequent difficulty initiating sleep (p = 0.04), and more frequent watching of television at bedtime (p = 0.03). The reason for more frequent nocturnal bathroom use was defecation for children with CF vs micturition for control subjects (p = 0.007).

Parents’ Responses: Compared to the parents of control subjects, the parents of children with CF reported that their children demonstrated more frequent awakenings with cough (p < 0.0001), more frequent awakenings for bathroom use (p = 0.02), more nocturnal sweating (p = 0.014), loud snoring (p = 0.007), and morning sleepiness (p = 0.007), and more frequent difficulty initiating sleep (p = 0.04). The reason for nocturnal bathroom use

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Table 1—Demographic Characteristics of Study Participants*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CF Group</th>
<th>Control Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>11.9 ± 2.8</td>
<td>12.6 ± 2.8</td>
<td>NS</td>
</tr>
<tr>
<td>Female (%)</td>
<td>23 (52)</td>
<td>22 (55)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight percentile</td>
<td>35 (26)</td>
<td>54 (29)</td>
<td>0.002†</td>
</tr>
<tr>
<td>BMI</td>
<td>18 ± 3</td>
<td>20 ± 5</td>
<td>0.02†</td>
</tr>
<tr>
<td>BMI percentile</td>
<td>31 ± 28</td>
<td>49 ± 33</td>
<td>0.02†</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD or No. (%), unless otherwise indicated. NS = not significant.
†Significant difference.

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Figure 1. Sleep efficiency of patients with CF measured by actigraphy across four levels of FEV₁. A significant trend across the four groups was measured (p = 0.01). A significant difference was found between patients with normal lung function vs patients with severely abnormal lung function (p = < 0.05), and between children with mild lung disease vs severe lung disease (p < 0.05).
Table 3—Results of 5 Consecutive Days of Actigraphy Recording

<table>
<thead>
<tr>
<th>Variables</th>
<th>CF Group</th>
<th>Control Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep efficiency</td>
<td>91.4 ± 8.9</td>
<td>94.5 ± 4</td>
<td>0.038</td>
</tr>
<tr>
<td>Waking episodes &gt; 5 min, No.</td>
<td>2.2 ± 1.9</td>
<td>1.5 ± 1.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Longest waking episode, min</td>
<td>14.1 ± 12.8</td>
<td>8.6 ± 6</td>
<td>0.016</td>
</tr>
<tr>
<td>Sleep duration, h</td>
<td>8.3 ± 0.9</td>
<td>8.7 ± 0.8</td>
<td>0.07</td>
</tr>
<tr>
<td>Waking after sleep onset, min</td>
<td>40 ± 38</td>
<td>29 ± 22</td>
<td>0.09</td>
</tr>
</tbody>
</table>

was defecation for children with CF vs micturition for control subjects (p = 0.015).

Agreement Between Measured and Reported Sleep Periods: For all participants, the duration of sleep measured by actigraphy correlated with the sleep period reported by children (r = 0.48; p ≤ 0.0001) and that reported by parents (r = 0.58; p ≤ 0.0001). A lower correlation between reported and measured sleep duration was observed in the CF group vs the control group. In the CF group, the duration of sleep measured by actigraphy showed no significant correlation with the duration of sleep reported by children (r = 0.18; p = 0.2) or with that reported by parents (r = 0.29; p = 0.06). However, in the control group, the duration of sleep measured by actigraphy showed a significant correlation both with that reported by children (r = 0.71; p = < 0.0001) and that reported by parents (r = 0.79; p = < 0.0001). For both the CF patients and control subjects, the measured sleep duration was shorter than that reported by either children or their parents. This difference was larger for the CF group (Table 4).

Agreement Between Children’s and Parents’ Responses: For both CF patients and control subjects, the reported sleep duration showed a strong correlation with that reported by parents (r = 0.83; p = < 0.0001).

