Benefits of Nocturnal Nasal CPAP in Patients With Cystic Fibrosis*

Jeff A. Regnis, PhD; Amanda J. Piper, MEd; Kathe G. Henke, PhD; Sally Parker, MSc (Med); Peter T.P. Bye, MB, BS, PhD, FCCP; and Colin E. Sullivan, MB, BS, PhD

Patients with cystic fibrosis (CF) often hypoventilate during sleep with marked falls in oxygen saturation (SaO₂%). This occurs most commonly during REM sleep, when there is a reduction in rib cage excursion and a fall in end-expiratory lung volume (EELV). The aim of this study was to examine the effect of nocturnal nasal continuous positive airway pressure (nCPAP) on SaO₂ and the respiratory disturbance index (RDI) during sleep in patients with CF and severe lung disease. Seven patients (FEV₁ % pred, 23 ± 5; range, 14 to 28%) were evaluated during sleep on two nights, control and nCPAP (11 ± 2 cm H₂O; range, 8 to 16 cm H₂O), with four patients breathing room air and three patients breathing supplemental oxygen on both nights. Mean awake SaO₂ was 91 ± 1% (range, 89 to 93%). All patients showed significant oxyhemoglobin desaturation and respiratory disturbance in the control study. The maximal falls in SaO₂ (15 ± 10%) were most often associated with phasic eye movements, and a decline in rib cage excursion and the sum signal (Respirac) during REM sleep. Nasal CPAP resulted in a significant improvement in the mean minimum oxygen saturation (MMOS) during both NREM (nCPAP 91 ± 3% vs control 88 ± 2%, p<0.05) and REM sleep (nCPAP 89 ± 6% vs control 83 ± 6%, p<0.05). Transcutaneous CO₂ measurements were not significantly different between the control and the nCPAP studies. The RDI was also significantly reduced with nCPAP especially during REM sleep (9 ± 7 events per hour vs control 25 ± 11 events per hour, p<0.05). Nasal CPAP caused no change in total sleep time or sleep efficiency yet significantly reduced the RDI and improved baseline SaO₂ during both NREM and REM sleep.

(Night of REM oxygen therapy has been shown to improve nocturnal oxygen desaturation in patients with CF but a long-term study did not show any demonstrable effects on mortality, the frequency of hospitalization, or on disease progression. Recently theophylline has also been shown to improve nocturnal oxygen saturation but it also caused significant sleep disruption in patients with CF. The benefits of nocturnal nasal continuous positive airway pressure (nCPAP) in the treatment of obstructive and central sleep apnea have been well documented. The purpose of the present study was to investigate whether the use of nocturnal nCPAP could decrease the extent of oxyhemoglobin desaturation and sleep disturbance in patients with CF and severe lung disease.

METHODS

Subjects

We studied seven patients (five male and two female) with CF,
age ranging from 14 to 39 years (mean ± SD, 25 ± 8 years) who were selected because of their severe pulmonary disease (defined as a FEV₁ < 40% of predicted) (Table 1). The study protocol was approved by the Hospital Ethics Review Committee and informed consent was obtained from all patients.

**Measurements and Procedures**

Spirometry and flow-volume curves were measured in a plethysmograph with the door closed. Lung volumes were determined by body plethysmography (Gould 2800; Gould Electronics, Dayton, Ohio). The predicted normal values for spirometry of Polgar and Promadhat were used for the patients younger than 18 years of age and those of Morris were used for the adult patients. For lung volume predictions, the values of Goldman and Becklake were used. Nutritional status was assessed in terms of the body mass index (BMI) (kg · m⁻²).

Arterial blood gas tensions and a measure of cooximetry were measured during the afternoon by a blood gas analyzer (Corning 175, Corning Glass, Medfield, Mass) in the sitting posture.

