Oxygen desaturation during sleep in patients with cystic fibrosis has been attributed to changes in the end-expiratory volume during rapid eye movement (REM) sleep, leading to worsening of the ventilation-perfusion distribution. The purpose of this study was to describe the changes in ventilation during sleep that may contribute to the oxygen desaturation. Six adolescent males with moderate to severe cystic fibrosis were studied. It was concluded that hypoventilation during REM may contribute to oxygen desaturation in patients with cystic fibrosis.

Arterial oxygen desaturation during sleep—especially in rapid eye movement (REM) sleep—in patients with cystic fibrosis (CF) has previously been reported. These episodes of desaturation were not coincident with apneas of either obstructive or central origin, but were associated with a reduced end-expiratory volume during REM sleep and therefore attributed to airway closure and the development of underventilated lung regions (i.e., low ventilation-perfusion [V/Q] areas). Our previous work in adult COPD patients showed that progressive hypoventilation and CO2 retention occurred from wake through NREM and REM sleep leading to a coincident worsening of arterial O2 desaturation. Also previously documented was that much of this hypoxemia was relieved with chronic ventilatory stimulation by pharmacologic means. The present study sought to determine the importance of sleep-induced hypoventilation per se as a determinant of arterial O2 desaturation in cystic fibrosis. To this end, we examined the effect of NREM and REM sleep stages on absolute levels and variability of ventilation, breathing pattern, inspiratory effort, and "arterIALIZED" blood acid-base status in adolescent CF patients.

Methods

Six adolescent males, ages 10 to 16, with the diagnosis of CF confirmed by an elevated pilocarpine iontophoretic sweat chloride, were studied both awake and asleep. Informed consent of patients and parents was obtained in all cases. The patients’ anthropometric data are presented in Table 1. The mean height was 155 cm (range of 137 to 175 cm); and the mean weight was 37.9 kg (range of 30.0 to 47.7 kg). Only one of six patients was <5 percent predicted for height, while five of six patients were <5 percent predicted for weight. All subjects were followed by the University of Wisconsin Cystic Fibrosis Center and attended school on a regular basis. The sleep studies on two of the patients were performed at the end of a two-week hospitalization for a pulmonary exacerbation treated with intravenously administered antibiotics. The other patients were studied coincident with routine outpatient clinic visits during asymptomatic periods. Three of six subjects were receiving long-term oral administration of antibiotics, two of six were taking long-term bronchodilators. Patient 1 used nocturnal oxygen at home and received daily oral doses of furosemide. No caffeine or alcohol was ingested for 24 hours prior to the sleep study, and concomitant medications were continued at the same dosage.

Awake Measurements

Pulmonary function studies were performed on the day of the sleep study. Spirometry was performed with a 13-L water seal spirometer (Warren E. Collins, Braintree, MA). Functional residual capacity was measured in a body plethysmograph using Boyle’s law techniques.

In four of six patients, "arterIALIZED" venous blood samples were obtained from a butterfly needle in the dorsum of the hand with the hand wrapped in a heating pad and the needle continuously infused with a dilute heparinized saline solution. Either two or three awake samples were drawn while the subject was in the supine position prior to the onset of sleep. Each 3-ml blood specimen was drawn over a 1 to 1 minute period and analyzed at 37°C for pH and Pco2, with a blood gas analyzer (Radiometer, Copenhagen, Denmark) or an Instrumentation Laboratory (Lexington, MA) apparatus. Calibration of Pco2 electrodes was frequently validated using tonometered blood. Oxygen saturation was continuously monitored with an ear oximeter.

Rib cage and abdominal motion were measured by a Respitrace jacket (Ambulatory Monitoring, Inc. Ardsley, NY). An isovolume maneuver was performed in the supine position, followed by a volume calibration with the patient breathing through a mouthpiece attached to a rolling seal spirometer (Ohio Products, Madison, WI). The sum of the rib cage and abdomen measurements correlated well with tidal volume measured on the spirometer (mean ± SD r = .97 ± .03). Inspiratory time (T1) measured from the spirometer was not significantly different (p > .05) from that measured from the Respitrace rib cage-abdomen sum tracing. Minute ventilation, tidal volume, and respiratory cycle timing were measured from the Respitrace tracing. In the single subject who subsequently slept in the lateral position, calibration was repeated in that position following sleep.