CF Group: In the CF group, children and parents differed in their responses to three questions. Compared to parents’ responses, children’s responses indicated more frequent positive responses to watching television at bedtime (p = 0.008), more frequent positive responses to eating and drinking during the night (p = 0.02), and less frequent nocturnal sweating (p = 0.025).

Figure 2. Relationship between FEV1 and sleep variables measured by actigraphy. A positive correlation between FEV1 and sleep efficiency (top left, A) and sleep duration (top right, B) was found. A negative correlation between FEV1 and duration of wakefulness after sleep onset (00-WAS) [bottom left, C] and the number of awakenings > 5 min in duration (#WEF > 5 min) [bottom right, D] was found.
Control Group: Compared to parents’ responses, children reported a higher degree of sleepiness on awakening (p = 0.01) and during the day (p = 0.01).

Relationship Between Nocturnal Symptoms and FEV1

Children’s Responses: In the multiple regression analysis, which included demographic variables, age, gender, BMI expressed as a percentile, and frequency of nocturnal cough, a model that consisted of BMI expressed as a percentile (β = 0.38; p ≤ 0.001), nocturnal cough (β = -4.7; p = 0.01), and gender (β = -9; p = 0.04) predicted FEV1 (R² = 0.44; p ≤ 0.0001).

Parents Responses: In the multiple regression, which included demographic variables, age, gender, BMI expressed as a percentile, and frequency of nocturnal cough, a model that consisted of BMI percentile (β = 0.25; p = 0.007) and nocturnal cough (β = -8.2; p = 0.001) predicted FEV1 (R² = 0.41; p = < 0.0001).

Discussion

For the first time (to our knowledge), this study provides both objective and subjective assessments of the sleep quality of clinically stable patients with CF and mild-to-moderate lung disease. The pulmonary function of children with CF typically fluctuates from nadir levels that precede the treatment of endobronchial infection to peak levels that follow treatment. This study assessed sleep quality when pulmonary function was neither at its nadir nor at its peak, but during the intervening period. This period better reflects the usual state of health of CF patients.

The objective measures of sleep quality provided by actigraphy and the subjective measures provided by questionnaires completed by children and their parents demonstrated that children with CF have lower sleep efficiency and more frequent nocturnal awakenings compared to age-matched and gender-matched control subjects. Sleep efficiency and duration were closely associated with FEV1. This independent and significant association between sleep variables and FEV1 was demonstrated when either sleep parameters or FEV1 was used as an outcome variable.

The effect of the severity of pulmonary disease on sleep has been examined in previous studies27–31 that have focused primarily on CF patients with moderate-to-severe lung disease. These studies proposed that sleep-related intermittent hypoxia and hypercapnia are likely mechanisms for sleep disruption. Although severe hypoxemia and hypercapnia could have contributed to increased frequency of arousals in these studies, it is unlikely that they played an important role in our study population. Ninety-three percent of our CF patient group had FEV1 in the normal to moderately abnormal range. In the absence of acute pulmonary infection and with only a mild abnormality of FEV1, it is less likely that severe blood gas abnormalities played an important role in causing sleep disturbance.

Our study explored the association between nocturnal pulmonary symptoms and sleep disturbance. The frequency of awakening with nocturnal cough was reported more frequently by patients with CF and their parents than by control subjects, and was independently associated with FEV1. This observation demonstrates that with the decline in lung function, the frequency of nocturnal cough increases. If nocturnal cough is a mechanism for sleep disturbance in clinically stable CF patients, then one would expect further sleep disruption when FEV1 approaches its nadir during pulmonary infection. However, a causal relationship between cough and sleep disturbance could not be substantiated. This indicates that cough can only occur during consciousness. Experiments performed on sleeping animals and humans have shown that cough is suppressed during sleep and occurs only following an arousal.39–41 It is possible that by different mechanisms the decline in pulmonary function in CF patients lowers the threshold for awakening, thereby allowing nocturnal cough to occur.