During all-night polysomnography, patients were monitored continuously, and all variables were recorded simultaneously on a polygraph (model 8-24 E Grass Instruments, Quincy, Mass). Sleep state was recorded with two channels of electroencephalogram (EEG: C3/A2 and C4/A1), two channels of electro-oculogram (ROC/A1 and LOC/A2), and one channel of submental EMG. Diaphragm and sternocleidomastoid (SCM) EMGs and ECG leads were placed according to standard technique. Nasal airflow was detected using a pressure transducer (Grass PT5, Quincy, Mass). Rib cage and abdominal movements were measured by inductance plethysmography (Respirac, Ambulatory Monitoring, Ardsley, NY). The bands were placed around the body such that the midline of the rib cage band lay over the nipples and the midline of the abdominal band lay over the umbilicus. The output of the bands was calibrated with the patient in a supine position by the isovolume technique. The rib cage and abdominal signals were summed and used as an estimate of relative tidal volume. The plethysmograph was used in the DC mode, thereby allowing us to examine acute changes in FRC by measuring changes in end-expiratory position of the sum signal. Oxygen/hemoglobin saturation (SaO₂%) was continuously monitored by ear oximetry (Biox 3700e, Boulder, Colo). Transcutaneous CO₂ (TeCO₂) was continuously monitored (Kontron Microrgas 7640 or Radiometer Copenhagen TCM3). CPAP was administered through a nose mask attached to a blower system as previously described from our laboratory.

**Protocol**

Each patient was studied while in a stable clinical condition and participated in two sleep studies within a 10-day period. The protocol consisted of a control sleep study and a study with the addition of nCPAP. Three patients (2, 3 and 7) receiving low-flow oxygen therapy during the daytime were studied on both nights with the addition of supplemental oxygen (1, 1.5 and 2 L·min⁻¹, respectively). All patients were premedicated with bronchodilator if prescribed.

Patients reported to the laboratory in the late afternoon on the day of the study. Spirometry, flow-volume curves, and lung volume measurements were obtained, and EEG, electro-oculogram, ECG and EMG electrodes were placed in position. Arterial blood gas values were obtained. The patients were allowed their usual suppertime and bedtime medications. At bedtime, the plethysmograph bands were positioned over the thorax and abdomen, taped in place, and the calibration performed. During sleep studies, patients were monitored from lights out at approximately 11 PM until awakening in the morning usually at 6 AM.

**Description of Sleep Study Measurements and Definitions**

Sleep recordings were scored in 60-s epochs and staged according to standard criteria. The respiratory disturbance index (RDI) was defined as the number of apneas and hypopneas per hour of sleep. Apnea was defined as cessation of airflow for at least 10 s with O₂ desaturation undefined or cessation of airflow for less than 10 s (but at least one respiratory cycle) if associated with an O₂ desaturation of more than 4%. Hypopnea was defined as a reduction in amplitude of airflow or thoracoabdominal wall movement of greater than 50% of the baseline measurement for more than 10 s (O₂ desaturation need not occur) or the same reduction with an accompanying O₂ desaturation of at least 4% (no time limit). These respiratory events were defined as obstructive if they occurred in association with continued diaphragm EMG activity and thoracoabdominal wall movement. Central events were defined as those accompanied by absence of diaphragm EMG activity and thoracoabdominal wall movement. Sleep efficiency was defined as the percentage of total sleep time (TST) over total monitoring time. Total sleep period was defined as TST minus the sleep latency. The number of arousals and the number of episodes of cough per hour of sleep were calculated by dividing the number of arousals and cough by the TST. The mean minimum oxygen/hemoglobin saturation (MMOS) was calculated by taking the mean of the minimum saturation for each minute of sleep. The mean maximum carbon dioxide tension (MMCO₂) was calculated in a similar fashion. The minimum SaO₂ or maximum TeCO₂ refers to the absolute minimum SaO₂ or maximum CO₂ in the whole sleep period or in a particular sleep stage.

**Statistical Analysis**

All data from control and nCPAP sleep studies were compared using a paired t test. All results unless otherwise stated are presented as mean ± SD. A p value < 0.05 was considered significant.
FIGURE 1. Effect of nCPAP on nocturnal SaO$_2$. Clear bars indicate the mean SaO$_2$ (±SD) during the control study night, and the hatched bars indicate mean SaO$_2$ (+SD) during the nCPAP night. Minimum SaO$_2$% during sleep was significantly improved by the use of nCPAP. Asterisk denotes p<0.05 compared with control night.

