Cystic Fibrosis Patients Have Poor Sleep Quality Despite Normal Sleep Latency and Efficiency*

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Study objectives: Cystic fibrosis (CF) patients may be predisposed to poor sleep quality due to upper and lower airway abnormalities and impaired gas exchange. Previous sleep investigations of CF patients using single-night polysomnography have reported conflicting results. We hypothesized that sampling sleep for a prolonged period in a patient’s normal environment may give a more representative assessment of sleep quality than a single-night polysomnogram, and that impaired sleep quality would correlate with pulmonary disease severity and self-assessed sleep quality.

Design: Using wrist actigraphy, we measured sleep quality in clinically stable CF patients and age-matched control subjects. In addition, each CF patient and control subject completed the following three questionnaires: the Epworth sleepiness scale; the Pittsburgh sleep quality index (PSQI); and the Medical Outcomes Study 36-item short form.

Results: Twenty CF patients and control subjects were enrolled in the study, and were well-matched for age, sex, and body mass index. The mean (± SD) FEV1 for CF patients was 61.0 ± 20.1% predicted. CF patients and control subjects had similar sleep duration, sleep latency, and sleep efficiency. However, CF patients had higher PSQI scores (6.45 vs 4.55, respectively; p = .04), a higher fragmentation index (FI) [31.72 vs 18.02, respectively; p < 0.001], and less immobile time (88.87 vs 91.89, respectively; p = 0.02). There was a significant correlation of FI with FEV1 and PSQI scores.

Conclusions: Stable CF patients have disrupted sleep, and sleep disruption may in part be related to the severity of pulmonary disease. In addition, the PSQI may be useful in detecting CF patients with poor sleep quality.

Key words: actigraphy; cystic fibrosis; fragmentation; Pittsburgh sleep quality index; sleep

Abbreviations: AI = arousal index; BMI = body mass index; CF = cystic fibrosis; CI = confidence interval; ESS = Epworth sleepiness scale; FI = fragmentation index; IT = immobile time; MAS = mean activity score; PSQI = Pittsburgh sleep quality index; SF-36 = Medical Outcomes Study 36-item short form; WA = wrist actigraphy
mised population such as CF patients. In order to optimize the complex medical management of CF patients, it is important to understand the magnitude of sleep disruption in this population and to identify the predictors of at-risk patients in whom further evaluation may be indicated.

Previous reports on sleep disturbances in CF patients have been conflicting. Some studies have found CF patients to have reduced total sleep time, whereas others found no differences in sleep time when compared with healthy control subjects. Moreover, some reports found CF patients to have poor sleep efficiency and increased sleep latency, while others found no differences compared to control subjects. Thus, the presence and/or extent of sleep disruption in CF patients seems unclear.

Conflicting results in the past could be in part due to the use of a single overnight polysomnogram, which is considered to be the “gold standard” for assessing sleep quality. Pulmonary symptoms and exacerbations are episodic in the CF population. Polysomnography may thus be limited in its usefulness because a single-night study in a laboratory may not accurately reflect sleep quality in a home environment over a period of time. A commonly used alternative to polysomnography for recording sleep and wakefulness is activity monitoring. Sleep-wake activity determined by activity monitoring correlates relatively highly with polysomnography in many healthy and patient populations. An advantage of activity monitoring is that it allows the continuous assessment of both wake and sleep behavior in the patient’s own environment over extended periods of time.

Using an activity monitor, we sought to determine whether sleep quality (e.g., sleep duration, sleep efficiency, and fragmentation index [FI]) in CF patients with varying severities of lung disease is diminished compared to age-matched control subjects. We also wished to ascertain whether sleep parameters correlated with pulmonary disease severity, and validated questionnaires assessing quality of life and sleep.

**Materials and Methods**

**Subjects**

CF patients who were ≥ 18 years of age were recruited from the adult CF clinic at Northwestern University from January 2002 to April 2003. CF diagnoses had been confirmed by an abnormal sweat chloride test result and/or the presence of two disease-causing mutations. Patients were ineligible if they had received oral or IV antibiotics for a pulmonary exacerbation in the 8 weeks prior to enrollment or had primary cardiac disease, psychiatric disorders, or a known sleep disorder. If a patient experienced a pulmonary exacerbation during the study, that patient was excluded from the study.