In one patient (1), measurements of dead space, O2 consumption, and CO2 production were obtained. The seated patient breathed room air on a mouthpiece attached to a two-way valve and mixed

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expired gas was obtained and analyzed for CO₂, O₂, and N₂, with a gas chromatograph, (Quinton Instruments, Milwaukee, WI) while "arterialized" venous blood was sampled. This was repeated while the patient breathed 50 percent oxygen.

Sleep Measurements

All patients were mildly sleep deprived on the evening prior to the sleep study, sleeping approximately five to six hours. Electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG) were recorded on a polygraph (Grass model 7D), (Grass Instruments, Quincy, MA) with sleep stages determined by the criteria of Rechtschaffen and Kales. 7 Continuous measurements were as described during the awake studies. All parameters were recorded on a Electronics for Medicine (Pleasantville, NY) or Gilson (Gilson Medical Electronics, Middleton, WI) recorder. Ventilatory measurements were made during REM and NREM sleep (stages 2, 3, and 4 only) as identified by EEG, EOG, and EMG criteria. Analysis of these measurements during REM sleep was difficult because of the nonsteady-state conditions produced by frequent interruption of tonic REM with phasic activity. The distinction between phasic and tonic REM sleep was based on the presence or absence of REM on the EOG. Reported values are the means of 20- to 40-second periods of tonic or phasic REM sleep. Only by taking this short interval could we be sure that the measurements were truly representative of a given subset of REM sleep. "Arterialized" venous blood samples were drawn over 1/4 to 1 minute periods during NREM (two to six samples per subject) and combined periods of tonic and phasic REM sleep (two samples per subject). One patient was also studied while breathing supplemental oxygen delivered by nasal cannulae at 1 L/min.

Variability of the ventilatory parameters was expressed as a coefficient of variation, σ (standard deviation divided by the mean) measured from 50 to 100 breaths during the awake, NREM, and tonic REM states and 14 to 37 breaths during phasic REM.

Data Analysis

Statistical differences between means were determined by combining two-way analysis of variance (subjects vs sleep state) and the Student's t-test for paired comparisons. Oxygen saturations were compared with the Wilcoxon nonparametric signed rank test. 4

RESULTS

Awake

The awake pulmonary function tests, oxygen saturation, and acid base status are shown in Table 1. The patients represent a heterogeneous group with respect to all the parameters. All patients demonstrated Airways obstruction of a moderate to severe degree, with a mean FEV/FVC = 0.52 ± 0.05 (range: 0.41 to 0.72), and a variable degree of air trapping (RV/TLC) with a reduced mean FVC of 61 percent predicted (range: 43 percent to 99 percent). All patients demonstrated oxygen desaturation at rest (mean SaO₂ = 90 percent, range 77 to 94), with only two subjects having SaO₂ less than 90 percent. (Table 1). Moderate to severe chronic CO₂ retention was present in two of four patients tested.

The awake ventilatory measurements, mean ± SEM for the group, are presented in Table 2. The minute ventilation was 6.69 L/min (range 4.17 to 9.52) with a tidal volume of 26 L (range 18 to .46) and a frequency of 26.2 BPM (range 21.6 to 34.5). The patient with the most severe pulmonary disease (I) had the largest tidal volume, minute ventilation, and mean inspiratory flow, Vt/Ti, and the lowest rib cage contribution to tidal volume. This is consistent with the large dead space ventilation we measured, Vd/Vt = 62 percent.