RESULTS

Anthropometric, pulmonary function, and arterial blood gas data for all patients are presented in Table 1. All patients had severe pulmonary disease with FEV$_1$ ranging from 14 to 28% of predicted values, while the RV/TLC ratio expressed as a percentage ranged from 67 to 69%. The awake arterial blood gas tensions indicated all patients had a PaO$_2$ below 70 mm Hg (range, 45 to 69 mm Hg) with two patients showing significant hypercapnia (PaCO$_2$ >45 mm Hg).

Control Study

The presence of nocturnal desaturation and respiratory disturbance was confirmed in the control study in all patients.

Awake supine oxyhemoglobin saturation was 91±1% (range, 89 to 93%) and TcCO$_2$ was 49±3 mm Hg (range, 43 to 53 mm Hg). Mean minimum oxygen saturation was reduced during non-REM (NREM) sleep from the awake baseline to 88±2% (range, 85 to 91%) and MMCO$_2$ increased slightly to 52±2 mm Hg (range, 48 to 55 mm Hg) (Fig 1). There was little respiratory disturbance during NREM sleep (RDI 3±2 events per hour; range, 1 to 5).

Most deterioration in gas exchange occurred during REM sleep. During REM sleep, MMOS was further reduced from NREM sleep to 83±6% (range, 75 to 91%) while MMCO$_2$ was further increased to 54±2 mm Hg (range, 51 to 77 mm Hg). The minimum SaO$_2$% for the group was 76±10% (range, 56 to 86%), while absolute mean maximum TcCO$_2$ was 57±2 mm Hg. The maximum increase in TcCO$_2$ from the awake baseline ranged from 4 to 21 mm Hg. There was a significant increase in respiratory disturbance during REM compared with NREM sleep (mean NREM 3±2 vs REM 25±11 events per hour; range, 14 to 38). Individual data for the RDI during the control study is presented in Table 2.

The transition from non-REM to REM sleep was associated with a decrease in the tonic activity of the diaphragm and SCM EMG signals. This decrease in EMG activity was associated with a concomitant decrease in the end-expiratory position of the plethysmograph sum signal, suggesting a decrease in end-expiratory lung volume (EELV). Phasic eye movements during REM sleep were associated with a further reduction in the diaphragm EMG signal and marked attenuation or abolition of accessory muscle (SCM) EMG activity, short hypopneic periods, and a

### Table 2—Individual Data for the RDI During the Control nCPAP Sleep Studies

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Control</th>
<th>nCPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NREM</td>
<td>REM</td>
</tr>
<tr>
<td></td>
<td>NREM</td>
<td>REM</td>
</tr>
<tr>
<td>1</td>
<td>1.85</td>
<td>14.4</td>
</tr>
<tr>
<td>2</td>
<td>4.73</td>
<td>37.5</td>
</tr>
<tr>
<td>3</td>
<td>4.11</td>
<td>22.1</td>
</tr>
<tr>
<td>4</td>
<td>0.93</td>
<td>25.9</td>
</tr>
<tr>
<td>5</td>
<td>4.00</td>
<td>38.4</td>
</tr>
<tr>
<td>6</td>
<td>1.11</td>
<td>14.69</td>
</tr>
<tr>
<td>7</td>
<td>2.78</td>
<td>25.5</td>
</tr>
<tr>
<td>Mean</td>
<td>2.45</td>
<td>19.14</td>
</tr>
<tr>
<td>SD</td>
<td>0.70</td>
<td>2.45</td>
</tr>
<tr>
<td></td>
<td>0.98</td>
<td>13.85</td>
</tr>
<tr>
<td></td>
<td>1.44</td>
<td>14.11</td>
</tr>
<tr>
<td></td>
<td>0.41</td>
<td>19.14</td>
</tr>
<tr>
<td></td>
<td>0.00</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>0.38</td>
<td>9.34</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>7.0</td>
</tr>
</tbody>
</table>

CHEST / 106 / 6 / DECEMBER, 1994 1719
further reduction in the amplitude and baseline of the plethysmograph ribcage and sum signals (Figs 2 and 3). The largest falls in \( \text{SaO}_2 \) and the largest increases in \( \text{TcCO}_2 \) were seen during periods of phasic REM sleep. No patient snored or showed any evidence of frank obstructive apnea.