Healthy, age-matched control subjects were enrolled in the same study protocol. Control subjects were excluded if they had any history of medical or sleep disorders, or consumed excessive quantities of alcohol or caffeine. The study was approved by Northwestern University Institutional Review Board, and informed consent was obtained for all participants.

**Study Design**

Age, sex, height, and weight were obtained on the day of study enrollment. Each CF patient and control subject completed spirometry (Vmax 20 C-series; SensorMedics; Yorba Linda, CA; and Morris-Polgar prediction equations) and three questionnaires, the Pittsburgh sleep quality index (PSQI), Epworth sleepiness scale (ESS), and the Medical Outcomes Study 36-item short form (SF-36), on the day of study enrollment. Patients and subjects were given a form for keeping a sleep log for 14 days.

The PSQI is a self-administered questionnaire that measures sleep quality during the previous month, and contains 19 self-rated questions yielding both a global score and seven “component” subscores. A global PSQI score of > 5 indicates that a person is a “poor sleeper.”

A subjective assessment of sleepiness was performed using the ESS questionnaire, which is a reliable and validated, self-administered questionnaire for measuring daytime sleepiness in adults. ESS scores significantly correlate with sleep latency (an indication of sleepiness) measured during multiple sleep latency testing and overnight polysomnography. Patients are considered to be sleepy if they have an ESS score of > 10.

The SF-36 is a quality-of-life questionnaire, yielding scores for eight domains, as well as two summary scores, a mental component summary score and a physical component summary score. This measure is constructed to satisfy the minimum psychometric standards that are necessary for group comparisons involving generic health concepts that are not specific to any age, disease, or treatment group. The eight domains consist of physical functioning, role limitations-physical, bodily pain, general health perceptions, vitality, social functioning, role limitations-emotional, and mental health. Each of the eight domains is scored on a scale of 100 points, with higher scores indicating better functioning. The scores are standardized to a mean (SD) of 50 in the general US adult population and can therefore be used to determine whether a group or individual in question scores above or below the US average. Scores above and below 50 indicate above and below average functioning, respectively.

**Wrist Actigraphy**

Wrist actigraphy (WA) detects physical motion, is a validated measure of sleep, and compares favorably to polysomnography. CF patients and control subjects wore a wrist actigraph (Mini Motionloggers or Actillume; Ambulatory Monitoring Co; Airdsley, NY) for 14 days. Data stored in memory was downloaded and analyzed using a commercially available program (Action 3; Ambulatory Monitoring Co) with the actigraph worn on the nondominant arm. A sample actogram is shown in Figure 1. The program can score activity/inactivity and derive from it periods of sleep or wakefulness using a computer-generated algorithm. Sleep log data are used in the computer algorithm to calculate sleep latency. It is also used in conjunction with activity monitoring to confirm bedtimes. WA data were analyzed cumulatively for the 2-week period during which subjects wore the actigraph and then separately for weekdays (i.e., Sunday to Thursday) and weekends (i.e., Friday and Saturday). There are
several measures that can be derived from these algorithms, such as the FI, mean activity score (MAS), and immobile time (IT). The FI measures restlessness and is calculated by summing the percentage of minutes spent moving with the percentage time spent in the immobility phase per minute. MAS is the magnitude of activity on a per-epoch basis during sleep, and it is calculated by dividing the total activity score by the number of epochs during the assumed sleep period. IT is derived by dividing the number of minutes spent immobile by the assumed sleep time and multiplying by 100 (Action 3; Ambulatory Monitoring Co).