Previous studies have shown that BMI3–5 and gender2,13,42 are factors that have an important effect on the rate of pulmonary function decline in CF patients. These reports indicate that malnutrition and female gender are associated with a worse outcome. The present study indicates that in addition to these variables, sleep disturbance has a negative correlation with FEV1.
The negative association between sleep disturbance and FEV1 could be explained by two possible mechanisms. Some human studies have suggested a supportive influence of regular nocturnal sleep on the immune responses to experimental infection. It has been shown that sleep shifts the Th1/Th2 balance toward Th1 activity favoring the cellular response to infection. This activity is blocked by sleep deprivation. Some animal studies have shown that in mice infected with Pseudomonas aeruginosa a Th1 response was associated with faster bacterial clearance and milder lung inflammation than that in mice showing a predominant Th2 response. These findings indicate that a Th1 response might be beneficial in CF patients with chronic P aeruginosa lung infection. Future studies are needed to determine whether sleep disturbance in CF patients affects the frequency of pulmonary exacerbations.

The second plausible mechanism occurs through the effect of sleep disruption on glucose metabolism. Several studies have linked various sleep disturbances to glucose intolerance. Gonzalez-Ortiz et al showed that 1 night of sleep deprivation in healthy subjects is associated with decreased insulin sensitivity. In the context of obstructive sleep apnea, there is also evidence that the severity of the disorder is associated with insulin resistance. This observation raises the question of whether sleep disturbance could add to the already existing susceptibility to glucose intolerance in CF patients. Diabetes mellitus is becoming increasingly prevalent in CF patients, and is associated with the deterioration of pulmonary function and increased mortality. Insulin deficiency is thought to be the primary cause for CF-related diabetes mellitus. However, there is evidence that decreased insulin sensitivity also contributes to abnormal glucose metabolism. The early diagnosis and treatment of CF-related diabetes mellitus is associated with improved nutrition, pulmonary function, and long-term outcomes. Although our study excluded patients with diabetes mellitus, it did not include a glucose tolerance test to determine whether CF patients were in a prediabetic state.

The present study showed a very modest difference in sleep parameters between CF patients and control subjects. These results are not unexpected, given the mild degree of severity of the disease. It is, however, important to note that the tight link between sleep parameters and pulmonary function indicates that those differences are of clinical significance.

The following two parameters have been identified as occurring more frequently in CF patients than in control subjects: nocturnal use of bathroom for defecation; and watching television at bedtime. These observations indicate that additional factors such as CF-related GI disorders and inadequate sleep hygiene might also contribute to disturbed sleep in CF patients.

This study has several limitations. First, the cross-sectional design did not ascertain a causal relationship between sleep disturbance and decline in FEV1. A longitudinal design will be better suited to answering this question. Second, the exclusion of CF patients with symptoms of pulmonary infection and/or drop in FEV1 by >10% from baseline led to the underrepresentation of patients with more severe lung disease.

In summary, the present study showed both objectively and subjectively that clinically stable pediatric patients with CF have a higher prevalence of sleep disturbance than do healthy children. Future research is needed both to examine the nature of the interaction between CF pulmonary disease and sleep, and to determine whether optimizing sleep quality in pediatric CF patients could modify the clinical course of the disease.

**REFERENCES**

3. Peterson ML, Jacobs DR Jr, Milla CE. Longitudinal changes in growth parameters are correlated with changes in pulmonary function in children with cystic fibrosis. Pediatrics 2003; 112:588–592
14 van der Schans C, Prasad A, Main E. Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis. Cochrane Database Syst Rev (database online). Issue 2, 2000
22 Punjabi NM, Sorkin JD, Katzel LI, et al. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med 2002; 165:677–682
35 Gruber R, Sadeh A. Sleep and neurobehavioral functioning in boys with attention-deficit/hyperactivity disorder and no reported breathing problems. Sleep 2004; 27:267–273