The group data for sleep architecture, arousal, and cough index during the control sleep study are summarized in Table 3. Cough (3 ± 2/h) and positional changes contributed to arousals from sleep (7 ± 2 arousals per hour).

**nCPAP Study**

Nasal CPAP was titrated to a mean pressure of 11 ± 2 cm H\(_2\)O, ranging from 8 to 16 cm H\(_2\)O. The MMOS during both NREM (nCPAP 91 ± 3% vs control 88 ± 2%, \( p<0.05 \)) and REM sleep (nCPAP 89 ± 6% vs control 83 ± 6%, \( p<0.05 \)) were significantly improved with the addition of nCPAP when compared with the control study in all patients (Fig 1). The absolute minimum \( \text{SaO}_2 \) during sleep was also significantly improved by nCPAP (nCPAP 84 ± 7% vs control 76 ± 10%, \( p<0.05 \)). Nasal CPAP resulted in significantly less percent of TST being spent with low oxyhemoglobin saturations, in particular below 85% (Fig 4). The addition of nCPAP had no significant effect on \( \text{TcCO}_2 \) during NREM sleep, REM sleep, or on the maximum \( \text{TcCO}_2 \) value when compared with the control study.

As was observed during the control study, the transition from non-REM to REM sleep was associated with a decrease in the tonic activity of the diaphragm and SCM muscle EMG signals. The resultant decrease in the end-expiratory position of the plethysmograph sum signal observed in all patients during the control study was less evident during the use of nCPAP. The amplitude of excursion and end-expiratory position of the plethysmograph sum signal was also maintained during periods of phasic eye movements. This resulted in a marked decrease in the number of hypopneic periods and also a reduction in the desaturation associated with these hypopneic periods (Figs 5 and 6). The RDI was significantly reduced by nCPAP in NREM sleep and especially so during REM sleep (Table 2).

The group data for sleep architecture, arousal, and cough index during the nCPAP sleep study compared with the control study are summarized in Table 3.

**FIGURE 2.** This is part of the sleep record of patient 6 during the control sleep study in non-REM sleep. Note the consistent activity of the SCM as an accessory muscle with each breath during non-REM sleep. \( \text{SaO}_2 \) is maintained at 88%.

**FIGURE 3.** This is part of the sleep record of patient 6 during the control sleep study in REM sleep. In the transition from non-REM to REM sleep, note the attenuation of the diaphragm and SCM EMG signals. With the onset of phasic eye movements, the SCM EMG disappears with a subsequent hypopnea, a decline in rib cage, and the sum signal excursions of the plethysmograph and a fall in \( \text{SaO}_2 \) from 87 to 81%.

Benefits of Nocturnal Nasal CPAP in Patients With CF (Regnis et al)
Nasal CPAP caused an increase in cough and arousal in one patient but for the group no significant differences were observed (Table 3).

In five of the seven patients, one night of nCPAP was associated with an improvement in sleep efficiency, a reduction in sleep latency, time spent awake and in stage 1/2 sleep, and an increase in SWS (stage 3/4) and REM sleep as a percentage of the total sleep period. Subjectively, quality of sleep was reported as “the same as usual” in two patients and “better than usual” in three patients. The other two patients in our study group had less satisfactory nights on nCPAP. One patient had pressure escaping from the mouth and was forced to use a chin strap, whereas in the other patient, nCPAP resulted in an increase in coughing and subsequent arousal. These events in the two patients resulted in a large increase in their awake time and reductions in their time spent in both SWS and stage REM. Both these patients reported their sleep was “worse than usual.” These differing responses meant that as a group nCPAP resulted in a slight but not significant increase in sleep efficiency, but no significant changes in sleep architecture (Table 3).