**Statistical Analysis**

Sample means and SDs were calculated for all variables. The independent sample Student t test for the comparison of two groups for all continuous variables was performed. (SPSS for Windows, version 11.5; SPSS; Chicago, IL). There are accepted cut points for the ESS and PSQI, indicating abnormal sleep parameters. For this reason, we performed χ² analysis to compare groups for ESS and PSQI. A p value of < 0.05 was considered to be significant. A Pearson correlation coefficient was calculated to determine the relationship of continuous variables. We performed jackknife estimates of correlation coefficients (obtained by eliminating one x-y pair at a time), which provide a robust estimate of the underlying linear relationship (correlation) between variables of interest.31 A 95% confidence interval (CI) was calculated, which provides the most plausible range for jackknife correlation coefficient under assumption of repeated sampling.

**RESULTS**

Twenty-one CF patients and control subjects were initially enrolled into the study, of whom 20 individuals in each group completed the study. The CF and control groups were well-matched for age, sex, and body mass index (BMI) [Table 1]. The airflow of CF patients ranged from normal to severe obstruction, with a mean (± SD) FEV₁ of 61.0 ± 20.1% predicted (95% CI, 31 to 91% predicted). None of the CF patients were receiving home oxygen therapy, and their mean oxygen saturation at the time of study enrollment was 96 ± 1% predicted.

**Questionnaire Data**

The mean PSQI for CF patients was 6.45 ± 3.31, which was significantly higher than that for control subjects (4.55 ± 2.21; p = .04). Furthermore, in the CF group there were 11 patients with a PSQI score of > 5, compared to only 5 subjects in the control group (p = .04). There was also a trend toward higher sleep disturbance (p = 0.07) and habitual sleep efficiency (p = 0.06) PSQI subscores in the CF group, although this did not reach statistical signifi-
cance. The mean ESS scores for the CF and control groups were 6.75 ± 3.32 and 5.72 ± 3.63, respectively (p = 0.39), with four CF patients and three control subjects having scores of > 10. The SF-36 scores for the CF patients were significantly lower for both the physical and mental components compared to our healthy control subjects as well as the population means.32

WA Data

Control and CF patients had similar total sleep time, sleep latency, and sleep efficiency. Sleep onset and offset times were also comparable, meaning that CF patients and control subjects were going to bed and waking up at approximately the same times. Both CF patients and control subjects went to sleep an average of 1 h later on the weekends than during the week. The total activity score and MASs were also similar. In contrast, CF patients had a higher FI and less IT than control subjects (Table 2). There were no differences between weekdays and weekends for these parameters in either group (data not shown). Compared to control subjects, CF patients also displayed greater night-to-night variability in FI (p < 0.003) and IT (p < 0.02), as evidenced by greater SDs when each night was assessed separately (Table 2). These findings are consistent with the overall more disrupted sleep for CF patients.

CF patients’ lung function, as assessed by FEV1, had small but significant associations with both the FI and the IT (Fig 2). The confidence interval calculated by jackknife analysis31 suggests a robust relationship between decrement in lung function and the severity of sleep disturbance. In contrast, there were no significant associations between resting room air O2 saturation or BMI and any measured sleep parameter (data not shown).

Table 1—Demographics and Questionnaires*

<table>
<thead>
<tr>
<th>Variables</th>
<th>CF Patients (n = 20)</th>
<th>Control Subjects (n = 20)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>25.85 (6.00)</td>
<td>25.35 (3.72)</td>
<td>0.75</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>23.2 (4.44)</td>
<td>24.27 (3.17)</td>
<td>0.39</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>61 (20.1)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>ESS</td>
<td>6.75 (3.32)</td>
<td>5.80 (3.52)</td>
<td>0.39</td>
</tr>
<tr>
<td>PSQI</td>
<td>6.45 (3.31)</td>
<td>4.55 (2.21)</td>
<td>0.04</td>
</tr>
<tr>
<td>SF-36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td>44.90 (10.12)</td>
<td>56.95 (3.30)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MCS</td>
<td>45.20 (9.78)</td>
<td>51.95 (7.83)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Values given as mean (SD), unless otherwise stated. PCS = physical component score; MCS = mental component score; NA = not applicable.

