Nocturnal Oxyhemoglobin Desaturation in COPD Patients with Arterial Oxygen Tensions Above 60 mm Hg*

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We studied 152 COPD patients with a daytime PaO₂≥60 mm Hg using formal polysomnography (EEG, airflow, respiratory muscle movement, ear oximeter) to detect the presence of nocturnal, nonapneic, oxyhemoglobin desaturation. Nine subjects were disqualified by the unexpected discovery of sleep apnea, as were another eight because they could not sleep in the laboratory setting. Of the remaining 135 subjects, 37 (27 percent) desaturated below a baseline sleep saturation of 90 percent for five minutes or more, reaching a nadir saturation of at least 85 percent. Anthropomorphic, pulmonary function, and historic factors comparing desaturators and nondesaturators failed to separate the groups. Awake PaO₂ at rest in the desaturators was significantly lower than in the nondesaturators. The PaCO₂ was higher in the desaturators. Reversibility of the desaturation phenomenon was demonstrated in three patients during subsequent polysomnographic studies following periods of clinical improvement. Continuous oxyhemoglobin monitoring during sleep remains the only reliable tool for detecting nocturnal desaturation.

Nonapneic, oxyhemoglobin desaturation associated with rapid-eye-movement (REM) sleep has been described in patients with COPD, cystic fibrosis, interstitial lung disease, and neuromuscular or skeletal diseases affecting the thorax. These often profound decreases in oxyhemoglobin saturation (SaO₂) may be accompanied by marked elevation of pulmonary artery pressure. Repetitive, transient episodes of nocturnal hypoxemia have been proposed as one mechanism by which chronic pulmonary hypertension can develop in patients with advanced lung disease. Since sleep studies are expensive and require the use of specialized equipment, many factors of daytime function have been examined trying to identify a subpopulation that might require studies to detect nocturnal desaturation. Clinical parameters frequently associated with the presence of nocturnal desaturation are as follows: (1) a low daytime PaO₂; (2) blunted chemosensitivity; (3) severe dysfunction on pulmonary function testing; and (4) the presence of the "blue bloater" or chronic bronchitic clinical picture. None of these has proven useful in predicting individual REM desaturators.

Nocturnal REM desaturation occurs more often among patients whose resting daytime PaO₂ is on the steep part of the oxyhemoglobin dissociation curve, that is, PaO₂<55 mm Hg. Since these patients often receive continuous home supplemental oxygen, their nocturnal desaturation will already be treated. More pertinent clinical questions are, "What is the incidence of REM desaturation in COPD patients whose daytime PaO₂ is above 55 mm Hg?" and "What parameters of daytime function indicate nocturnal desaturation is present?"

Materials and Methods

We studied 152 male United States veterans from a medical chest clinic with the diagnosis of COPD using nocturnal polysomnography to detect oxyhemoglobin desaturation. Requirements for inclusion were as follows: (1) a clinical diagnosis of COPD characterized by symptoms of chronic cough, exertional dyspnea, or wheezing; (2) spirometry consistent with irreversible expiratory airflow obstruction (FEV₁<80 percent predicted, FEV₁/FVC<0.75) or evidence of airtrapping on body plethysmography; and (3) an average daytime resting PaO₂≥60 mm Hg with samples spread over three to six months preceding polysomnography. Daytime PaO₂ values were taken as the average of three blood gas levels drawn with the patient seated. Body plethysmography was not available in all subjects for technical reasons. All patients were judged to be clinically stable at the time of study.

Each subject slept at least one night in our laboratory. Electroencephalographic (C3A2 and C4A1), bitemporal electro-oculographic, submental electromyographic, and electrocardiographic leads were placed appropriately. Nasal/oral airflow was detected by thermistor or end-tidal CO₂ analyzer attached to a loose fitting face mask. Thoracic and abdominal pneumobolts connected to pressure transducers detected changes in chest and abdominal wall circumference. The SaO₂ was continuously monitored by ear oximetry. All parameters were recorded simultaneously on polygraphic recorders. Sleep stages and SaO₂ were scored by a trained technician according to standard criteria. Nocturnal desaturation was defined as a baseline

For editorial comment see page 579

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reach 85 percent or lower but was not required to remain at or below 85 percent for five minutes (Fig 1). These periods usually coincided with but were not limited to REM sleep.