**Discussion**

The present study demonstrates that in patients with CF and severe lung disease, nocturnal nCPAP improved oxyhemoglobin saturation during both non-REM and REM sleep and decreased the amount of respiratory disturbance. Nasal CPAP resulted in a significantly less percentage of TST being spent with low oxyhemoglobin saturations. With the addition of nCPAP, episodes of sleep-disordered breathing, especially during phasic REM sleep, were reduced, without adverse effects on sleep efficiency or sleep architecture in most patients. The beneficial effect of nCPAP on oxyhemoglobin saturation was also evident in the three patients who received low-flow oxygen therapy on both study nights. These studies suggest a potential role for nocturnal nCPAP in patients with CF and severe lung disease.

Our results confirm the previous findings that patients with CF have periods of oxyhemoglobin desaturation during sleep that is most marked during REM sleep. Previous interventions in patients with CF have been shown to improve oxygen saturation without improving sleep quality. Spier and coworkers found that nocturnal low-flow oxygen therapy at 2 L \cdot min^{-1} significantly improved oxygen saturation, without inducing “clinically important hypercapnia.” Likewise, a long-term low-flow oxygen trial has not shown any beneficial effects in terms of mortality, frequency of hospital admissions, or disease progression. Our experience with a number of adult patients with CF is that nocturnal oxygen may not always prevent oxygen desaturation associated with periods of phasic REM and that nocturnal low-flow oxygen therapy can on occasions lead to morning headaches and worsening hypercapnia. A recent report indicated that a 10-day course of theophylline therapy reduced nocturnal desaturation yet also significantly reduced sleep efficiency. In contrast to these results, we have shown that one night of
nCPAP not only improves oxyhemoglobin desaturation but also reduces respiratory disturbance and does not cause a significant decrement in sleep efficiency or sleep architecture.

There is a considerable literature on the mechanisms of action of nocturnal CPAP in patients with obstructive sleep apnea and patients with lung disease. The beneficial effects of CPAP include the prevention of airway closure with maintenance of EELV, reduction in upper airway resistance, and the unloading of inspiratory muscles with a possible reduction in the oxygen cost of breathing. It was not the purpose of this study to determine the mechanisms by which nCPAP improved nocturnal oxygenation in patients with CF; however, some inferences can be drawn from our findings.

During the transition from non-REM to REM sleep and again during phasic eye movements in REM sleep, we observed a reduction in the plethysmograph sum signal in the control study suggesting a decrease in end-expiratory dimensions of the rib cage and abdomen and thus a decrease in functional residual capacity. This is in agreement with findings originally reported by Muller and colleagues. There was not a similar decline in the plethysmograph sum signal when the patients were receiving nCPAP, suggesting that EELV is maintained by nCPAP in these patients, especially during REM sleep. Thus, nCPAP may improve nocturnal oxygenation by preventing a reduction of lung volume and airway closure during REM sleep. Nasal CPAP has also been shown to improve oxygenation and lung mechanics in patients recovering from acute respiratory failure, and to prevent the decrease in EELV in patients recovering from abdominal surgery. While nCPAP may relieve airway obstruction, the increase in EELV may also increase the elastic load to breathing. These opposing effects may explain why there was no net reduction in TcCO₂ with nCPAP in our study.

A second possible explanation for the observed benefits with nCPAP is that oxygenation was improved as a result of the reduction in the work of breathing. Martin and coworkers have demonstrated that in patients with histamine-induced asthma, CPAP can reduce the load on inspiratory muscles, improve their efficiency, and decrease the energy cost of breathing. The use of CPAP during

![Figure 5](image-url)  
**Figure 5.** This is part of the sleep record of patient 6 in non-REM sleep in the nCPAP study.