Table 2—WA Data*

<table>
<thead>
<tr>
<th>Variables</th>
<th>CF (n = 20)</th>
<th>Controls (n = 20)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep onset</td>
<td>12:52 AM</td>
<td>12:49 AM</td>
<td>0.91</td>
</tr>
<tr>
<td>Awakening time</td>
<td>8:29 AM</td>
<td>8:01 AM</td>
<td>0.36</td>
</tr>
<tr>
<td>Sleep duration, h</td>
<td>7.52 (.74)</td>
<td>7.1 (.94)</td>
<td>0.12</td>
</tr>
<tr>
<td>Sleep latency, min</td>
<td>12.75 (14.77)</td>
<td>13.85 (10.05)</td>
<td>0.79</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>85.2 (6.15)</td>
<td>85.4 (5.60)</td>
<td>0.91</td>
</tr>
<tr>
<td>IT, %</td>
<td>88.97 (4.99)</td>
<td>91.89 (2.35)</td>
<td>0.02</td>
</tr>
<tr>
<td>Total activity score</td>
<td>8,429 (3,330)</td>
<td>6,908 (4,110)</td>
<td>0.21</td>
</tr>
<tr>
<td>Mean activity score</td>
<td>9.13 (3.78)</td>
<td>7.68 (3.88)</td>
<td>0.24</td>
</tr>
<tr>
<td>FI</td>
<td>31.72 (12.40)</td>
<td>18.04 (6.22)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Night-to-night IT variability</td>
<td>4.97 (1.03)</td>
<td>2.17 (0.31)</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>Night-to-night FI variability</td>
<td>12.91 (1.64)</td>
<td>6.81 (0.84)</td>
<td>&lt; 0.003</td>
</tr>
</tbody>
</table>

*Values given as mean (SD), unless otherwise indicated.
Comparison of Activity and Questionnaire Data

There were significant correlations for FI, IT, and MAS with the PSQI for CF subjects, but not for control subjects (Fig 3). In contrast, there were no significant correlations between the ESS and SF-36 instruments and any sleep parameter measured by WA (data not shown).

Discussion

Total sleep time, sleep efficiency, and sleep latency were similar between CF patients and age-matched control subjects. However, sleep was significantly more fragmented, with more night-to-night variability. Self-perceived sleep quality was also poor in CF patients. In addition, there is evidence that the degree of sleep disruption may be related to pulmonary disease severity (as measured by FEV1).

Previous investigations in CF patients using polysomnography have reported conflicting results in sleep parameters including, sleep efficiency, sleep latency, and arousal index (AI). In the current study, using wrist activity monitoring, we found no differences in sleep efficiency and latency between control subjects and CF patients. In addition, sleep duration was 2 h longer in our CF patients than previously reported. In contrast to control subjects, CF patients had a higher FI and a lower IT (ie, they spent less time lying still), which is consistent with more disrupted sleep. The FI, unlike sleep efficiency, measures the number of times an individual moves rather than the percentage of time that they spend awake during the sleep period. The FI may be a more useful measure to examine sleep disturbance because it may better detect repetitive short events that disrupt sleep.

The discrepancies between our results and previous findings may be due at least in part to methodological differences. WA is less cumbersome and can be performed in a subject’s natural sleep environment, as opposed to polysomnography, which is usually performed in a sleep laboratory. In addition, we sampled sleep for a 2-week period compared to a single night, which is typical for studies using polysomnography. By measuring sleep for 2 weeks in the home environment, we think that our study offers a more representative assessment of sleep-wake habits of CF patients and age-matched control subjects, especially in light of the greater night-to-night variability displayed by our CF subjects.

While CF patients have more disrupted sleep and rate their sleep as being worse than control subjects on the PSQI, they do not report greater sleepiness on the ESS. Self-assessed ratings such as the ESS, however, can have limited correlation to objective measures of daytime sleepiness. Therefore, the increased sleep fragmentation observed in the CF patients may still have consequences for daytime function. Future studies of CF patients should evaluate the relationship between sleep fragmentation and objective measures of daytime sleepiness such as the multiple sleep latency test and/or neurocognitive performance.