Sleep

Our patients had a mean (± SEM) total sleep time of 4.5 ± 0.6 hours with 82 ± 3 percent in NREM and 18 ± 3 percent in REM sleep. The effect of sleep state upon oxygen saturation is presented in Table 2. The minimum oxygen saturation decreased between the awake, NREM, tonic and phasic REM states from 89 to 85 to 82 to 76 percent, respectively, with only phasic REM being statistically different from the awake state (p < 0.05). Comparing the awake state to NREM and tonic REM, only two of six and three of six patients decreased their SaO₂ by greater than 2 percent (ranges 1-11; 0-26). However, during phasic REM, all patients decreased their SaO₂ greater than or equal to 2 percent (range 2-40). The CF patient with the worst awake SaO₂ (77 percent) developed a severe oxygen desaturation to 34 percent during REM sleep, which was not associated with an apneic episode.

The effect of sleep state upon minute ventilation, tidal volume, and respiratory frequency is presented in Table 2. Sleep induced a decrease in both tidal volume and minute ventilation between the awake, NREM, and REM states with the exception of the REM sleep state, where tidal volume was greater than awake.

Table 1—Anthropometric and Pulmonary Function Data

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<th>RV/TLC</th>
<th>SaO₂†</th>
<th>Pco₂ (mm Hg)</th>
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*Percent of normal predicted.
†Minimum awake oxygen saturation.
and REM sleep states. Non-REM sleep, in comparison to the awake state, produced a decrease in Vt and Ve of 22 and 30 percent, respectively (p < .02). There was further depression of ventilation between tonic and phasic REM sleep with both Vt and Ve decreased by 26 percent (p < .05). Sleep state compared to the awake state, produced no significant or consistent change in respiratory frequency (p > .10) although two of six patients showed rather marked reductions in frequency with sleep.

The effect of sleep state upon the mean inspiratory flow (Vt/Ti), the respiratory cycle timing (Ti/Ttot), and the percent rib cage contribution to tidal volume are presented in Table 2. In comparison to the awake state, NREM sleep produced a 22 percent decrease in the Vt/Ti (p < .01) without any significant change in Ti/Ttot (p > .30). Between tonic and phasic REM, Vt/Ti decreased by 38 percent (p < .025) with no significant change in either Ti or Ti/Ttot (p > .10). The percent rib cage contribution to tidal volume was highest during NREM sleep in five or six patients and was the lowest during phasic REM sleep in all patients (p < .01).

We examined the effect of sleep state upon the variability in the patients' tidal volume. There was no statistical difference in the coefficient of variation for the awake and NREM states, .20 and .18, respectively, although four of six patients had their lowest variability during NREM sleep. The REM sleep was more variable, σ = .27, than NREM sleep (p < .05). Figure 1 illustrates the percent distribution of tidal breaths of varying sizes for the awake, NREM, and REM sleep states for two of the patients. The upper panel (A) represents a patient with moderate pulmonary disease. Non-REM sleep had the least variability in tidal volume, and REM sleep had both a larger variability and a larger percentage of tidal breaths skewed towards the lower volumes. The lower panel represents the patient with the worst airway obstruction. Compared to the patient with moderate disease, this patient showed a larger variability of his tidal volume, particularly during REM sleep.

In four patients, "arterialized" venous blood was sampled during the awake, NREM, and REM sleep state. The individual mean results are illustrated in Figure 2. Three of four patients increased their PaCO2 during NREM as compared to the awake state (+3, +5, and +10 mm Hg), and all four increased PaCO2 in REM (+3 to +12 mm Hg) (p < .05). The patient with the worst pulmonary disease (I) developed severe hypoxemia during REM, SaO2=34 percent, and a mixed metabolic and respiratory acidosis as evidenced by an increase in PaCO2 (59 vs 71 mm Hg) and a decrease in calculated [HCO3-] 35.5 vs 31.6 mEq/L resulting in a marked acid shift in pH (7.39 to 7.26).

![Figure 1](https://example.com/image1.png)

**Figure 1.** Percent distribution of tidal breaths (Vt) of varying sizes for the awake, NREM, and REM sleep states. A is patient with mild pulmonary disease; and B, patient with severe pulmonary disease.