![Figure 6](image-url)  
**Figure 6.** This is part of the sleep record for patient 6 in REM sleep in the nCPAP study. Note that during phasic REM, despite the absence of SCM EMG, nCPAP (10 cm H₂O) has prevented the hypventilation, the fall in end-expiratory position of the Respiracem sum signal, and the resultant fall in SaO₂%, observed in the control study.

**Benefits of Nocturnal Nasal CPAP in Patients With CF (Regnis et al)**

Downloaded From: http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21704/ on 06/04/2017
exercise in patients with severe chronic obstructive pulmonary disease (COPD) has been reported to result in increased endurance time and a reduction in respiratory effort and a decrease in dyspnea.\textsuperscript{24-26} Likewise, Henke and coworkers\textsuperscript{27} have shown that in patients with CF and advanced lung disease, CPAP unloaded inspiration during exercise with a reduction in oxygen uptake, diaphragm work, and sensation of dyspnea. It has been reported recently that nocturnal nCPAP can effectively reduce respiratory muscle effort during sleep in patients with severe COPD.\textsuperscript{28}

There is an increase in upper airway resistance during sleep in normal subjects and in patients with chronic airflow limitation.\textsuperscript{29-31} This may add an additional load to ventilation and to the muscles of inspiration, especially in the patients with COPD. Nasal CPAP has been shown to reduce upper airway resistance.\textsuperscript{32} Chan and colleagues\textsuperscript{33} have shown improvement in both nocturnal and daytime peak expiratory flow rates in patients with asthma and obstructive sleep apnea following nocturnal nCPAP. Interestingly, in a recent study of nCPAP in nonapneic nocturnal asthma, the use of CPAP was associated with a worsening of sleep architecture.\textsuperscript{34}

It is possible that the two patients who did not sleep well on their first night of nCPAP may have tolerated it better with more prolonged use. A number of our patients claimed a subjective improvement in the quality of sleep even with the first night of use and most of these have continued on nCPAP long term. In five of our seven patients, nCPAP led to a decrease in time spent awake and an increase in time spent in SWS and REM sleep. Although the preliminary results in this small group of patients are encouraging, not all patients tolerated nCPAP well in this single-night study; also, the order of studies was not randomized and therefore limited conclusions can be drawn in regard to patient tolerance and the effect of nCPAP on sleep quality.

The benefits of nocturnal nCPAP are of potential clinical relevance in patients with CF and severe lung disease in view of the significant improvement in oxyhemoglobin saturation and the reduction in respiratory disturbance. The use of nCPAP has also proved to be of additional benefit in preventing nocturnal desaturation and respiratory disturbance in a number of patients already using supplemental oxygen. A long-term controlled trial of nCPAP is needed in patients with CF to determine its effect on mortality, frequency of hospitalization, progression of disease, and quality of life.

REFERENCES

2 Tepper RS, Skatrud JB, Dempsey JA. Ventilation and oxygenation changes during sleep in cystic fibrosis. Chest 1983; 84:385-93
9 Issa FG, Sullivan CE. Reversal of central sleep apnea using nasal CPAP. Chest 1986; 90:165-71
21 Katz JA, Marks JD. Inspiratory work with and without continuous positive airway pressure in patients with acute respiratory failure. Anesthesiology 1985; 63:598-607
22 Lindner KH, Lotz P, Aehnfeldt FW. Continuous positive airway pressure effect on functional residual capacity, vital capacity and its subdivisions. Chest 1987; 92:66-70
23 Martin JC, Shore S, Engel LA. Effect of continuous positive
airway pressure on respiratory mechanics and pattern of breathing in induced asthma. Am Rev Respir Dis 1982; 126:612-17

American Board of Internal Medicine
1995 Certification and Qualifying Examinations in Cardiovascular Disease

Registration Period: January 1 - April 1, 1995
Certification Examination Dates: November 9 - 10, 1995
Qualifying Examination Date: November 9, 1995

Contact: Registration Section, American Board of Internal Medicine, 3624 Market Street, Philadelphia, PA 19104. Tel: 1 800 441-2246 or 1 215 243-1500; Fax: 1 215 382-5515.