Compared to previous studies of sleep in CF

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**Figure 3.** Top, A: correlation between MAS and PSQI. There was a statistically significant positive relationship between the MAS on WA and the PSQI. The Pearson correlation coefficient between the MAS on WA and the PSQI was 0.80. Middle, B: correlation between IT and PSQI. There was a statistically significant inverse relationship between the IT and PSQI. The Pearson correlation coefficient between the IT on WA and the PSQI was −0.64. Bottom, C: correlation between FI and PSQI. There was a statistically significant inverse relationship between the FI on WA and the PSQI was −0.45.
patients, our study included patients with milder disease. Our patients had an average FEV₁ of 61% predicted and a BMI of 23, both of which are higher than those values in CF patients, in whom sleep data has been previously reported.²⁰–²³ Nearly two thirds of CF patients who are ≥18 years of age have an FEV₁ of <70% predicted.² Our results need to be validated in a larger study but suggest that a significant proportion of CF patients may experience sleep disruption, which would put them at risk for reduced neurocognitive function, and potentially poorer health and sense of well being.²²

There is limited information about sleep fragmentation in CF patients and how this relates to measures of pulmonary disease severity.²¹,²² While daytime hypoxemia predicts nocturnal oxygen hemoglobin desaturation in CF patients,²¹,³⁵ and nocturnal hypoxemia correlated with sleep efficiency in one study,²² oxygen supplementation has not resulted in improved sleep quality.²⁰,³⁶,³⁷ In another study, maximum expiratory strength correlated with rapid eye movement respiratory disturbance index scores, but spirometric function and arterial blood gas levels did not correlate with the respiratory disturbance index scores.²¹ This suggests that lung function and gas exchange are not good predictors of sleep fragmentation but respiratory muscle strength may be. However, in our study the FEV₁ correlated with actigraphically recorded FI, a measure of disrupted sleep. One reason for this apparent discrepancy may be that prior studies did not assess the relationship between pulmonary function and the AI. The AI is the one polysomnography parameter that is most closely analogous to the FI in our study.

Previous studies²⁵,²⁹ have shown inverse correlations between PSQI scores and polysomnography-measured sleep efficiency. When combined with our results, the PSQI appears to be a useful screening tool to identify CF patients who are at risk for sleep disturbance, especially if they have a decreased FEV₁. Compared to polysomnography, the PSQI is simple to perform, inexpensive, could be followed over time, and does not involve a hospital stay. If the PSQI suggests poor sleep quality, then WA and/or polysomnography studies may be obtained for further evaluation of the underlying sleep disorders. Given the night-to-night variability observed in CF patients and the relative cost of polysomnography, it may be more accurate and cost-effective to obtain wrist activity monitoring.

That many CF patients experience poor sleep is clear from the present study, but the underlying etiology of the sleep disturbance is not. Possibilities include nocturnal coughing,⁴⁰,⁴¹ the use of β₂-agonists before sleep, increased work of breathing,⁴²,⁴³ psychiatric disorders, and/or periodic leg move-

ments. While our data do not allow us to distinguish between these possibilities, they do suggest avenues for future investigation. Future studies evaluating these potential mechanisms may suggest therapeutic interventions (eg, cough suppression, anxiolytics, biventricular positive airway pressure ventilation), which could be tested in clinical trials.

There are potential limitations of this study. The sample size was relatively small, which may limit the generalizability of these findings and should be confirmed in a larger study. A limitation of WA is the inability to detect differences between quiet wakefulness and sleep, resulting in an underestimation of sleep disruption or duration. However, in the current study CF patients had greater sleep disruption than control subjects. There is also the potential to overestimate total sleep time if subjects are lying quietly awake, which would lead to an overestimation of sleep efficiency. Based on these considerations, CF patients may actually have a greater number of sleep abnormalities than those measured in our study. While we do not have concomitant polysomnography data to confirm the WA data, several previous studies²⁵ in other patient populations have successfully used activity monitoring to characterize sleep-wake characteristics.

Sleep fragmentation and decreased sleep quality are common in CF patients and likely to contribute to decreased daytime function and quality of life. It is not known whether improving sleep quality can reduce disease severity or associated health problems in this population. In light of the consequences of prolonged sleep loss/sleep disruption on health and well-being, the identification and treatment of sleep disorders in CF patients should be an integral part of disease management.

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