Differences in observed values between desaturators and non-desaturators were compared using the Wilcoxon nonpaired rank sum test for interval variables. The Anderson-Darling test was used as a test of normal distribution of groups. The Chi square test was used to compare yes/no answers to questions about clinical symptoms. Stepwise logistic regression was applied to 18 parameters of morphometry, blood gas, and pulmonary function in attempt to determine a combination of clinical characteristics that might discriminate desaturators from nondesaturators. The protocol was reviewed and approved by appropriate human research committees at the Houston VAMC and Baylor College of Medicine, and all subjects signed informed consents.

RESULTS

Eight subjects were disqualified because of inability to achieve or maintain adequate sleep (more than one to two hours of NREM sleep) for sleep stage and SaO₂ analysis. Most of these were studied on two or more occasions. Nine were disqualified because of the presence of five or more obstructive apneas per hour in spite of the absence of clinical symptoms of sleep apnea. Thirty seven (27 percent) of the remaining 135 subjects showed nocturnal oxyhemoglobin desaturation as described above (Fig 1). Ninety eight did not show desaturation to the above described level. All 98 nondesaturators achieved at least two minutes of REM sleep. Ninety five experienced ten or more minutes of REM sleep. The mean time spent in REM sleep by both groups is shown in Table 1.

Desaturators tended to have less efficient sleep with more time in bed and less total sleep than non-desaturators but the differences were not significant. There was a highly significant difference in baseline NREM sleep SaO₂ (excluding periods of episodic

Table 1—Demographic Data on COPD Patients with and without Nocturnal Desaturation*

<table>
<thead>
<tr>
<th></th>
<th>Nondesaturators</th>
<th>Desaturators</th>
<th>&quot;p&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>MEAN</td>
<td>(SD)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>98</td>
<td>61.9</td>
<td>(6.3)</td>
</tr>
<tr>
<td>% of Ideal weight</td>
<td>98</td>
<td>97.2</td>
<td>(17.0)</td>
</tr>
<tr>
<td>Hemoglobin (mg/dl)</td>
<td>98</td>
<td>15.1</td>
<td>(1.5)</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>98</td>
<td>75.5</td>
<td>(8.2)</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>98</td>
<td>38.2</td>
<td>(4.9)</td>
</tr>
<tr>
<td>FEV₁ (L/S)</td>
<td>98</td>
<td>1.32</td>
<td>(0.5)</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>98</td>
<td>43.0</td>
<td>(12.4)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>98</td>
<td>3.1</td>
<td>(0.9)</td>
</tr>
<tr>
<td>RV (L)</td>
<td>42</td>
<td>4.4</td>
<td>(1.2)</td>
</tr>
<tr>
<td>FRC (L)</td>
<td>42</td>
<td>5.4</td>
<td>(1.2)</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>42</td>
<td>7.6</td>
<td>(1.4)</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>98</td>
<td>297.7</td>
<td>(69.5)</td>
</tr>
<tr>
<td>Time in bed</td>
<td>98</td>
<td>353.5</td>
<td>(53.0)</td>
</tr>
<tr>
<td>Time in NREM (min)</td>
<td>98</td>
<td>252.5</td>
<td>(62.0)</td>
</tr>
<tr>
<td>Time in REM (min)</td>
<td>98</td>
<td>44.7</td>
<td>(22.9)</td>
</tr>
<tr>
<td>Base NREM SaO₂ (%)</td>
<td>98</td>
<td>94.3</td>
<td>(1.6)</td>
</tr>
</tbody>
</table>

*Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; FRC, functional residual capacity; TLC, total lung capacity; BASE, baseline (during stable breathing periods of nondesaturation); REM, rapid-eye-movement; and NREM, non-REM.
desaturation) between groups (Table 1).

There were no differences between desaturator and nondesaturator groups comparing anthropomorphic data, blood hemoglobin, and various parameters of pulmonary function (Table 1). Using linear regression analysis, there was no significant relationship between resting daytime PaCO\textsubscript{2} or PaO\textsubscript{2} and the nadir SaO\textsubscript{2} during NREM or REM sleep in either group. Desaturators had significantly higher PaCO\textsubscript{2} and lower PaO\textsubscript{2} levels than nondesaturators (Table 1), but the overlap between groups was sufficient to make these parameters alone of little help in separating individual desaturators. A large portion of desaturators gave a classic history of chronic bronchitis (31 of 36) but compared to nondesaturators (64 of 96), the difference was not significant by chi square analysis.