![Figure 2](https://example.com/image2.png)

**Figure 2.** Oxygen saturation, ventilatory volumes, and pattern during sleep.
Central apneas were noted in only one patient (4). They occurred twice during NREM sleep lasting 10 to 15 seconds and were not associated with the minimal saturation observed for that sleep state.

**DISCUSSION**

This study examined the contributions of alveolar hypoventilation and ventilatory pattern to sleep-induced arterial hypoxemia in patients with CF. Although these patients varied substantially, the general trend during NREM and REM sleep showed a reduced minute ventilation and tidal volume along with a more variable breathing pattern during REM as compared to either NREM or wakefulness. The contribution of alveolar hypoventilation and CO₂ retention to oxygen desaturation was most evident during REM sleep. The ventilatory pattern and gas exchange in both waking and sleeping states in these CF patients resembled those previously observed in adult patients with COPD and in asthmatic adolescents.

Our patients with CF had an abnormal awake breathing pattern. Compared to the values reported for normal adolescents also obtained using a Respitrace jacket, the CF patients demonstrated a normal to elevated minute ventilation (6.69 ± 0.85 vs 6.14 ± L/min) with a high frequency (27.9 ± 3.7 vs 17.4 ± 0.43 breaths/min), low tidal volume (.26 ± .04 vs .35 ± .02 L), and low inspiratory time (.96 ± .12 vs 1.2 ± .03 sec). Inspiratory flow Vr/Ti (.27 ± .04 vs .30 ± .1 L/sec), Ti/Ttot (.40 ± .02 vs .37 ± .02), and the percent contribution of the rib cage to the tidal volume (37.1 ± 4.2 vs 39.5 ± 3.0 percent) were similar to the normal adolescents.

A high inspiratory effort is likely in our patients since VE and Vr/Ti were normal despite an increased airways obstruction. Indeed, this increase in inspiratory effort as measured by mouth occlusion pressure (P0.1) has been shown in asthmatic patients and children with CF and also in many adult patients with COPD and chronic CO₂ retention. In this regard, CF patients may be like adult patients with COPD in whom chronic CO₂ retention often occurs in the presence of high inspiratory effort and VE, and inspiratory flows which are normal or high but inadequate to produce sufficient alveolar ventilation in the presence of existing ventilation-perfusion maldistribution, high VD/VT, and tachypneic breathing patterns. This combination of parameters existed in three of our six CF patients, and the patient with the most severe CO₂ retention and airway obstruction showed the highest Vr and Vr/Ti. A more detailed analysis of these factors in a larger population of patients with and without CO₂ retention is needed to test properly this proposed schema. In CF.

Our subjects with CF had large coefficients of variation (σ) for tidal volume (0.20), respiratory frequency (0.19), and minute ventilation (0.17) while awake. In contrast, normal adolescents had a large σ with respect to tidal volume (0.25), but these estimates of variability were less than 10 percent for both frequency and minute ventilation. Adults with COPD and hypercapnea also show a relatively large coefficient of variation in VT compared to both nonocapneic patients and normal subjects. The large coefficients of variation, particularly during REM sleep, may reflect the instability of the control of ventilation in the presence of obstructive airways disease. In addition, a wide distribution of tidal breaths about the mean will contribute to large fluctuations in oxygenation, particularly in the presence of occlusion.
ventilation-perfusion mismatching.

During sleep, all CF patients showed hypoventilation, CO₂ retention, and oxygen desaturation associated with decreased minute ventilation, tidal volume, and mean inspiratory flow compared to the awake state. These changes were always observed during phasic REM and associated with a marked decrease in the rib cage contribution to tidal volume. The tachypneic breathing pattern observed in CF patients while awake was preserved in NREM and REM sleep, and the breath-to-breath variability in VT distribution was unchanged or decreased in NREM sleep but significantly increased in REM. In comparison, normal adolescents demonstrate either minimal or no change with sleep in oxygen saturation, tidal volume, minute ventilation, and inspiratory flow. Adolescent asthmatic patients and adults with COPD demonstrate a pattern more similar to the subjects with CF with a decrease in oxygen saturation, tidal volume, minute ventilation, and inspiratory flow between the awake, NREM, and REM sleep states.