A stepwise logistic regression equation was derived using 18 parameters of blood gas, pulmonary function, symptoms, and vital statistics. Because all 18 parameters were not available in each patient, the equation was derived from a sample size of 110. Stepwise logistic regression showed the combination of a high PaCO\textsubscript{2}, low PaO\textsubscript{2}, and a positive history of chronic bronchitis to be significantly related but not very predictive of the presence of nocturnal desaturation. The equation derived using these three parameters was:

\[
\text{Predicted Probability} = \frac{\exp(0.932+0.122 \times \text{PaCO}_2 - 0.069 \times \text{PaO}_2 + 1.604 \times \text{B})}{1 + \exp(0.932+0.122 \times \text{PaCO}_2 - 0.069 \times \text{PaO}_2 + 1.604 \times \text{B})}
\]

where \(\exp\) is the exponential function (2.71) and \(\text{B}\) is the bronchitis score (1 = no, 0 = yes).

The results of this equation were applied to 132 (history of chronic bronchitis was indeterminant in three) desaturation screen patients. The distribution of the 132 patients within desaturator and nondesaturator groups was based upon the estimated probability calculated from their PaCO\textsubscript{2}, PaO\textsubscript{2}, and history of chronic bronchitis (Fig 2). There was a high degree of overlap except at extremely high and low probabilities, making this approach unhelpful in clinical screening.

During the course of this study, three patients showed reversible nocturnal desaturation. Two of these underwent initial polysomnography on the day of discharge following a ten-day and 14-day hospitalization for acute exacerbations of COPD. At the time of study, the patients felt better than their usual state of health, were free of wheezes on quiet respiration, and were judged to be clinically stable. Another outpatient using oral theophylline and an inhaled beta-2 agonist was also studied during what he termed to be his "usual state of health." Physical examination on the day following polysomnography showed marked expiratory wheezes. A course of corticosteroids resulted in clearing of wheezes with improvement in clinical symptoms. All three of these subjects showed nocturnal REM desaturation to 85 percent or below during REM sleep on their initial sleep study. Each was screened two to four weeks later during a sham study (compressed air by loose face mask) in preparation for inclusion in a long-term nocturnal oxygen protocol and did not show evidence of desaturation. The patient who cleared with a short course of steroids was restudied a third time, three months after the initial screen (while off steroids) and again showed no evidence of REM desaturation.

Sleep apnea was discovered in nine subjects in whom it was not suspected prior to polysomnography. The mean apnea index of these subjects was 40 events per hour with a range of five to 87. The apneas were predominantly obstructive and mixed with about 10 percent central. Nadir oxyhemoglobin saturations reached as low as 61 percent but averaged between 80 and 90 percent. These subjects had minimal symptoms and could not be separated clinically from those with COPD alone.

**DISCUSSION**

Transient oxygen desaturation in chronic lung disease probably results from a combination of alveolar hypventilation and gas exchange abnormalities contributed to by REM sleep muscular atonia and changes in respiratory control.\textsuperscript{20-22} Attention has been given to the role of transient alveolar hypoxia and hypoxic vasoconstriction as possible causes of sustained pulmonary hypertension.\textsuperscript{13-14} Several authors\textsuperscript{30-38} have demonstrated that repetitive episodes of transient hypoxia in experimental animals can lead to many of the changes seen in chronic pulmonary hypertension. Thus, a theoretical mechanism has been offered by which such transient episodes of hypoxemia could, after many years, contribute to the development of chronic pul-

![Distribution of Predicted Probabilities of Being A Desaturator Using A Logistic Model](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21568/ on 06/14/2017)
monary hypertension. Low flow supplemental oxygen during sleep has been shown to ameliorate or eliminate these desaturations.\textsuperscript{26} Thus, a readily available, albeit expensive, form of therapy is available that could reverse these episodes, potentially ameliorating the insidious progression of pulmonary hypertension in COPD patients without substantial daytime hypoxemia. Continuous (day and night) supplemental oxygen has been shown to improve longevity in COPD patients who are hypoxic (\(\text{PaO}_2 \leq 55\) mm Hg) during the day.\textsuperscript{26} Correction of nocturnal desaturation may be one of the factors improving survival.

The main goal of this study was to examine the incidence of REM desaturation in those COPD patients whose \(\text{PaO}_2\) is greater than 60 mm Hg. A second goal was to identify parameters of daytime function that may be used to better define the subpopulation of desaturators. We feel that this group deserves close examination because they do not qualify for supplemental oxygen by current ATS criteria\textsuperscript{26} and because they are probably at an earlier stage of their disease than patients with severe daytime hypoxemia. It should be emphasized that the degree of nocturnal desaturation in this study was generally not as severe as that reported in previous studies examining this phenomenon in patients with daytime hypoxemia.\textsuperscript{2,12} Indeed, among the 37 desaturators, the mean nadir (not average) \(\text{SaO}_2\) was 81 ± 3.2%.

Considering that the average time spent in REM sleep by desaturators was only 44 minutes (a figure that may be low because of the manipulations involved in polysomnography), this is not a striking degree of hypoxemia. Therefore, it could be that nocturnal REM hypoxemia may simply be a marker for the future development of pulmonary hypertension rather than the cause of it. Furthermore, the efficacy of nocturnal supplemental oxygen in preventing progression of pulmonary hypertension in the above setting has not been proven.

Several areas of bias may have affected the reported incidence of REM desaturation in this study. First, while a minimum \(\text{PaO}_2\) of 60 mm Hg was the only blood gas requirement for study and no limitations were placed upon age or \(\text{FEV}_1\), the survey population of veterans may be somewhat older with more severe pulmonary dysfunction than the general COPD population. Second, patients disqualified because of poor sleep in the laboratory and patients with greater than five apneas per hour of sleep eliminated from analysis may have removed potential desaturators lowering the calculated incidence. On the other hand, sleep at home in a less artificial environment may produce longer periods of desaturation, perhaps accentuating the effect of the hypoxemia.

Of particular interest in this study were the three patients with reversible desaturation. This phenomenon is reminiscent of a notable discovery in the NOTT trials.\textsuperscript{30,31} Over a one-month period after discharge, 175 of 409 hypoxic (\(\text{PaO}_2 \leq 55\) mm Hg) patients who were symptomatically stable following an acute exacerbation of COPD improved their \(\text{PaO}_2\) to levels that exceeded 59 mm Hg. There appears to be a period of slow recovery following COPD exacerbations such that, despite general symptomatic improvement, pulmonary mechanics and gas exchange continue to recover. During such periods, patients are subject to either continuous or episodic periods of hypoxemia.

We are confident that the other desaturators did not exhibit this reversibility since 31 of 37 desaturators have had at least one follow-up study prior to nocturnal oxygen randomization, verifying persistent REM hypoxemia.

While ear oximetry is now widely used to detect oxyhemoglobin desaturation during "sleep studies," we emphasize that polysomnography with electroencephalographic monitoring is essential in ruling out this diagnosis. Because of overbooking of patients for our sleep lab, in some subjects an initial sleep night included ear oximetry only. The overwhelming majority of these simple screens were negative for desaturation. Later, formal polysomnography where sleep staging was available to ensure the presence of REM sleep then showed REM-related desaturation. Several subjects claimed "adequate" sleep in the lab and showed good quality NREM sleep by EEG but required up to three, and in one case five, formal studies to ensure the presence of REM sleep and associated desaturation. Thus, ear oximetry alone can theoretically detect nocturnal REM desaturation but it cannot be used to rule such desaturation out since the presence of REM sleep must be verified by EEG.

In conclusion, nocturnal REM-related oxyhemoglobin desaturation occurs in 27 percent of COPD patients with a \(\text{PaO}_2 \leq 60\) mm Hg who are able to sleep adequately during polysomnography and who do not have obstructive sleep apnea. Desaturators tend to have lower \(\text{PaO}_2\), higher \(\text{PCO}_2\), and more chronic bronchitis than nondesaturators, but these parameters are not highly predictive of desaturation. In some patients, particularly those who are under less than optimal control or who are recovering from acute exacerbations of COPD, nocturnal REM desaturation may be a temporary or reversible phenomenon. Finally, the clinical relevance of these data to the treatment of COPD patients is unknown.

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CHEST / 92 / 4 / OCTOBER, 1987 607


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