The causes of this proportionately greater alveolar hypoventilation in our CF patients in sleep are not apparent and even the reduced V̇e and mild CO₂ retention commonly observed in normal adult (NREM) sleep is not well understood. The reduced VT/Ti in CF patients during sleep may reflect the importance of the wakefulness state as a contributor to their abnormally high inspiratory effort. On the other hand, airway resistance may have increased in sleep, secondary to upper airway obstruction, reduced FRC, paradoxical chest wall movement, or increased airway tone and secretions. While such an increase in resistive load would usually promote an augmentation of inspiratory effort and VT in the waking state, these compensatory responses are either greatly suppressed or absent in NREM sleep in healthy adults.

Subject 1 represents the extreme effects of sleep on ventilatory control and oxygen desaturation in CF patients. This patient had the most severe pulmonary disease with awake hypoxemia (Sao₂, 77 percent) and chronic hypercarbia (PCO₂, 59 mm Hg). Although he maintained an elevated VT/Ti and minute ventilation, there was a very large dead space ventilation, (VT/VD = 0.62), resulting in CO₂ retention. To illustrate the sleep-induced ventilatory changes and oxygen desaturation observed in this patient, representative sections of his sleep record are presented in Figure 3. During NREM sleep compared to the awake state (Fig 3, upper), there was a decrease in both tidal volume and oxygen saturation, but the rib cage and abdominal movements remain synchronous with each other. Less variability in both tidal volume and oxygen saturation is noted during NREM sleep in comparison to the awake state (also see Fig 1). The REM sleep (Fig 3, lower) results in not only a further decrease in both tidal volume and oxygen saturation, but also greater variability in breathing pattern in comparison to NREM sleep. During episodic phasic REM, there is paradoxical inward movement of the rib cage during inspiration, which is associated with a further decrease in both tidal volume and oxygen saturation. Apneic periods were not evident in any sleep stage; however, a significant fraction of tidal volumes were less than the patient's awake dead space volume of 260 ml (Fig 1).

In this patient, the episodic hypoventilation, the increased variability in tidal volume distribution, paradoxical rib cage movement, and decreased inspiratory flows during phasic REM, along with previously reported decreases in end-expiratory lung volume, all could contribute to a worsening distribution of ventilation and the observed CO₂ retention and oxygen desaturation. The fact that his pulmonary disease already displaced his waking arterial Po₂ to the steep portion of the HbO₂ dissociation curve added significantly to the marked fall in Sao₂ that occurred during sleep.

The severe hypoventilation and oxygen desaturation during REM sleep in this patient resulted in a mixed metabolic and respiratory acidosis as already noted in Figure 2. In addition, he developed a bigeminal ventricular arrhythmia during REM. Neither the hy-
poxia nor the acidosis resulted in any measurable compensatory ventilatory response nor any sign of arousal from the REM sleep state.

It has been postulated by several investigators that the repeated episodic oxygen desaturation during sleep may be a significant etiologic factor in the premature development and progression of cor pulmonale reported in patients with CF. In this patient, 1 L/min of nasal O₂ during REM maintained his SaO₂ between 85 and 90 percent, raised PaCO₂ 4 to 5 mm Hg, and corrected his cardiac arrhythmia. The use of nocturnal oxygen in this patient with severe pulmonary involvement of CF appears to be beneficial in correcting his severe oxygen desaturation resulting from hypoventilation and V/Q inequalities, without producing clinically significant further retention of CO₂ or acidosis. Well-controlled prospective studies will be required to determine whether the use of nocturnal oxygen by patients with CF prior to significant hypoxemia in the waking state is beneficial in preventing the development of cor pulmonale.

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